Hereditary Cancer Risk Assessment

ACOG District II
Agenda

- Review Cancer Genetics Basics
- Review Hereditary Cancer Syndromes
- Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
- Discuss Who to Refer and How to Make a Referral
  - What Happens in Cancer Genetics Consultations and Counseling?
  - What Happens in Genetic Test Selection and Result Interpretation?
- Consider Long-Term Clinical Management Issues

Disclaimer: The following material is an example only and not meant to be prescriptive. ACOG accepts no liability for the content or for the consequences of any actions taken on the basis of the information provided.
Learning Objectives

1. To provide an overview of relevant hereditary cancer syndromes
2. To encourage ob-gyns to obtain a thorough family history
3. To educate ob-gyns about available risk assessment strategies for the detection of patients at risk for hereditary cancer syndromes as set forth in current guidelines
4. To inform ob-gyns about the spectrum of available genetic tests, the content of genetics consultations, and the meaning and implications of genetic test results
5. To guide ob-gyns about when to refer to a genetics professional, gynecologic oncologist, and/or other specialists as needed
Role of the OB-GYN

- The Ob-gyn is a crucial primary care provider
  - Often the only provider for women
  - Ongoing contact and care for women
  - Captive audience
- Ob-gyns may coordinate care and have close collaborations with other specialists, including: Genetics Professionals, Gynecologic Oncologists, Breast Surgeons, and other specialists, as indicated
- Ob-gyns often oversee the implementation of a personalized cancer-risk management plan
  - Prophylactic surgery decisions and sequelae
  - Appropriate preventive and screening modalities
- Ob-gyns may be involved in reproductive counseling and decisions related to findings
- Ob-gyns may be involved in treatment decisions and protocols for patients diagnosed with cancer

Have an essential role in identifying patients who warrant cancer risk assessment

Have an essential role in long-term management of patients at increased risk for cancer

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Agenda

• Review Cancer Genetics Basics
  • Inheritance
  • Penetrance and Expressivity
  • New Mutations and Recessive Disease
  • Genetic Changes and Cancer

• Review Hereditary Cancer Syndromes

• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment

• Discuss Who to Refer and How to Make a Referral
  • What Happens in Cancer Genetics Consultations and Counseling?
  • What Happens in Genetic Test Selection and Result Interpretation?

• Consider Long-Term Clinical Management Issues
Cancer Genetics Basics

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

Cancer Genetics Basics

Penetrance:
Incomplete → not all individuals will show the effect(s) of the mutation(s)
Complete → all individuals will show the effects of the mutation(s)

Cancer susceptibility genes vary in their penetrance

Expressivity:
Variance in severity, type, and number of symptoms of the disease among affected patients

Cancer susceptibility genes often have quite variable expressivity with regard to symptom types and presentations

Note variety in ages of onset

Some hereditary cancers are due to **NEW MUTATIONS** in the patient’s germline. The predisposition to cancer was not *inherited*, the parents are not at increased risk, but the patient can pass the mutation on to offspring.

Some hereditary cancer genes can cause *different and more severe* recessive hereditary syndromes when a person inherits a mutation in the *same* gene from *both* parents.

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**Cancer Genetics Basics**

- **NO p53 mutation in this generation**
  - **New p53 gene mutation, causing Li-Fraumeni Syndrome**
  - **Inherited the p53 gene mutation**

- **MSH6 mutation, leading to Lynch Syndrome**
  - **Inherited BOTH MSH6 mutations, leading to Constitutional Mismatch Repair Deficiency: high risk of multiple childhood and adult cancers**
  - **Inherited NEITHER MSH6 mutation**
  - **MSH6 mutation, leading to Lynch Syndrome**

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Genetic Changes and Cancer

• 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.
Summary: Cancer Genetics Basics

• Most cancer syndromes are inherited in an autosomal dominant manner, but some are recessive.
  • Other complex inheritance patterns and risks also exist.
• Cancer susceptibility syndromes vary in their penetrance and expressivity.
• People born with a tumor suppressor gene mutation are “one step closer” to developing a tumor, but may never develop a tumor.
Agenda

• Review Cancer Genetics Basics

• Review Hereditary Cancer Syndromes
  • \textit{BRCA1} and \textit{BRCA2}
  • Lynch Syndrome
  • Hereditary Diffuse Gastric Cancer
  • Li-Fraumeni Syndrome
  • Other Cancer Risk Genes

• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment

• Discuss Who to Refer and How to Make a Referral
  • What Happens in Cancer Genetics Consultations and Counseling?
  • What Happens in Genetic Test Selection and Result Interpretation?

• Consider Long-Term Clinical Management Issues
Hereditary Cancer Syndromes

• Many germline mutations are known to confer an increased risk for various types of cancer.
• Each gene is associated with a specific spectrum of organs at risk and degree of cancer risk.
• Some cancer syndromes can be caused by more than one gene and the person may have different risks depending on which gene is identified.

Structure and Binding Partners of BRCA1

Lessons: Paternal history is of equal importance AND pick the best family member to test

Genetic testing reveals a BRCA1 mutation in the cousin

- Pancreas, dx 50, d. 61
- 86
- 84
- 92
- Ovary, dx 59, d. 62
- 71
- 67
- 65
- 93
- 89
- 49
- Breast, dx 45
- BRCA1 mutation
- 45
- 42

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Hereditary Cancer Syndromes: *BRCA1* and *BRCA2*

- *BRCA1* mutations in about 1/300 people; *BRCA2* in 1/800
- Many (but not all) *BRCA1* breast cancers are triple negative (ER/PR/her2-neu-negative); other pathologies in *BRCA2*
- Increased frequency in Ashkenazi Jewish, Icelandic, Mexican Hispanic, and other ethnic groups
- Recessive disease risk in *BRCA2* = Fanconi Anemia

<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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Lessons: Check both sides + note precancerous & relevant features, including pathology

**LYNCH SYNDROME**
- Endo. Ca Dx 50
- 66 yr
- 68 yr
- CRC dx 48
- 70 yr
- 4 colon adenomas
- d. 53 yr

**Hereditary Diffuse Gastric Cancer**
- GI cancer?? d. 45
- 71 yr
- Lobular(?) Breast dx 45
- 50 yr
- 2 colon adenomas
- 20 yr

"Abdominal Bleeding or Cancer??"
Gastric? Colon? dx 40, d. 41

**KEY:**
- Endometrial Cancer
- Colorectal Cancer
- Adenomatous polyps
- Breast Cancer

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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 is appropriate for all colorectal and endometrial cancers (microsatellite instability (MSI) and/or immunohistochemistry (IHC) testing)**
- **Various criteria and risk models exist to identify individuals at risk**
  - New guidelines in NCCN, v3.2017
  - Bethesda Guidelines
  - Amsterdam Criteria

