Cancer genetics in Gynecology

Dana Zakalik, M.D.
Director, Nancy and James Grosfeld Cancer Genetics Center
Professor of Medicine, OUWB Medical School
SEMCME Postgraduate Course in OB/GYN
January 24th, 2018

Outline

• Introduction
• Hereditary Breast and Ovarian Cancer (HBOC)
• Multi-gene panel testing and “other” genes
• Hereditary colorectal cancer syndromes
  – Lynch syndrome
    • Gyn Cancers
  – (Polyposis syndromes)
• Genetics and the law
Impact of Genetics on Cancer

- Molecular Diagnostics
- Tumor Classification
- Prognostic/Predictive Information
- Targeted Therapies
- Pharmacogenomics
- Molecular Monitoring

Hereditary Cancer Syndromes
Risk Assessment
High Risk Surveillance
Early Detection
Better Outcomes & Improved Survival
Cancer Prevention
### Breast Cancer

- 235,000 new cases diagnosed 2017
- ~44,000 deaths 2017
- Lifetime risk: 12.6% for invasive breast cancer
- Risk Factors:
  - **Familial/Genetic**
    - Age, Reproductive history
  - Environmental Factors → thoracic RT (Hodgkin lymphoma), HRT
  - Other Factors → atypia, breast density, BMI, LCIS

### Ovarian Cancer

- 22,000 new cases diagnosed in 2017
- 14,000 deaths
- Lifetime risk 1-2% (1 in 70)
- Factors influencing risk of ovarian cancer
  - Age
  - Family history
  - **Genetics** – 15% due to a genetic mutation
  - Obesity
  - Reproductive/hormonal factors
Cancer Etiology

• ~5-10% of cases have a strong hereditary component
• ~15-20% are “familial” or multifactorial
• ~70-75% are sporadic

Sporadic vs Hereditary Cancer

In **sporadic** cancer, damage to both genes is acquired.

2 normal genes → 1 broken gene → 2 normal genes → Tumor Develops

1 broken gene
1 normal gene

In **hereditary** cancer, one damaged gene is inherited.

1 broken gene
1 normal gene → 2 broken genes → Tumor Develops

2 broken genes

Genetic Testing Red Flags

- Early onset breast cancer (or multiple cases)
- **Ovarian cancer**
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish ancestry
- Male breast cancer
- Pancreatic cancer
- Triple negative breast cancer
SGO Clinical Practice Statement: Genetic Testing for Breast/Ov Cancer  (Oct 2014)

- Breast cancer at age 45 or younger
- Breast cancer and a close relative under 50 y
- Breast cancer under 50 y with a limited family history
- Breast cancer any age with 2 or more relatives with pancreatic cancer, aggressive prostate cancer
- Triple negative breast cancer under 60 y
- Two breast primaries, with the first being under 50 y
- Breast cancer in an Ashkenazi individual
- Pancreatic cancer with 2 or more close relatives with breast/ovarian/tubal/prostate/pancreatic cancer...
SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer

October 2014

Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of a family history.

Germline BRCA1 and BRCA2 mutations account for approximately 15% of invasive ovarian carcinomas, and a somewhat higher proportion of fallopian tube or peritoneal carcinomas (1,2,3). In contrast, borderline ovarian neoplasms are not associated with mutations in BRCA1 and BRCA2 (4). BRCA1 and BRCA2 mutations lead to a 15-50% lifetime risk of ovarian carcinoma, with an increased risk and earlier onset associated with BRCA1 compared to BRCA2 mutations. A number of other genes have also been shown to cause hereditary ovarian carcinomas.

Nearly one third of women with hereditary ovarian carcinoma have no close relatives with cancer, and 35% of women with hereditary ovarian carcinoma are older than 60 years at diagnosis. Therefore, all women diagnosed with ovarian, fallopian tube or peritoneal carcinoma, regardless of age or family history, should receive genetic counseling and be offered genetic testing. Careful pre-and post-test counseling is essential to understanding genetic testing options and results. Genetic counseling and testing can be conducted by genetic counselors, as well as other knowledgeable medical professionals.