<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>4.5%</td>
<td>52-82%</td>
<td>10-22%</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</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.6%</td>
<td>11-24%</td>
<td>1%</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</td>
<td>&lt;1% each</td>
<td>1-7% each</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1-9%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt;1%</td>
<td>1-6%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
</tbody>
</table>

Table adapted from NCCN GUIDELINES FOR DETECTION, PREVENTION, & RISK REDUCTION: Genetic/Familial High-Risk Assessment: Colorectal v3.2017

[1](http://www.nchpeg.org/documents/crc/11-0456%20Fact%20sheets%20(Revised%20Bethesda%20guidelines).pdf)

[2](http://www.nchpeg.org/documents/crc/11-0456%20Fact%20sheets%20(Amsterdam%20II%20criteria).pdf)

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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>
<tr>
<th>Cancer Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIFFUSE Gastric Cancer</td>
<td>67% (men)-83% (women)</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>

Pay attention to pathology. It can give you clues!!

*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.

Lesson: Look for certain **constellations** of tumors

Li-Fraumeni Syndrome

- **Affected with cancer**
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 Chompret criteria (see NCCN guidelines)**
- **Associated with many different tumors, 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
- Soft tissue sarcoma
- Breast cancer (all women with breast cancer < age 31 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>


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“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 (see NCCN guidelines)
• 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* and *BRCA2*
- *TP53*
- *CDH1*
- *PTEN*
- *ATM*
- *CHEK2*
- *PALB2*
- *STK11*
- *NBN*
- *NF1*
- Many more ...

**Gyn Cancer Risk**
- *BRCA1* and *BRCA2*
- Lynch Syndrome
- *PTEN*
- *PALB2*
- *STK11*
- *FH*
- *BRIP1*
- *RAD51C/RAD51D*
- *RB1*
- *SMARCA4*
- *DICER1*
- Many more ...

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

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“Other” Hereditary Cancer Predisposition Genes and Clinical Clues

**d. 68 Heart disease**

- **HLRCC:** Hereditary leiomyomatosis and renal cell cancer (HLRCC)
  - Benign tumors containing smooth muscle tissue (leiomyomas) in the skin and, in females, also in the **uterus** (fibroids).
  - Women with HLRCC tend to have numerous large fibroids that appear earlier than in the general population. Make sure pathology from myomectomy goes to a cancer center for analysis
  - Increased risk for renal cell (kidney) cancer.

- **Caused by FH gene:** fumarate hydratase
  - Reproductive risk for autosomal recessive FH deficiency

**d. 55 Cancer, type??**

**Hysterectomy at 22 Uterine Fibroids**

**Benign skin bumps**

“Other” Hereditary Cancer Predisposition Genes and Clinical Clues

- Pathology shows small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)
- SCCOHT accounts for ~1% of ovarian cancers with median age of onset at 24 years
- Estimated ~43% of SCCOHT due to germline mutations, mostly in the **SMARCA4 gene**

**Similar Examples of “Clinical Clues” (see cancer risks for these genes in appendix):**

- **PTEN gene:** Skin findings, macrocephaly, autism, intellectual disability, thyroid lesions, vascular anomalies and other features + breast & gyn cancers
- **RB1 gene:** History of Retinoblastoma and now is having pelvic pain and bleeding - think about risk for RB1-related uterine leiomyosarcoma
“Other” Hereditary Cancer Predisposition Genes and Specific Variants

- **CHEK2**
  - **I157T** (2.6% in the Finnish pop) modest breast & colon cancer risk
  - **1100delC** (0.7% in N. European pop) truncating mutation, increased breast & colon risk
  - **S428F**, possible risk for breast & colon, conflicting risk reports, even among labs!!

**Similar Examples of Common Variants**

- **APC I1307K**: 6-10% frequency in Ashkenazi Jewish population, confers 2X colon risk in AJ population, but unclear risk in other groups

- **MUTYH**
  - 2 common N. European mutations
  - Homozygous (2 mutations): increased colon risk vs 1 mutation (unclear risk)

Sources: NCCN GUIDELINES FOR DETECTION, PREVENTION, & RISK REDUCTION: Genetic/Familial High-Risk Assessment: Breast and Ovarian v1.2018; NCCN GUIDELINES FOR DETECTION, PREVENTION, & RISK REDUCTION: Genetic/Familial High-Risk Assessment: Colorectal v3.2017; CHEK2 I157T: PMIDs: 22799331, 25051370, 27139477, 15492928, 15087378, and 25798211; CHEK2 1100delC: PMIDs: 18172190, 25431674, and 27296296; MUTYH mutations: PMIDs: 11818965 and 17489848; APC I1307K: PMIDs 23576677, 9288102, and 23896379; MUTYH variants: PMIDs 11818965 and 17489848

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Hereditary Cancer Predisposition Genes

For more information about these, and other cancer risk genes:

• Ask your genetics professional
• NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian v1.2018
• NCCN Genetic/Familial High-Risk Assessment: Colorectal v3.2017
• Gene reviews
• Current literature
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.
Agenda

• Review Cancer Genetics Basics
• Review Hereditary Cancer Syndromes

**Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment**
  • Recommendations from the Guidelines
  • Liability Issues
  • Family History Collection and Features

• Discuss Who to Refer and How to Make a Referral
  • What Happens in Cancer Genetics Consultations and Counseling?
  • What Happens in Genetic Test Selection and Result Interpretation?

• Consider Long-Term Clinical Management Issues
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)
Hereditary Breast & Ovarian Cancer Syndrome (PB #182, 2017)
Counseling about Genetic Testing & Communication of Genetic Test Results (CO #693, 2017)
Cascade Testing: Testing Women for Known Hereditary Genetic Mutations Associated with Cancer (CO #727, 2018)

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 (v3.2017)
Genetic/Familial High Risk Assessment, Breast/Ovarian (v1.2018)

EGAPP: Genetic Testing Strategies (2009)

Please consult individual organizations for any updates to these guidelines after February 2018.