- All women diagnosed with epithelial ovarian cancer should receive genetic counseling and testing
  - 35% of gene carriers are over 65 years at diagnosis
- Germline BRCA1/2 mutations account for 15% of ovarian cancer (5-6% “other” genes)
- One third of women with hereditary risk have no family history
- 15-50% lifetime risk of ovarian cancer
- Pre- and post-test counseling by individuals with expertise in genetics is important
- “SGO encourages medical community to offer genetic counseling and testing to all women with ovarian, fallopian, and peritoneal cancer”
**Clinical Questions**

- Is there a genetic predisposition to breast cancer in this family?
- Should this patient undergo genetic testing?
- Which gene test(s) should be ordered?
- Can her risk of cancer be lowered?
- What are the implications of risk-reducing interventions for her health?
- Should other family members be tested?
Hereditary Breast Cancer Genes

- **Breast Cancer Gene 1** – BRCA1 (1994)
  - Chromosome 17
- **Breast Cancer Gene 2** – BRCA2 (1995)
  - Chromosome 13
- **Tumor Suppressor Genes** – DNA repair
  - Important in repair of double-strand DNA breaks
    - Maintains normal DNA in all individuals
- **Alteration (mutation)** → high risk of breast cancer
  - Cause inherited breast and ovarian cancer
- **Seen more often in Ashkenazi Jews** (1 in 40)

---

**BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population**

An estimated 1 in 40 Ashkenazi Jews carries a BRCA1 or BRCA2 mutation

- **BRCA1**
  - 185delAG
    - Prevalence = −1%
  - 5382insC
    - Prevalence = −0.15%

- **BRCA2**
  - 6174delT
    - Prevalence = −1.5%

### BRCA1/2 Mutations: Lifetime Cancer Risks

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer to age 80</td>
<td>55-87%</td>
<td>50-65%</td>
</tr>
<tr>
<td>Ovarian cancer to age 80</td>
<td>20-45%</td>
<td>up to 20%</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>&lt;6%</td>
<td>6-8%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Slight incr.</td>
<td>20%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2-3%</td>
<td>3-6%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>No incr.</td>
<td>Slight incr.</td>
</tr>
</tbody>
</table>

#### Possible Test Results

- **Positive Result**: Increased Cancer Risk
- **Negative Result**
  - Has a mutation previously been found in your family? (individualized risk estimate)
    - Yes: No increased Cancer Risk (same as general population) “True Negative”
    - No: Cancer Risk Not Fully Defined (individualized risk estimate) “Uninformative negative”
- **Uncertain Variant**: Cancer Risk Not Yet Known (individualized risk estimate)
Management Of BRCA Carriers

• High Risk Surveillance
  – Breast MRI and mammography
  – Other: Ovary, prostate, pancreas ...

• Chemoprevention
  – Tamoxifen – 50% reduction of breast cancer risk
  – Novel agents (research)

• Prophylactic Surgery
  – Bilateral Mastectomy – 90-95% reduction of risk
  – Risk-reducing salpingo-oophorectomy – 90% reduction

Surveillance for Breast Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>18 yrs</td>
<td>Monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>25 yrs</td>
<td>6 months to a year</td>
</tr>
<tr>
<td>Mammography</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Surveillance for Ovarian Cancer

• May be considered starting at age 30-35 y:
  • CA-125
  • Transvaginal ultrasound

• No data showing that surveillance lowers mortality from ovarian cancer

• Annual gyn screening of BRCA mutation carriers “not effective.”

Surveillance for Ovarian Cancer

• NCCN 2017 Guidelines:

• For patients who elect not to do RRSO, “while there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening. TVUS has not been shown to be sufficiently sensitive/specific to support a positive recommendation... Ca-125 has similar caveats”
Screening for Other Cancers

- Prostate (starting at age 45):
  - *BRCA1* Consider prostate screening
  - *BRCA2* Recommend prostate screening
- Male breast:
  - Breast Self Exam training and education at age 35
  - Clinical Breast Exam every 12 mos starting at age 35
- Pancreas – no proven benefit
  - Consider EUS in high risk families
  - Screening registry enrollment
  - Research trials e.g. CAPS-5

Prophylactic Surgery

Bilateral Mastectomy
Risk-reducing salpingo-oophorectomy
Prophylactic Surgery

- Bilateral Mastectomy
  - 90% - 95% reduction of breast cancer risk
  - Options of reconstruction varied
    - Nipple sparing option
- Risk-reducing salpingo-oophorectomy (RRSO)
  - 80-90% reduction of ovarian cancer risk
  - Also reduces risk of breast cancer (in patients < 50 y)
  - Should be considered upon completion of childbearing or between ages of 35-40 y
  - Occult cancer found in 2-18% of specimens
  - Decreased mortality in BRCA mutation carriers (Domchek et al JAMA 2010)