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Liability Exposure: Failure to Recognize Hereditary Risk

- All women should have a family history evaluation and the threat of liability should be a serious consideration.
- ~170 judgments involving allegations of malpractice related to cancer genetics
- Failure to diagnose cancer in a timely manner is the second-most expensive type of claim

FAILURE TO:
- Recognize family history and personal risk factors for hereditary cancer
- Recommend genetics consultation and possible testing
- Implement appropriate medical management

JUDGMENTS AGAINST OB-GYNs

<table>
<thead>
<tr>
<th>Award</th>
<th>Basis of Case</th>
<th>What Happened</th>
</tr>
</thead>
</table>
| $5 million | Failure to inform patient she was at increased risk for ovarian cancer because of family history and failure to remove ovaries during hysterectomy | • Patient had a strong family history of breast cancer; had bilateral prophylactic mastectomies due to fear of genetic predisposition for breast cancer  
• Patient later had a hysterectomy, but the doctor left her ovaries.  
• One year after surgery, was diagnosed with late-stage ovarian cancer |
| $700K  | Failure to diagnose breast cancer                                              | Doctor did not take patient’s age and family history of breast cancer into consideration                     |

Source: Gary E. Marchant, PhD, JD and Rachel A. Lindor, JD. Genetics in Medicine, Volume 15; Number 12, December 2013.
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

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### Examples of Notable Family History Features

**This is NOT an exhaustive list of features that warrant referral**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusually early age of cancer onset</td>
<td>Breast, colon, or uterine cancer &lt; age 50</td>
</tr>
<tr>
<td>Multiple primary cancers in a single individual</td>
<td>Colorectal and uterine cancer in one person</td>
</tr>
<tr>
<td>Bilateral cancer in paired organs or multifocal disease</td>
<td>Bilateral breast cancer, multifocal renal cancer</td>
</tr>
<tr>
<td>Clustering of the same type of cancer or related cancers in close relatives</td>
<td>Mother with breast cancer with a daughter with ovarian cancer</td>
</tr>
<tr>
<td>Cancers occurring in multiple generations of a family</td>
<td>Grandmother, father and daughter with colon cancer</td>
</tr>
<tr>
<td>Rare tumors</td>
<td>Retinoblastoma, adrenocortical carcinoma, ovarian granulosa cell tumor, ocular melanoma, duodenal cancer</td>
</tr>
<tr>
<td>Unusual presentation of cancer</td>
<td>Male breast cancer</td>
</tr>
<tr>
<td>Uncommon tumor histology</td>
<td>Lobular breast cancer, diffuse gastric cancer</td>
</tr>
<tr>
<td>Rare cancers associated with birth defects</td>
<td>Wilms tumor and genitourinary abnormalities</td>
</tr>
<tr>
<td>Non-cancerous skin growths or skeletal abnormalities</td>
<td>Keratoacanthoma, trichilemmoma</td>
</tr>
<tr>
<td>Geographic or ethnic populations known to have a higher prevalence of deleterious mutations</td>
<td>Ashkenazi Jewish heritage and BRCA1/BRCA2 mutations</td>
</tr>
</tbody>
</table>
Summary: Ob-Gyns and Family History

• Ob-gyns should collect, and regularly update, a detailed family history.

• There is liability exposure related to the failure to ask about, and recognize, hereditary risk.

• Ob-gyns should have an understanding of the key information to collect and the notable family history findings.
Agenda

• Review Cancer Genetics Basics
• Review Hereditary Cancer Syndromes
• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment

• Discuss Who to Refer and How to Make a Referral
  • Tools and Referral Criteria
  • Finding a Genetics Provider
  • Other Providers and Cancer Genetic Testing

• What Happens in Cancer Genetics Consultations and Counseling?
• What Happens in Genetic Test Selection and Result Interpretation?
• Consider Long-Term Clinical Management Issues
Office-Based Assessment Tools

• There are many checklists available to determine who warrants referral; some are more comprehensive than others
  • Some may focus only on breast cancer, some may have BRCA1 and BRCA2 and Lynch criteria only, and some may include many genes/syndromes

• Some practices develop their own checklists. Ask your genetics professionals for assistance with an office-based tool

• Some are completed by patients, some by providers

• Many guidelines have been published about which patients should be referred
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 v1.2018 includes: BRCA1 and BRCA2, Cowden Syndrome, Li-Fraumeni Syndrome, HDGC, other genes
  https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection

• NCCN Guidelines Genetic/Familial High Risk Assessment: Colorectal Cancer v3.2017 includes: Lynch syndrome, Polyposis syndromes (APC, MUTYH, Juvenile Polyposis, Serrated Polyposis), Peutz Jeghers syndrome, other genes
  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/
Special Assessment/Referral Issues

• 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


Created by ACOG District II in 2017 / Updated February 2018
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 v1.2018: “...multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.”
Locate a Genetics Professional

• Find a clinical geneticist or genetic counselor in your area:
  • American College of Medical Genetics: https://www.acmg.net/
  • National Society of Genetic Counselors: http://www.nsgc.org/page/find-a-gc-search
  • NYS provides grant awards to genetic centers across the state. Health insurance is billed if the patient has it, but all services are available whether or not the patient is able to pay for them. (518) 474-7148 or https://www.health.ny.gov/publications/0548/genetic_services_program.htm

• Other options when there is no local genetics professional:
  • A growing number of genetics providers are beginning to offer telegenetics options
  • Some clinical testing laboratories offer telegenetic counseling services for their tests
  • NYMAC, a genetics network that covers NYS, can help locate telegenetics providers: http://www.wadsworth.org/programs/newborn/nymac
  • NSGC and ACMG listings can also identify telegenetics service options
Other Providers Who Offer Genetic Testing

• Must have training, experience, and expertise in cancer genetics

• Must be able to provide all of the elements of genetic counseling, including cancer risk assessment, genetics education, review of testing options and limitations, psychosocial counseling, and comprehensive interpretation of test results

• Must stay up to date with genetics and testing and feel comfortable in choosing the appropriate test, obtaining informed consent, verifying insurance reimbursement, understand regulatory issues (including GINA*, NYS consent and laboratory approval) and have the capability to refer to a genetics professional for complex cases and results

• Providers may include:
  • Various physicians, including obstetrician-gynecologists and gynecologic, medical or surgical oncologists, breast surgeons
  • Other health professionals with training and experience in cancer genetics: Advanced Practice Nurse in Genetics (APNG), Oncology Nurse
  • Some insurance companies require a provider with certain credentials to see the patient before testing will be authorized

* GINA – Genetic Information Nondiscrimination Act of 2008, protects against genetic discrimination regarding employment and health insurance, but does not include long-term care or life insurance.
Documented Liability Exposure When Non-Genetics Professionals Offer Genetic Testing

- Failure to obtain a comprehensive family history
- Failure to select the appropriate testing
- Failure to refer to a genetic counselor or geneticist
- Misinterpretation of test results (false reassurance when negative; misunderstanding of variants of uncertain significance)
- Inappropriate medical management (e.g., unnecessary prophylactic surgery)
  - Recent lawsuit against an ob-gyn accused of erroneously telling a patient her genetic test results indicated an MLH1 Lynch Syndrome mutation, and recommending a prophylactic hysterectomy and prophylactic mastectomy. The patient underwent BOTH surgeries and then discovered her genetic test result was negative. ([http://media.oregonlive.com/pacific-northwest-news/other/mastectomy.suit.pdf](http://media.oregonlive.com/pacific-northwest-news/other/mastectomy.suit.pdf))
- Failure to identify at-risk family members based on test results (cascade testing)
- Failure to obtain appropriate consent (e.g., for large panels with much uncertainty)
- Obligation to follow up with patients on variant status changes from the laboratory
- Failure to comply with regulations and laws (e.g., NYS consent and lab approval regulations)