RRSO

- Counseling re: quality of life, management of menopausal symptoms, possible short-term HRT, degree of protection
  - Short course HRT does not adversely impact cancer risk
  - Estrogen therapy alone appeared safe in WHI study
- “Salpingectomy alone is not the standard of care and is discouraged outside a clinical trial” (NCCN 2016)
- Decrease in all cause mortality (Domchek at al JAMA ‘10)
- Removal of uterus not mandated; may be considered if patient opting to take Tamoxifen or HRT
Chemoprevention

Tamoxifen
Oral Contraceptives

Tamoxifen Chemoprevention

- SERM – Selective estrogen receptor modulator
  - Blocks estrogen receptor
- 50% reduction in breast cancer risk in high risk women (NSABP-P1 Trial)
- Increase in endometrial cancer, DVT, PE (>50y)
- Improved bone density
- Limited data in BRCA mutation carriers
- Prevents ER + breast cancers
  - More effective in BRCA2 mutation carriers
Chemoprevention of Ovarian Cancer

- Up to 60% risk reduction for ovarian cancer in general population
- BRCA+ patients have similar benefit
- Breast Cancer Risk → Minimal to none with modern, low dose formulations
ACOG COMMITTEE OPINION
Number 727 • January 2018

Committee on Gynecologic Practice
The Society of Gynecologic Oncology endorses this document. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists’ Committee on Gynecologic Practice in collaboration with committee member Catherine Witkop, MD, MPH.

Cascade Testing: Testing Women for Known Hereditary Genetic Mutations Associated With Cancer

ABSTRACT: "Cascade testing" refers to the performance of genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations. Testing protocols and other interventions may save lives and improve health and quality of life for these family members. Obstetrician-gynecologists should know who is eligible for cascade testing and should use all available resources to ensure that cascade testing is offered and occurs in a timely manner. Despite the clear health benefits for specific populations and individuals, obstetrician-gynecologists should be aware of the potential barriers to cascade testing and should know which options can help patients overcome those barriers. Such barriers, however, may be overcome with health care provider awareness and participation in local and state initiatives to improve implementation of cascade testing. Resources available within federal and state agencies, professional societies, and in advocacy and community groups are critical to the successful implementation of cascade testing. This Committee Opinion focuses specifically on cascade testing and the role of the obstetrician-gynecologist in clinical and public health efforts to increase identification of women with hereditary cancer syndromes.

Box 1. Example of a Letter Given to a Potentially Affected Family Member

Dear Family Member:

This letter is to inform you that a member of your family, [name], has tested positive for a [gene name] gene mutation. [name] is associated with hereditary breast and ovarian cancer syndrome.

Approximately 10% of cases of breast cancer and 20% of cases of ovarian cancer are due to a specific inherited genetic alteration. Having an altered gene does not mean that you necessarily will develop breast or ovarian cancer, but it does increase your risk. Women with an altered [gene name] gene have up to an 85% lifetime risk of breast cancer and a 27-44% lifetime risk of ovarian cancer. Men with an altered gene have an increased risk of prostate cancer, breast cancer, and other types of cancer, which tend to occur at a young age. Early detection and prevention is important.

Depending on your family structure, you may have as high as a 50% chance of also having inherited this alteration in the gene. This gene is passed to males and females. Both males and females have risks of cancer if they inherit the alteration, and they can each pass the gene to their sons and daughters.

You may want to talk with your personal physician or a genetic counselor about being evaluated for your risk of having inherited this genetic mutation and your risk of developing related types of cancer. The cost of testing for this mutation ranges from $200 to $2000, and most insurance companies cover the cost. I would be happy to discuss this information further with you on the telephone. You can reach me at [contact information].

Adapted with permission from The Cancer Genetics Department, The University of Texas Southwestern Medical Center.
The “Other” Breast Cancer Genes

The “Other” Ovarian Cancer Genes
Gene Panel Testing

- Allows for efficient analysis of multiple genes
- Next generation sequencing (NGS) technology
- Rapid, simultaneous gene analysis
- Made available for multiple tumor types
- Caveat: Variants of uncertain significance (VUS)
  - Potential for misinterpretation
  - May lead to confusion re: management of risk
- Clinical utility not proven – which genes are “actionable”?
- Potential for uncertainty re: optimal management
- Lack of evidence-based guidelines for many genes
- Genetic evaluation/counseling imperative
PROMPT

- **Prospective Registry of Multiplex Panel Testing**
- Data collection research project open to any patient undergoing panel testing
- Goal to collect large numbers of mutation carriers, learn about cancer risks, outcomes, and facilitate classification of uncertain variants
- Will need to input results from large numbers of patients
- Biologic sample collection for translational research