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Summary: Making a Referral

• Office-based tools are available to identify patients who warrant a referral.
• Various published referral criteria exist.
• Patients with previous testing, negative family histories, and those previously assessed to be at low risk may still warrant referral.
• Guidelines recommend referral to a specialist in cancer genetics or a health care provider with expertise in genetics.
  • Liability exposure should be considered by any provider who offers genetic testing.
Agenda

• Review Cancer Genetics Basics
• Review Hereditary Cancer Syndromes
• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
• Discuss Who to Refer and How to Make a Referral
  • What Happens in Cancer Genetics Consultations and Counseling?
    • Content and Process
    • Outcomes
    • Informed Consent
  • What Happens in Genetic Test Selection and Result Interpretation?
  • Consider Long-Term Clinical Management Issues
Pre-Test Cancer Genetic Consultation and Counseling

• Genetic counseling helps people understand and adapt to the **medical, psychological, and familial implications** of genetic contributions to disease

• Entails much more than just consent for a test, and *does not* always lead to genetic testing
  • For some patients, there is no medically appropriate genetic testing
  • Some **eligible** patients **choose** not to pursue genetic testing for personal/family/financial reasons

• With a full clinical and family history, the provider gives a comprehensive assessment of:
  • The likelihood that a family has a **mutation** **AND**
  • The patient’s risk for a variety of **cancers** based on their personal and family risk factors

• The provider facilitates informed decisions about testing by exploring the patient’s needs and motivations and making patients aware of the possible outcomes of testing, their likelihood, meaning, and possible impact on clinical management **before** making a decision to undergo testing.


Created by ACOG District II in 2017 / Updated February 2018
# Pre-Test Cancer Genetic Consultation and Counseling

<table>
<thead>
<tr>
<th>Phase</th>
<th>Topics</th>
</tr>
</thead>
</table>
| ASSESS                 | - Personal & family medical history (including support to engage family members to get family history information or records)  
                         - The patient’s risk perception  
                         - Psychosocial issues: anxiety, coercion, family illness experience, and communication |
| EDUCATE                | - Basic genetics & inheritance  
                         - Cancer genetics and risk |
| DISCUSS                | - Risks, benefits, & limitations of testing  
                         - Test procedure  
                         - Alternatives to testing  
                         - Management options  
                         - Concerns about discrimination and privacy |
| ANTICIPATORY GUIDANCE  | - Walk patients through “what if” scenarios |
| CONSIDERATION OF MOTIVATION FOR TESTING | - Why does the patient want to be tested?  
                         - What does she hope to accomplish? |
| FACILITATE INFORMED DECISION MAKING AND CONSENT | - With regard to testing |


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Informed Consent Requirements

NYS law: Section 79-1 of the New York State Civil Rights Law requires a SIGNED, WRITTEN, informed consent prior to any genetic testing. This includes (among other things):

- A description of the test being performed, the condition in question, the meaning of test results, and the reason for testing
- Information about who will receive a copy of the test results
- **Statement that the patient may wish to obtain genetic counseling prior to testing**
- Notification that the sample will be destroyed within 60 days unless otherwise indicated
- Notification that results may be released to a health insurance company for the purpose of processing a claim

*Consent is a process, not a piece of paper.*

Source: https://www.genome.gov/27552194/

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## Cancer Genetic Consultations and Counseling Should Determine:

<table>
<thead>
<tr>
<th>WHO...</th>
<th>Is the best person in the family to test (ideally, test a person who has had cancer)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHAT...</td>
<td>Is the appropriate test to do? (IF ANY)</td>
</tr>
<tr>
<td>WHEN...</td>
<td>Should testing be done? (STAT tests, DNA banking)</td>
</tr>
<tr>
<td>WHERE...</td>
<td>Should testing be done? (lab selection is guided by numerous factors, incl. approval by NYS’s Clinical Lab Evaluation Program: <a href="https://www.wadsworth.org/regulatory/clep">https://www.wadsworth.org/regulatory/clep</a>)</td>
</tr>
<tr>
<td>WHY...</td>
<td>What is the medical reason for testing? What is the patient’s motivation for testing? How will the results benefit them? What will they do if they test positive? Who else in the family will this impact?</td>
</tr>
<tr>
<td>HOW...</td>
<td>Will the test and results communication be coordinated logistically and financially?</td>
</tr>
</tbody>
</table>
Summary: Consultation and Counseling

Formal Genetics Consultation and Counseling:

• May not lead to genetic testing.
• Will outline the who, what, when, where, why, and how of genetic testing.
• Will facilitate the process of the patient making appropriately informed decisions, consistent with their goals and values.
Agenda

• Review Cancer Genetics Basics
• Review Hereditary Cancer Syndromes
• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
• Discuss Who to Refer and How to Make a Referral
  • What Happens in Cancer Genetics Consultations and Counseling?
  • What Happens in Genetic Test Selection and Result Interpretation?
    • Overview of Genetic Tests
    • Genetic Variants
    • Interpreting Results, Next Steps, and Management
      • Positive
      • Variant
      • Negative
      • Complex Results
• Consider Long-Term Clinical Management Issues
Genetic Testing

• Hereditary cancer genetic testing is a diagnostic tool. It is not a screening test.
• New technology allows testing of many genes at once for a relatively low cost (multi-gene panels) - new opportunities AND new complexities.
• There are MANY labs: each with their own “menu” of tests, prices, logistics for ordering and billing, and policies (inc NYS test approval).
• Test selection is guided by various medical, legal, financial, and logistical factors.
• Test result interpretation is complex and patient-specific.
• Families who had previous single gene/syndrome genetic testing are often candidates for “updated” testing with a multi-gene panel.
Genetic Testing Options

- Single-site mutation test *(for a known family mutation)*
  - There are circumstances when, even in the setting of a known family mutation, more comprehensive tests are indicated.