**JOURNAL of MEDICINE**

**Breast-Cancer Risk in Families with Mutations in PALB2**


**The New York Times**

**Study Shows Third Gene as Indicator for Breast Cancer**

By NICHOLAS BAKKANARAJ AUG 6, 2016
**PALB2 and Cancer Risk**

- **Breast Cancer Risk** (association with triple negative type)
  - 14% by age 50
  - 35% by age 70
  - Impact of family history
    - 33%-58%
- **Pancreas Cancer Risk**
  - Identified in 3-4% of familial pancreatic cancer cases
- **Ovarian Cancer Risk** – conflicting results
- **Other cancers (?)**

---

**Beyond BRCA: Other Hereditary Breast Cancer Syndromes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>Cowden Syndrome</td>
</tr>
<tr>
<td>P53</td>
<td>Li Fraumeni Syndrome (LFS)</td>
</tr>
<tr>
<td>PALB2</td>
<td>PALB2</td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary Diffuse Gastric Cancer (HDGC)</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz Jeghers Syndrome (PJS)</td>
</tr>
</tbody>
</table>
### Beyond *BRCA*: Other Hereditary Breast Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden Syndrome</td>
<td>Breast, Uterine, and Thyroid Cancers; Large head size; Skin findings</td>
</tr>
<tr>
<td>Li Fraumeni Syndrome (LFS)</td>
<td>Breast, Brain, and Lung Cancers, Sarcomas, and Adrenocortical Carcinoma; very early age at diagnosis</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>Breast and Pancreatic Cancers</td>
</tr>
<tr>
<td>Hereditary Diffuse Gastric Cancer (HDGC)</td>
<td>Breast and Stomach Cancers</td>
</tr>
<tr>
<td>Peutz Jeghers Syndrome (PJS)</td>
<td>Breast, Colon, Pancreatic, and Stomach Cancers; freckling of lips in childhood</td>
</tr>
</tbody>
</table>

### Cowden’s Syndrome

- PTEN hamartoma syndrome
- Breast (30-60% lifetime risk), thyroid cancer (3-10%), *endometrial* cancer (19-28%)
- Skin manifestations:
  - papillomatous papules
  - Trichilemmomas
  - Acral keratoses
- Macrocephaly
- Thyroid nodules, goiter
- Uterine fibroids
Two "moles" removed from the back and head grew back.

ACOG PRACTICE BULLETIN
Clinical Management Guidelines for Obstetrician-Gynecologists
Number 182, September 2017
(Replaces Practice Bulletin Number 103, April 2009)

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is an inherited cancer-susceptibility syndrome characterized by multiple family members with breast cancer, ovarian cancer, or both. Based on the contemporary understanding of the origins and management of ovarian cancer and for simplicity in this document, ovarian cancer also refers to fallopian tube cancer and primary peritoneal cancer. Clinical genetic testing for gene mutations allows more precise identification of those women who are at an increased risk of inherited breast cancer and ovarian cancer. For these individuals, screening and prevention strategies can be instituted to reduce their risks. Obstetrician-gynecologists play an important role in the identification and management of women with hereditary breast and ovarian cancer syndrome. If an obstetrician-gynecologist or other gynecologic care provider does not have the necessary knowledge or expertise in cancer genetics to counsel a patient appropriately, referral to a genetic counselor, gynecologic or medical oncologist, or other genetics specialist should be considered (1). More genes are being discovered that impact varying risks of breast cancer, ovarian cancer, and other types of cancer, and new technologies are being developed for genetic testing. This Practice Bulletin focuses on the primary genetic mutations associated with hereditary breast and ovarian cancer syndromes, BRCA1 and BRCA2, but also will briefly discuss some of the other genes that have been implicated.
## Table 1. Genetic Mutations Associated With Hereditary Breast and Ovarian Cancer Syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk</th>
<th>Ovarian Cancer Risk*</th>
<th>Other Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased</td>
<td>No increased risk</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Increased</td>
<td>Increased</td>
<td>Prostate</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Increased</td>
<td>Increased</td>
<td>Melanoma, pancreas, prostate</td>
</tr>
<tr>
<td>BRIP1</td>
<td>No increased risk</td>
<td>Increased</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>CDH1</td>
<td>Increased</td>
<td>No increased risk</td>
<td>Stomach</td>
</tr>
<tr>
<td>CHK2</td>
<td>Increased</td>
<td>No increased risk</td>
<td>Colon</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>Insufficient evidence</td>
<td>Increased</td>
<td>Colon, uterine, renal pelvis, small bowel, and others</td>
</tr>
<tr>
<td>Genes: MSH2, MLH1, MSH6, PMS2, and EPCAM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>Increased</td>
<td>No increased risk</td>
<td>Unknown</td>
</tr>
<tr>
<td>PTEN</td>
<td>Increased</td>
<td>No increased risk</td>
<td>Cowden Syndrome</td>
</tr>
<tr>
<td>RAD51C</td>
<td>No increased risk</td>
<td>Increased</td>
<td>Unknown</td>
</tr>
<tr>
<td>RAD51D</td>
<td>No increased risk</td>
<td>Increased</td>
<td>Unknown</td>
</tr>
<tr>
<td>STK11</td>
<td>Increased risk</td>
<td>Increased risk of sex cord stromal tumors</td>
<td>Peutz-Jegher Syndrome</td>
</tr>
<tr>
<td>TP53</td>
<td>Increased</td>
<td>No increased risk</td>
<td>Li-Fraumeni Syndrome</td>
</tr>
</tbody>
</table>