- Ethnicity-specific mutation panel
  *(e.g., Ashkenazi Jewish BRCA1/BRCA2 panel)*

- Single gene or syndrome test *(e.g., CDH1 only)*

- Small panels, mid-size panels, big panels
  - Some focused on certain types of cancer, some pan-cancer panels
  - Some limited to genes with management guidelines and some include genes with unestablished cancer risks and lacking management guidelines: **must choose carefully**

- Rarely: whole exome, whole genome

- Wide variation in comprehensiveness and cost of different tests

- Insurance authorization is often necessary

*Professional organizations such as the NCCN and SGO have begun to recommend that multi-gene panels only be ordered in consultation with a genetics professional due to their intrinsic complexity.*
“Variant of uncertain significance” (VUS) is a genetic change that has not been definitively classified as to whether it can cause a cancer predisposition.

- VERY common: ~2-10% on single gene tests; ~40% chance of a VUS on mid-size panels, ~10% chance of >1 VUS on panels, the bigger the panel, the more likely there will be a VUS.
- Each lab performs their own interpretation of pathogenicity of variants; labs may disagree.
- Sometimes family studies are offered through the lab to try to clarify meaning.
- Registries for patients with variants of uncertain significance:
  - PROMPT Study: http://promptstudy.info/
  - GenomeConnect: https://www.genomeconnect.org/
- Over time, many variants are re-classified:
  - The lab sends an updated report to the ordering provider.
  - The ordering provider will be responsible for re-contacting patients.
# Genetic Variant Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of pathogenicity</th>
<th>Clinical testing</th>
<th>Surveillance recommendations</th>
<th>Research testing for family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>&gt; 0.99</td>
<td>Test at risk relatives for variant</td>
<td>Full high risk surveillance guidelines</td>
<td>Not indicated</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>0.95-0.99</td>
<td>Test at risk relatives for variant</td>
<td>Full high risk surveillance guidelines</td>
<td>May be helpful to further classify variant</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05-0.949</td>
<td>Do not use for predictive testing in relatives</td>
<td>Based on family history (and other risk factors)</td>
<td>May be helpful to further classify variant</td>
</tr>
<tr>
<td>2</td>
<td>Likely benign</td>
<td>0.001-0.049</td>
<td>Do not use for predictive testing in relatives</td>
<td>Treat as “no mutation detected”</td>
<td>May be helpful to further classify variant</td>
</tr>
<tr>
<td>1</td>
<td>Benign</td>
<td>&lt;0.001</td>
<td>Do not use for predictive testing in relatives</td>
<td>Treat as “no mutation detected”</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>


Created by ACOG District II in 2017 / Updated February 2018
# Post-Test Genetics Consultation and Counseling

<table>
<thead>
<tr>
<th>REVIEW</th>
<th>• The meaning of test result in the context of patient and family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCUSS</td>
<td>• Findings and limitations of the testing</td>
</tr>
<tr>
<td></td>
<td>• Patient’s personalized cancer risk in light of test results and relevant risk factors</td>
</tr>
<tr>
<td></td>
<td>• Medical management recommendations and options</td>
</tr>
<tr>
<td></td>
<td>• Patient’s plans for sharing the results with family</td>
</tr>
<tr>
<td>ASSESS</td>
<td>• And explore patient response to the results</td>
</tr>
<tr>
<td>PROVIDE</td>
<td>• Anticipatory guidance about what to expect next</td>
</tr>
<tr>
<td></td>
<td>• Direction about how to access more information now or in the future</td>
</tr>
</tbody>
</table>


Created by ACOG District II in 2017 / Updated February 2018
## Positive Results: Interpretation and Management

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Post-Test Consultation and Counseling</th>
<th>Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSITIVE</td>
<td>Conclusive: Known cancer risks</td>
<td>• Clinical management plan</td>
</tr>
<tr>
<td>(mutation identified)</td>
<td>• Discussion of cancer risks</td>
<td>• Communicating results and identifying at-risk family members (CASCADE testing)</td>
</tr>
<tr>
<td></td>
<td>• Reproductive risks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Family members’ risks</td>
<td>**see next slide for details</td>
</tr>
<tr>
<td></td>
<td>• Options for prevention and early detection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Impact on prognosis and treatment (e.g. BRCA1/BRCA2 and PARP inhibitors, type of surgery recommended)</td>
<td></td>
</tr>
<tr>
<td><strong>Also include:</strong> variant suspected or likely deleterious</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If testing was ordered by another provider, always refer these patients to a genetics professional.
Positive Results: Management

*(depends on gene and the organs at risk)*

| Clinical management plan may include: | • Early/increased surveillance (e.g. mammogram, colonoscopy, ultrasound, MRI)
• Lifestyle changes (e.g., sun avoidance, diet, exercise)
• Chemoprevention (e.g., oral contraceptives, Tamoxifen)
• Prophylactic surgery (e.g., oophorectomy, mastectomy, colectomy)
• Tailored cancer treatment strategies (e.g.: PARP inhibitors, type of surgery) |
| Refer to published guidelines for detailed management protocols | • NCCN guidelines outline management for some syndromes/genes, e.g., BRCA1 and BRCA2, Lynch, Li-Fraumeni, FAP, Cowden, Peutz Jeghers
• NCCN may not fully address all the cancer risks and management needs for other cancer risk genes, e.g., ATM, CHEK2, PALB2, BRIP1, RAD51C/D, FH, NF1
  • Genetics consultation is prudent for such cases
  • Other published resources may exist |
| Refer to other specialists | As needed for surveillance, surgery, etc. |
| Cascade testing for at-risk family members | • Unique situation: it’s not just about YOUR patient, it’s about the family
• Assist in identifying family members at increased risk, facilitating family communication of results and linking other family members to genetics professionals |
### Test Results: Interpretation and Management

<table>
<thead>
<tr>
<th>Variant of uncertain significance (with no known family mutation)</th>
<th>Inconclusive</th>
<th>Post-Test Consultation and Counseling</th>
<th>Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Explain that cancer risk associated with the variant is not yet known</td>
<td>• Consider family variant studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Do not use the variant for clinical management, instead....</td>
<td>• Consider testing other affected family members for mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Provide individualized risk assessment based on personal and family risk factors</td>
<td>• Refer patients to studies and registries</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Keep a database of patients with variants in case they need to be re-contacted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Personalized clinical management plan (<strong>see next slide for details</strong>)</td>
</tr>
</tbody>
</table>

If testing was ordered by another provider, always refer these patients to a genetics professional.
## VUS Results: Management

*Use personalized cancer risk estimates based on relevant risk factors using models and epidemiologic data*

| VUS with **NO KNOWN** mutation in the family | • Manage according to their personalized cancer risk estimate  
• Some risk models can incorporate personal and family history AND patient test results into remaining cancer risk predictions |

**THESE patients may qualify for and/or warrant enhanced screening based on these assessments:**

• Breast MRI and enhanced surveillance if breast cancer risk >20% (*see NCCN guideline*)
• More frequent colonoscopy, dermatological exam, or other organ screening in some patients
• “10-year rule:” start cancer screening 10 years before the earliest diagnosis of that cancer in their family
• Some clinical diagnostic and management guidelines call for people meeting certain criteria to have specific enhanced screening whether or not they have an identifiable mutation (e.g., HDGC)
Negative Results: Interpretation

**No known mutation in family:**
Breast Ca risk = 33.2%(pre-test)  
32.3%(post-test)

**INCONCLUSIVE:**
Patient must be managed based on family history and personal risk factors; often warrants enhanced screening; testing still indicated for affected relatives

**Family with known mutation (BRCA1):**
Breast Ca risk = 43.5%(pre-test)  
14.7%(post-test)

**NEGATIVE:** Patient is negative for the familial genetic alteration, and the hereditary risks associated with that (*but could still have other genetic and non-genetic cancer risk factors*).