*Includes fallopian tube cancer and primary peritoneal cancer.

### Genetic/Familial High-Risk Assessment: Breast and Ovarian

#### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;<strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td><strong>Increased risk of OC</strong>&lt;br&gt;<strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
</tr>
<tr>
<td>PALB2</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;<strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
</tr>
<tr>
<td>PTEN</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;<strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
</tr>
<tr>
<td>NRF1/2</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;<strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
</tr>
<tr>
<td>ATM</td>
<td><strong>Increased risk of BC</strong>&lt;br&gt;<strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
<td><strong>Screening:</strong> Annual mammogram with consideration of breast and ovarian cancer susceptibility genes.&lt;br&gt;<strong>Early Clinical Trials:</strong> No increased risk of OC.</td>
</tr>
</tbody>
</table>

#### Notes

- **BRCA1/2:** For patients with a known mutation in BRCA1 or BRCA2, consider genetic counseling and testing for other cancer susceptibility genes.
- **Palb2:** Consider genetic counseling and testing for other cancer susceptibility genes.
- **Nrf1/2:** Consider genetic counseling and testing for other cancer susceptibility genes.
- **Atm:** Consider genetic counseling and testing for other cancer susceptibility genes.

---

*From the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2018*
Genetics and Personalized Care

• PARP inhibitors - targeted agents
• Novel treatments targeting the defect in DNA repair in BRCA mutation carriers
  – Poly ADP ribose polymerase (PARP)
  – Olaparib; Veliparib
  – Promising treatments – early studies with good results
  – Molecularly targeted treatments for cancer
  – Clinical trials now open at Beaumont
    • Newly diagnosed breast cancer in BRCA mutation carriers
      – Personalized Medicine

Targeting DNA Repair

[Diagram showing DNA repair processes and treatments]
NSABP B-55 Clinical Trial

- Inclusion Criteria:
  - Triple Negative Breast Cancer (> 2cm or lymph node +)
  - ER+ expected to open in near future
  - BRCA1/2 +
- Chemotherapy given to each patient per standard of care
  - Anthracycline, taxane or both
- Olaparib 300mg (vs placebo) orally twice a day for 12 mos
- Patients followed every 3 months for 2 yrs, then every 6 months for 3 years, then annually
- Beaumont enrolls first patient in U.S. (10/14)
Lynparza (Olaparib)- FDA approval

- Oral PARP inhibitor
- Approved 12/19/14 for advanced ov ca in BRCA + women
- 4th line treatment
- Single open label trial of 137 patients
  - Overall response rate 34%
  - Median duration of response 7.9 months
  - Side effects fatigue, nausea, vomiting, headache
- Further studies in progress
- Companion diagnostic test approved

Lynparza (Olaparib)- FDA approval

FDA approves first treatment for breast cancer with a certain inherited genetic mutation

Summary

FDA approves first treatment for breast cancer with a certain inherited genetic mutation
Colorectal Cancer Genetics

- 3rd most common cancer in the U.S.
  - 145,000 new cases per year
- 3rd most common cause of cancer-related death
- Most common form of hereditary CRC is Lynch Syndrome (LS)
- Stepwise progression
  - Benign mucosa → polyp → cancer
- Effective screening → prevention
Risk Factors for Colorectal Cancer (CRC)

- Aging
- Personal history of CRC or adenomas
- Dietary patterns
- Inflammatory bowel disease
- Family history of CRC
- Hereditary colon cancer syndromes

Epidemiology of Colorectal Cancer

- Sporadic 60%
- Familial/Multifactorial 30%
- Rare Syndromes ~4%
- MUTYH Associated Polyposis (MAP) ~1%
- Familial Adenomatous Polyposis (FAP) ~1%
- Lynch Syndrome ~2-4%
Risk of Colorectal Cancer

Hereditary Colorectal Cancer Syndromes

Multiple Polyposis Syndromes:
- FAP
  - Familial Adenomatous Polyposis Syndrome
- AFAP
  - Attenuated Familial Adenomatous Polyposis
- MYH-Associated Polyposis (MAP) Syndrome
  - Similar to AFAP

NonPolyposis Syndromes:
- Lynch syndrome
  - Also known as: Hereditary Nonpolyposis Colorectal Cancer = HNPCC

Slides Courtesy of WBH Cancer Genetics Program
Red Flags for Lynch Syndrome

• **Lynch Syndrome**
  – Colon or endometrial cancer under age 50
  – More than one LS-associated cancer in one individual/family
  – Characteristic pathology of colon cancer
    • Right sided, poorly differentiated, mucinous
    • Microsatellite instability-High
  – **Amsterdam Criteria**

*LS cancers: colorectal, endometrial, gastric, ovarian, ureter/renal pelvis, biliary tract, small bowel, pancreas, brain, sebaceous adenoma

Lynch Syndrome

• **Amsterdam I Criteria**
  – **Three** or more relatives with CRC
  – **Two** or more successive generations
  – **One** diagnosed before age 50
  – FAP excluded

  – Amsterdam II – includes extracolonic cancers: endometrial, stomach, ovarian, uroepithelial
**MMR System and LS**

- DNA MMR system maintains genomic integrity by correcting DNA errors during replication
- Recognizes base-pair mismatches and repairs them
- Failure to repair DNA mismatches leads to genomic instability
- Occurs in regions of repetitive nucleotide sequences - microsatellites

**Mismatch Repair Genes**

- **MSH6** (10%)
- **MSH2** (40%)
- **MLH1** (45%)
- **PMS2** (5%)

- Chr 2
- Chr 3
- Chr 7
Lynch Syndrome - Cancer Risks

Avg age dx = 42-61

*range of risk for colorectal cancer differs by gene


Lynch Syndrome - Cancer Risks

- Women with Lynch Syndrome may present with a gynecologic cancer first.

EC Avg age dx = 47-55

*range of risk for endometrial cancer differs by gene

Lynch Syndrome - Cancer Risks

<table>
<thead>
<tr>
<th>CANCER</th>
<th>GENERAL POPULATION RISK</th>
<th>RISKS IN LYNCH SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>&lt;1%</td>
<td>Up to 13%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Ureter/renal pelvis</td>
<td>&lt;1%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Brain/central nervous system (usually glioblastoma)</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Sebaceous adenoma or carcinoma</td>
<td>&lt;1%</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Colon Cancer

Surveillance:
Colonoscopy every 1-2 y starting at age 20-25 y

Surgery:
Prophylactic Colectomy Consider if:
- Cancer diagnosis
- Large polyp burden
- Pt unwilling to undergo surveillance

Endometrial & Ovarian Cancer

Surveillance:
(no clear evidence to support)
- Transvaginal U/S
- Endometrial sampling
- Starting at age 30-35 y

Surgery:
- Hysterectomy
- RRSO
Lynch Syndrome: Management

- Gastric and Small Bowel cancer (?)
  - EGD with extended duodenoscopy
  - Capsule endoscopy for small bowel cancer
    2-3 y intervals starting at age 30-35 y
- Uroepithelial cancer
  - Consider annual urinalysis
- CNS cancer
  - Annual neurologic exams staring at 25-30 y
- Pancreatic cancer
  - No formal recommendation, limited data

PRACTICE BULLETIN

Number 147, November 2014

Lynch Syndrome

Lynch syndrome, previously known as hereditary nonpolyposis colorectal cancer, is an autosomal dominant inherited cancer susceptibility syndrome caused by defects in the mismatch repair system. This system depends on a family of genes that are conserved across most living organisms and is responsible for repairing single-base mismatches that occur during DNA replication. In addition to colorectal cancer, hallmark diseases of Lynch syndrome include...
Case Example

- 21-year-old male presented with a bowel obstruction due to carcinomatosis
- Found to have adenocarcinoma of the colon with liver metastases
  - Treatment included a left hemicolectomy and palliative chemotherapy
- Patient was referred to cancer genetics due to his early age of diagnosis of CRC
Immunohistochemistry (IHC) for MSH2 expression:

a: Normal MSH2 expression in control
b: Absent MSH2 expression in patient's colon tissue