Often follows population screening guidelines.
## Negative Results: Interpretation and Management

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Post-Test Consultation and Counseling</th>
<th>Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative (known family mutation)</strong></td>
<td>Conclusive (oftentimes, based on current knowledge)</td>
<td>Personalized clinical management plan <strong>see next slide for details</strong></td>
</tr>
<tr>
<td></td>
<td>• Risk of sporadic cancer and adherence to population screening guidelines UNLESS:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• other family/personal risk factors are present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• if the family mutation is a risk modifier and residual cancer risk is expected (e.g., CHEK2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Provide individualized risk assessment based on personal and relevant family risk factors</td>
<td></td>
</tr>
<tr>
<td>Negative (No known family mutation)</td>
<td>Inconclusive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Risk of unidentified or undetected mutation OR mutation in other family members</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Provide individualized risk assessment based on personal and family risk factors</td>
<td></td>
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</tbody>
</table>

If testing was ordered by another provider, many of these patients can still benefit from post-test consultations with genetics professionals.
Negative Results: Management

*Use personalized cancer risk estimates based on relevant risk factors using models and epidemiologic data*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| Negative for a known family mutation | • Manage according to their personalized cancer risk estimate  
• There are some genes where patients who test negative for family mutations are still considered at elevated cancer risk, and some families with more than one cancer syndrome  |
| Negative with NO KNOWN mutation in the family | • Manage according to their personalized cancer risk estimate  
• Some risk models can incorporate personal and family history AND patient test results into remaining cancer risk predictions  |

**AND AGAIN…..**

**THESE patients may qualify for and/or warrant enhanced screening based on these assessments:**

- Breast MRI and enhanced surveillance if breast cancer risk >20% *(see NCCN guideline)*
- More frequent colonoscopy, dermatological exam, or other organ screening in some patients
- “10-year rule:” start cancer screening 10 years before the earliest diagnosis of that cancer in their family
- Some clinical diagnostic and management guidelines call for people meeting certain criteria to have specific enhanced screening whether or not they have an identifiable mutation (e.g., HDGC)
Management of Patients who Decline Testing

*Use personalized cancer risk estimates based on relevant risk factors using models and epidemiologic data*

| Patients who decline genetic testing | Manage according to their personalized cancer risk assessment  
Make patient aware they can undergo testing at a later date  
Encourage patient to return if history changes |

**AND AGAIN......**

**THESE patients may qualify for and/or warrant enhanced screening based on these assessments:**

- Breast MRI and enhanced surveillance if breast cancer risk >20% (*see NCCN guideline*)
- More frequent colonoscopy, dermatological exam, or other organ screening in some patients
- “10-year rule:” start cancer screening 10 years before the earliest diagnosis of that cancer in their family
- Some clinical diagnostic and management guidelines call for people meeting certain criteria to have specific enhanced screening whether or not they have an identifiable mutation (e.g., HDGC)
Other Complex Testing Results & Issues

- **Families/patients with multiple hereditary cancer syndromes or variants**: Some patients with known family mutations still need comprehensive testing based on family history; with multiple findings it is very challenging to understand combined risk and management.

- **Mosaicism for a mutation**: Could be real, circulating malignancy, artifact of testing.

- **Unexpected findings**: A mutation in a gene you didn’t expect, non-paternity.

- **Phenocopy**: A person can test negative for a family cancer gene mutation, but still be affected by a related cancer by chance.

- **Recessive disease risk for carriers of some genes**: When mutations in the SAME gene are inherited from both parents, different, more severe and often childhood onset conditions can result (e.g., BRCA2, Lynch genes, ATM).

- **New mutations in patients**: Some syndromes (e.g., Li-Fraumeni, FAP) have an appreciable number of cases of new mutations, which have different family risks, and often present with no family history of disease.

*ALWAYS REFER TO A GENETICS PROFESSIONAL FOR COMPLEX ISSUES*

- **Who?** The paternal aunt
- **What?** A panel that includes BRCA1/BRCA2 as well as ovarian and pancreatic genes
- **When?** Bank DNA ASAP and do testing when family is emotionally ready
- **Where?** A DNA bank for now
- **Why?** To inform risk and surveillance for unaffected family members
- **How?** Coordinate with family and hospice to draw and ship blood; testing can later proceed with unaffected relatives first (and banked DNA if needed) or with the banked sample first
Summary: Test Selection and Results

• A large variety of genetic tests are now clinically available, with various risks, benefits, and costs.

• Genetic variants are frequently identified, especially in larger panels, and their classification may differ between labs, and may change over time.

• Post-test consultations will review the meaning of the test result in the context of the specific patient and family history.

• Personalized risk assessments and clinical management plans should be created based on the results in combination with relevant patient and family history.

• Some particularly complex interpretation issues exist, and always warrant referral to a genetics professional.
Agenda

- Review Cancer Genetics Basics
- Review Hereditary Cancer Syndromes
- Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
- Discuss Who to Refer and How to Make a Referral
  - What Happens in Cancer Genetics Consultations and Counseling?
  - What Happens in Genetic Test Selection and Result Interpretation?
- Consider Long-Term Clinical Management Issues
  - The Role of the OB-GYN
  - Collaboration with Other Providers
Role of the OB-GYN in Clinical Management

• Ob-gyns will often oversee decisions about, and the implementation of, the personalized clinical management plan
  • Prophylactic surgery decisions
  • Appropriate preventive and screening modalities

• Ob-gyns may be involved in needed reproductive counseling and decisions related to findings

• Ob-gyns may manage the post-treatment sequelae for patients undergoing premature menopause or surgeries

• Ob-gyns may be involved in treatment decisions and protocols for patients diagnosed with cancer

• Ob-gyns may coordinate care and closely collaborate with other specialists, including: Genetics Professionals, Gynecologic Oncologists, Breast Surgeons, and other specialists, as indicated
Consulting with a Gynecologic Oncologist

Organizations that support gynecologic-oncologist involvement:

- **Known/suspected gynecologic cancer:** Early referral leads to:
  - Complete surgical staging with early disease
  - Optimal cytoreductive surgery with advanced disease
  - Improved median and overall survival

- **If there is an incidental finding during surgery and the appropriate operation cannot be performed:**
  - Consider aborting scheduled surgery and refer patient to gynecologic oncologist as soon as possible

- **Gyn Onc has an important role in complex reproductive and risk reduction counseling**

**Source(s):**
Collaboration with Other Providers

**Ongoing collaboration with genetics professional; patients encouraged to check back yearly**

- New information about the personal or family history could change the risk assessment
- Participation in research studies that could inform cancer risk
- Ongoing emotional support
- Facilitation of counseling and testing for family (cascade testing)
- New information for currently tested genes or newly discovered genes may become available

**Other collaborating providers:**

- Breast surgeons and plastic surgeons for prophylactic mastectomy discussions
- Surgeons who specialize in unique surgeries or rare conditions (available in some facilities)
- Dermatology, GI, ophthalmology, neurology, and other specialists depending on the organs at risk (referrals sometimes needed)
- Specialists are harder to access in rural areas; some families are motivated to travel. Explore telemedicine consult options when possible
Summary: Long-Term Clinical Management

- Ob-gyns have many important roles in various issues related to long-term management of patients at increased risk for cancer.
- Close collaboration with the patient and other providers is essential.
Conclusion
Conclusion

• Ob-gyns play an important role in identifying patients who could benefit from hereditary cancer risk assessment.

• Office tools are available for family history collection and referral assessment.

• Genetics professionals and some other trained clinicians provide a comprehensive cancer risk assessment and facilitate patient decisions about genetic testing.

• Test options are expanding and results are increasingly complex.
  • Previously tested patients may warrant updated testing.
  • Due to its complexity, panel testing should be offered in the context of professional genetics expertise.

• Clinical management should be guided by test results and personal/family history risk factors.

• Collaboration with genetics professionals, gynecologic oncologists, and other specialists is beneficial to the patient.

• Various resources exist to learn more, including the attached appendix, ACOG DII, the SGO/ACOG/NSGC toolkit, NCCN guidelines, other guidelines, and many more …
Contact ACOG District II

For questions on this project:

Kristin Zielinski, MA, MPP
Senior Director of Operations
kzielinski@ny.acog.org

Linda Calamaras
Assistant to the Medical Education Department
lcalamaras@ny.acog.org

ACOG District II
100 Great Oaks Boulevard
Suite 109
Albany, NY 12203
518.436.3461 (p)
518.426.4728 (f)
info@ny.acog.org

@ACOGNY
@ACOGD2
APPENDIX
## Hereditary Cancer: Some Breast Risk Genes

<table>
<thead>
<tr>
<th>GENE</th>
<th>CANCER RISKS</th>
<th>OTHER FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1 and BRCA2</strong></td>
<td>Breast: 38-72% Ovarian: 12-44% Pancreatic: 2-5% Male Breast: increased</td>
<td>Prostate: increased Melanoma: may be increased Recessive disease risk</td>
</tr>
<tr>
<td><strong>TP53</strong> (Li-Fraumeni syndrome)</td>
<td>Breast: 54% Sarcoma: 21-33% Brain: 6-19%</td>
<td>Increased risk of adrenocortical carcinoma and various other tumors High new mutation rate</td>
</tr>
<tr>
<td><strong>CDH1</strong> (HDGC syndrome)</td>
<td>Diffuse Gastric: 67-83% Lobular Breast: 39-52%</td>
<td>Possible colorectal cancer risk Clinical diagnostic criteria are important</td>
</tr>
<tr>
<td><strong>PTEN</strong> (PTEN hamartoma tumor syndrome, AKA Cowden Syndrome)</td>
<td>Breast: 25-85% Follicular Thyroid: 3-38% Renal Cell: 15-34%</td>
<td>Uterine: 5-28% Colorectal: 9-16% Melanoma: 6% Benign skin findings, macrocephaly, intellectual disability, autism, thyroid lesions, vascular anomalies and other features Clinical diagnostic criteria (NCCN, v1.2018)</td>
</tr>
<tr>
<td><strong>ATM</strong></td>
<td>Breast: 30-69% Pancreatic: elevated</td>
<td>Colorectal: unclear Prostate: unclear Recessive disease risk</td>
</tr>
<tr>
<td><strong>CHEK2</strong></td>
<td>Breast: 18-37% Colorectal: possibly elevated Possibly other cancer risks</td>
<td>Truncating mutations seem to provide higher cancer risks compared with missense. CHEK2 I157T (low risk variant) up to 2.6% frequency in the Finnish population (ExAC): increased risk of breast cancer (OR=1.48-1.58) and colorectal cancer (OR=1.48-1.67), and possibly prostate, thyroid, and kidney cancers. CHEK2 S428F increases breast cancer 2-fold in Ashkenazi Jewish women CHEK2 1100delC and other truncating mutations confer a risk of breast cancer prostate cancer, and possibly colon cancer.</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>Breast: 30-58% Pancreatic: elevated</td>
<td>Ovarian: Possibly elevated (need more evidence) Recessive disease risk</td>
</tr>
<tr>
<td><strong>STK11</strong> (Peutz-Jeghers Syndrome)</td>
<td>Breast: 45-50% Colon: 39% Stomach: 29% Small Bowel: 13% Pancreas: 11-36%</td>
<td>Ovarian: 18-21% Cervix: 10% Uterine: 9% Testes: elevated Lung: 7-17% Peutz-Jeghers-type hamartomatous GI polyps Mucocutaneous hyperpigmentation</td>
</tr>
<tr>
<td><strong>NBN</strong></td>
<td>Breast: 30%</td>
<td>Recessive disease risk; Data primarily derived from Slavic mutation 657del5</td>
</tr>
<tr>
<td><strong>NF1</strong> (Neurofibromatosis 1)</td>
<td>Breast &lt;50 years: 8.4% by age 50 Malignant peripheral nerve sheath tumors: 10%</td>
<td>GIST, CNS tumors, Optic nerve gliomas, Leukemia, Retinal tumors: elevated Numerous clinical features including multiple café-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, iris Lisch nodules, and learning disabilities, among others (<a href="https://www.ncbi.nlm.nih.gov/books/NBK1109/">https://www.ncbi.nlm.nih.gov/books/NBK1109/</a>) Recommend referral to an NF specialist for evaluation and management</td>
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## Hereditary Cancer: Some Breast Risk Genes

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## Hereditary Cancer: Some GYN risk genes