Immunohistochemistry (IHC) Schematic

IHC Normal

- CRC > 50 yo
- & no family hx
- no personal hx

STOP

IHC Abnormal

- Absent Staining

CRC ≤ 50 or FDR w/ CRC or multiple primaries

MSH2 & MSH6, MSH6, or PMS2 absent

MLH1 & PMS2 absent

Refer to Genetics

STOP

BRAF
Hereditary Colorectal Cancer Syndromes

Multiple Polyposis Syndromes:

• FAP
  – *Familial Adenomatous Polyposis Syndrome*
• AFAP
  – *Attenuated Familial Adenomatous Polyposis*
• MYH-Associated Polyposis (MAP) Syndrome
  – *Similar to AFAP*

NonPolyposis Syndromes:

• Lynch syndrome
  – Also known as: Hereditary Nonpolyposis Colorectal Cancer = HNPCC

Red Flags for Hereditary Polyposis Syndromes

• Multiple colorectal adenomas (polyps)
  – May range in # from 10- 1000’s of adenomas

• Colorectal cancer associated with **multiple adenomas**

• Possible extracolonic manifestations
  – Non-colonic polyps (i.e. duodenal, gastric)
  – Desmoid tumors, osteomas, soft tissue tumors, dental abnormalities, CHRPE
Clinical Features of FAP

- 100-1000s of adenomatous polyps, “carpet-like”
- 10-12 yo = age of onset
- Nearly 100% penetrance for CRC
- AD inheritance
  - 30% de novo mutation
- Extracolonic features
- APC gene

Gardner Syndrome: A Variant of FAP

- Features of FAP plus extraintestinal lesions
  - Desmoid tumors
  - Osteomas
  - Supernumerary teeth
  - CHRPE
  - Soft tissue skin tumors
# Case Example - FAP

- 15 y/o male
- Referred by family practice physician for colonoscopy
- Family history of early onset polyposis
- Colonoscopy reveals numerous adenomatous polyps

---

## Pedigree

![Pedigree Diagram](image)

- Due to J.S.'s personal history of numerous polyps and family history, he meets criteria for APC testing.
Pedigree

J.S. – Test Results
# FAP - Management

- **Colon Cancer**
  - **Surveillance**
    - Colonoscopy: Begin as child/young adult dependent on family history and polyp load—more often (annually)
  - **Chemoprevention**
    - NSAIDS: Reduce polyp load
    - Clinical trial
  - **Surgery**
    - Prophylactic Colectomy
      - Timing based on polyp load
      - Timing <18 yrs individualized
- **OTHER GI Cancer**
  - Stomach and Duodenal Cancer
    - EGD with side-viewing endoscope

**GOAL**: Prevent a cancer, or detect at earlier stage → decrease mortality

---

## Screening for other FAP related cancers

- **Thyroid Cancer**
  - Annual thyroid exam in late teens; consider U/S (data lacking)
- **CNS Cancer**
  - Annual physical exam
- **Intra-abdominal Desmoids**
  - Annual abdominal palpation, consider MRI or CT
- **Small bowel polyps/cancer**
  - Consider small bowel visualization or capsule endoscopy
- **Pancreatic cancer**
  - Limited data, no recommendation
- **Hepatoblastoma**
  - No recommendations?, AFP/abdominal ultrasound during 1st 5 yrs of life
Legislation on Genetic Discrimination

**GINA = Genetic Information Nondiscrimination Act of 2008**

Legal protection against discrimination based on genetic information

- Prohibits *employment and health insurance discrimination* (both private & group insurances)
- Prohibits insurers from requiring genetic testing; individuals cannot lose insurance due to testing
- Went into effect on 5/21/09

[www.geneticfairness.org](http://www.geneticfairness.org)
# Multi-disciplinary Summit on Genetics Services for Women with Gynecologic Cancers: A Society of Gynecologic Oncology White Paper

*Leslie M. Randall, Bhava S. Porhuri, Elizabeth M. Swisher, John P. Diaz, Adam Buchanan, Catherine T. Witkop, C. Bethan Powell, Ellen Blair Smith, Mark E. Robson, Jeff Boyd, Robert L. Coleman, Karen Lu*

---

## Article Info

**Article history:**
- Received: 30 April 2017
- Revised: 25 May 2017
- Accepted: 1 June 2017
- Available online 7 June 2017

---

## Table 1

Summary of societal recommendations on genetic assessment in women with ovarian and uterine cancers.