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</table>
| **BRCA1 and BRCA2**  
Cancer risks may differ depending on which gene has the mutation | Breast: 38-72%  
Ovarian: 12-64%  
Pancreatic: 2-5% | Male Breast: increased  
Prostate: increased  
Melanoma: may be increased | Recessive disease risk |
| **Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)**  
Cancer risks differ depending on which gene has the mutation | Colon: 10-82%  
Uterine: 15-60%  
Gastric: up to 13%  
Ovarian: up to 24%  
Urinary Tract: up to 4% | Some genes have an increased risk for other tumors including: small bowel, brain, CNS, hepatobiliary tract, sebaceous neoplasms, and pancreatic cancer | Recessive disease risk  
Tumors may show microsatellite instability and/or loss of protein expression on MSI/IHC |
| **PTEN**  
(PTEN hamartoma tumor syndrome, AKA Cowden Syndrome) | Breast: 25-85%  
Follicular Thyroid: 3-38%  
Renal Cell: 15-34% | Uterine: 5-28%  
Colorectal: 9-16%  
Melanoma: 6% | Benign skin findings, macrocephaly, intellectual disability, autism, thyroid lesions, vascular anomalies and other features  
Clinical diagnostic criteria (NCCN, v1.2018) |
| **PALB2** | Breast: 30-58%  
Pancreatic: elevated | Ovarian: Possibly elevated (need more evidence) | Recessive disease risk |
| **RAD51C/RAD51D** | Ovarian: 6-14%  
Breast: unknown/ insufficient evidence | | Recessive disease risk (RAD51C) |
| **STK11**  
(Phosphatase and tensin homolog deleted on chromosome 11)  
(FA) | Breast: 45-50%  
Colon: 39%  
Stomach: 29% | Ovarian: 18-21%  
Cervix: 10%  
Uterine: 9%  
Lung: 15-17%  
Sm. Intestine: 13%  
Testes: elevated | Peutz-Jeghers-type hamartomatous GI polyps  
Mucocutaneous hyperpigmentation |
| **FH**  
(Fumarate hydratase) gene  
HLRCC (Hereditary Leiomyomatosis Renal Cell Cancer Syndrome) | Renal cell carcinoma: (papillary type 2 or collecting duct) 20-34%  
Other tumors (uncommonly) associated: bladder, prostate, breast, gastrointestinal stromal tumors, pheochromocytomas, testicular Leydig cell tumors, adrenal adenomas, and ovarian cystadenomas. | Benign uterine fibroids (often requiring TAH at early age)  
Skin leiomyomas ("skin bumps")  
Penetration approaches 90-100%  
Recessive disease risk |
| **BRI1** | Ovarian: 4-13% | Recessive disease risk |
| **RB1** (retinoblastoma) | Retinoblastoma – mostly bilateral, 90-95% penetrant | Risk of 2nd malignancy is ~20% in those who have been irradiated |
| **SMARCA4** | Small cell carcinoma of the ovary hypercalcemic type (SCCOHT) | 43% of SCCOHT due to germline mutations, with 98% of these due to SMARCA4 mutations. Median age of onset of ~24 years. |
| **DICER1** | Ovarian Sertoli-Leydig cell tumors (SLCTs)  
ALSO: Pleuropulmonary blastoma (PPB), Cystic nephroma (CN), Nasal chondromesenchymal hamartoma, thyroid carcinoma, Ciliary body medulloepithelioma, Wilms tumor, and Cervical embryonal rhabdomyosarcoma, among others | Multinodular goiter |

Sources: See next slide
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<tr>
<td>Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)</td>
<td>NCCN GUIDELINES FOR DETECTION, PREVENTION, &amp; RISK REDUCTION: Genetic/Familial High-Risk Assessment: Colorectal v3.2017</td>
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### Hereditary Cancer: Some GYN risk genes

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### Hereditary Cancer: Some Non-Breast/Gyn Risk Genes

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<th>GENE</th>
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<tr>
<td>APC (Familial Adenomatous Polyposis (FAP) + Attenuated FAP (AFAP))</td>
<td>Colon: 70% (AFAP)-100% (FAP)</td>
<td>FAP:100s-1000s colon adenomas</td>
</tr>
<tr>
<td></td>
<td>Duodenum: 4-12%</td>
<td>AFAP:10-100 adenomas</td>
</tr>
<tr>
<td></td>
<td>Hepatoblastoma: 1-2%</td>
<td>Desmoid tumors, CHRPE</td>
</tr>
<tr>
<td></td>
<td>Thyroid: &lt;2%</td>
<td>Sometimes other physical findings</td>
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<tr>
<td>APC − moderate risk variant (I1307K)</td>
<td>Low/moderate risk (2-fold) of colon cancer in AJ population, unclear risk in other populations (PMID: 23576677)</td>
<td>Common in the AJ population (6-10%) (PMID:9288102, 23896379)</td>
</tr>
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<tr>
<td>Biallelic MUTYH (MUTYH-associated polyposis (MAP)) **must have 2 mutations</td>
<td>Colon: 43-100%</td>
<td>GI Polyposis</td>
</tr>
<tr>
<td></td>
<td>Duodenal: 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased risk of other malignancies</td>
<td></td>
</tr>
<tr>
<td>Heterozygous MUTYH mutation (carrier)</td>
<td>Cancer risks may depend on whether or not there is a family history of colon cancer in a close relative. It is not clear whether those with a single mutation, but without a family history of colon cancer, are at increased risk for colon cancer.</td>
<td>Common Variants: The two most common MAP-associated MUTYH mutations (Y165C and G382D) are present as heterozygous changes in approximately 1%-2% of individuals in N.American and N.European populations.</td>
</tr>
</tbody>
</table>

**Sources:**  
NCCN GUIDELINES FOR DETECTION, PREVENTION, & RISK REDUCTION: Genetic/Familial High-Risk Assessment: Colorectal v3.2017; MUTYH mutations: PMIDs: 11818965 and 17489848; MUTYH variants: PMIDs 11818965 and 17489848; APCI1307K: PMIDs 23576677, 9288102, and 23896379

Created by ACOG District II in 2017 / Updated February 2018
Hereditary Cancer Syndromes: Cowden Syndrome

- AKA: *PTEN* hamartoma tumor syndrome
- Caused by mutations in the *PTEN* gene
- Characterized by cancer risk, benign skin findings, macrocephaly, intellectual disability, autism, thyroid lesions, vascular anomalies and other features
- Clinical diagnostic criteria of major and minor features *(see NCCN, v1.2018)*

**Increased Cancer Risks**

<table>
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<tr>
<th>Cancer Type</th>
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<tr>
<td>Breast</td>
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<td>Follicular Thyroid</td>
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<td>Renal Cell</td>
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</tr>
<tr>
<td>Colorectal</td>
<td>9-16%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6%</td>
</tr>
</tbody>
</table>


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