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Date(s) Issued</th>
<th>Ovarian Cancer Recommendations</th>
<th>Uterine Cancer Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society of Gynecologic Oncology (SGO)</td>
<td>2014</td>
<td>Genetic counseling and testing for all ovarian, fallopian tube, and peritoneal cancers</td>
<td>Joint ASCO/SGO recommendations: Tumor testing for MSI/MMR RIC on any endometrial or colorectal tumor from a woman at risk for Lynch syndrome by focused personal and family medical history, or all endometrial cancers age &lt; 60. Germline testing for mismatch repair loss on tumor tissue</td>
</tr>
</tbody>
</table>
| American College of Obstetricians and Gynecologists (ACOG) | 2009 | Patients with greater than an approximate 20-25% chance of having a mutation | Endometrial cancer age < 50
- Endometrial cancer in a relative of any age
- Synchronous or metachronous colorectal or endometrial cancer in the same person
- Endometrial cancer with mismatch repair deficiency on tumor screening
- Endometrial cancer and 2 additional cases of any U-associated cancer (Table 6) in the same person or in close relatives
- Epithelial endometrial cancer and 2 additional Cowden syndrome criteria (Table 4) in the same person |
| National Society of Genetic Counsellors (NSG) | 2014 | Single case of ovarian, fallopian tube, or peritoneal cancer present in the patient or a first degree relative | Endometrial cancer age < 50
- Endometrial cancer in a relative of any age
- Synchronous or metachronous colorectal or endometrial cancer in the same person
- Endometrial cancer with mismatch repair deficiency on tumor screening
- Endometrial cancer and 2 additional cases of any U-associated cancer (Table 6) in the same person or in close relatives
- Epithelial endometrial cancer and 2 additional Cowden syndrome criteria (Table 4) in the same person |
Immunohistochemistry-based tumor testing for mismatch repair gene expression to assess for possible Lynch syndrome.

**Table 2**
Barriers to the provision of genetic counseling and testing services to cancer patients with proposed solutions.

<table>
<thead>
<tr>
<th>Barrier(s)</th>
<th>Proposed solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider-mediated</td>
<td>Provider education, reinforcement of societal recommendations</td>
</tr>
<tr>
<td>Lack of awareness of testing benefit</td>
<td></td>
</tr>
<tr>
<td>Lack of time during patient encounter</td>
<td></td>
</tr>
<tr>
<td>Concerns over cost</td>
<td></td>
</tr>
<tr>
<td>Perception that information detrimental to patient well-being</td>
<td></td>
</tr>
<tr>
<td>Payer-associated</td>
<td>Payment reform</td>
</tr>
<tr>
<td>Lack of reimbursement for genetic counseling services</td>
<td></td>
</tr>
<tr>
<td>Lack of reimbursement for genetic tests</td>
<td></td>
</tr>
<tr>
<td>System-associated</td>
<td>Research into optimal operational processes</td>
</tr>
<tr>
<td>Lengthy authorization processes</td>
<td></td>
</tr>
<tr>
<td>Lack of infrastructure/staff to process authorizations</td>
<td></td>
</tr>
<tr>
<td>Lack of tracking mechanisms to monitor execution of physician orders for testing</td>
<td></td>
</tr>
<tr>
<td>Patient-associated</td>
<td>Public education through public and professional societal advocacy</td>
</tr>
<tr>
<td>Misunderstanding of counseling/testing intent</td>
<td></td>
</tr>
<tr>
<td>Disinterest in results</td>
<td>Payment reform</td>
</tr>
<tr>
<td>Fear of social or financial discrimination</td>
<td></td>
</tr>
<tr>
<td>Racial disparities in testing due to education and access</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Rapid increase in knowledge and use of genetics in clinical medicine
- Increasing movement of genetic knowledge from research labs into clinical practice
  - Need for oversight and practice guidelines (moving target)
  - Need for more research and collaborations
- Patients learning about genetics/genomics in the media often turn to their physicians for information and advice
- Primary care and Ob/Gyn providers play an increasingly important role in determining who needs genetic eval

Beaumont Cancer Genetics Program

Genetic Counselors:
Ashley Reeves, MS, CGC
Sarah Campion, MS, CGC
Amy Sufka, MS, CGC
Kristina Ivan, MS CGC
Hannah Henige, MS
Travis Washburn, MS

248-551-3388
http://cancer.beaumont.edu/genetics

Mutant Jeans