Genetics in the High Risk Breast Patient

Courtney M. Cook, MS, LCGC
Oncology Genetic Counselor
University of Tennessee Medical Center – Cancer Institute
University Genetics Oncology Clinic
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Disclosures

• I have no disclosures.
Objectives:

1. Learn the “red flags” for referring patients to cancer genetic counseling
2. Identify which patients meet insurance criteria for genetic testing coverage
3. Incorporate genetic testing results into practice
4. Recognize social considerations of genetic testing
Cancer Classifications

- 5-10% Hereditary
- 10-20% Familial
- Sporadic

Greenwood Genetics Center Counseling Aids, 6th Edition
5 “Red Flags” for Hereditary Cancer

1. Cancers at young ages
2. Multiple generations affected
3. One person with 2+ cancers
4. Rare cancers
5. Ancestry
Insurance Criteria for Genetic Testing

There are rules for a reason!
BRCA1/2 TESTING CRITERIA

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
- Personal history of breast cancer + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary
    - ≥1 close blood relative with breast cancer at any age
    - ≥1 close relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - An unknown or limited family history
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
    - ≥1 close blood relative with breast cancer diagnosed ≤50 y
    - ≥1 close blood relative with ovarian carcinoma
    - A close male blood relative with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required
- Personal history of ovarian carcinoma
- Personal history of male breast cancer

BRCA testing criteria met

If BRCA testing criteria not met, consider testing for other hereditary syndromes

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

See Follow-up (BRCA-2)
LI-FRAUMENI SYNDROME TESTING CRITERIA

- Individual from a family with a known TP53 mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:
  - Combination of an individual diagnosed age <45 y with a sarcoma
  - AND
  - A first-degree relative diagnosed age <45 y with cancer
  - AND
  - An additional first- or second-degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age
- Chompret criteria:
  - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 y or with multiple primaries at any age OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 y OR
  - Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history OR
  - Breast cancer before age 31 y

FOLLOW-UP

- LFS testing criteria met
  - See Follow-up (LIFR-2)
- If LFS testing criteria not met, consider testing for other hereditary syndromes, if appropriate
  - Individualized recommendations according to personal and family history
# Cowden Syndrome/PHTS

**Cowden Syndrome/PTEN Hamartoma Tumor Syndrome Testing Criteria**

<table>
<thead>
<tr>
<th>Major criteria:</th>
<th>Minor criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Breast cancer</td>
<td>- Thyroid structural lesions (e.g., adenoma, nodule(s), goiter)</td>
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<tr>
<td>- Endometrial cancer</td>
<td>- Renal cell carcinoma</td>
</tr>
<tr>
<td>- Follicular thyroid cancer</td>
<td>- Single GI hamartoma or ganglioneuroma</td>
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<tr>
<td>- Multiple GI hamartomas or ganglioneuromas</td>
<td>- Testicular lipomatosis</td>
</tr>
<tr>
<td>- Macrocephaly (megaloccephaly) (i.e., ≥97%, 58 cm in adult women, 60 cm in adult men)</td>
<td>- Vascular anomalies (including multiple intracranial developmental venous anomalies)</td>
</tr>
<tr>
<td>- Maculocutaneous lesions</td>
<td>- One biopsy-proven trichilemmoma</td>
</tr>
<tr>
<td>- Maculocutaneous lesions</td>
<td>- Multiple palmpoplantar keratoses</td>
</tr>
<tr>
<td>- Macular pigmentation of glans penis</td>
<td>- Multifocal or extensive oral mucosal papillomatosis</td>
</tr>
<tr>
<td>- Multiple cutaneous facial papules (often verrucous)</td>
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</tbody>
</table>

**Follow-up**

<table>
<thead>
<tr>
<th>CS/PHTS testing criteria</th>
<th>Individualized recommendations according to personal and family history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed</td>
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<tr>
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<td>The at-risk individual must have the following:</td>
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<tr>
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<td>- Any one major criterion or</td>
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<td></td>
<td>- Two minor criteria</td>
</tr>
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<td>CS/PHTS testing criteria not met, consider testing for other hereditary syndromes, if appropriate</td>
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1. Breast cancer
2. Endometrial cancer
3. Follicular thyroid cancer
4. Multiple GI hamartomas or ganglioneuromas
5. Macrocephaly (megaloccephaly) (i.e., ≥97%, 58 cm in adult women, 60 cm in adult men)
6. Maculocutaneous lesions
7. One biopsy-proven trichilemmoma
8. Multiple palmpoplantar keratoses
9. Multifocal or extensive oral mucosal papillomatosis
10. Multiple cutaneous facial papules (often verrucous)
“Buy one gene, get more free”
Possible Results

1. Positive
2. Negative
3. Variant of Unknown Significance (VUS)
Distribution of Results

• Positive = 10%
• Negative = 60%
• VUS = 30%

❖ Standard across labs for panel testing
❖ Even those patients with lots of red flags who meet criteria
Results are back!

Now what do we do?
Positive

Make a plan!
Increased Screening is the **Recommendation**

- Annual mammogram
- Annual breast MRI with contrast

- Alternate every 6 months
- Ages may vary
Option of Risk-Reducing Mastectomy (RRM)

• *BRCA1*
• *BRCA2*
• *PTEN* (Cowden syndrome)
• *TP53* (Li-Fraumeni syndrome)
Consider RRM Based on **Family History**

- **ATM**
- **CDH1** (Hereditary Diffuse Gastric Cancer)
- **PALB2**
Insufficient Evidence for RRM

- CHEK2
- NBN
- NF1
- STK11

- “Manage based on family history”
Genes possibly associated with breast cancer...?

• **BRIP1**
• **RAD51C**
• **RAD51D**
• Lynch syndrome genes (**MLH1, MSH2, MSH6, PMS2, EPCAM**)
But that’s not all...

Some cancer genes have associated autosomal recessive conditions!
Risk to Offspring: Autosomal Recessive Conditions (i.e. biallelic mutations in the gene)

- **ATM**: Ataxia Telangiectasia
- **BRCA2**: Fanconi Anemia
- **NBN**: Nijmegen Breakage syndrome
- **PALB2**: Fanconi Anemia
- **RAD51C**: Fanconi Anemia
Negative

Great news, but not necessarily an answer.
The “uninformative negative”...

What do you do when an unaffected patient tests negative?
ID:
Woman's age is 38 years.
Age at menarche was 12 years.
Age at first birth was 32 years.
Person is premenopausal.
Height is 5 ft 6 in.
Weight is 10 at 10 lb.
Woman has never used HRT.

Risk after 10 years is 4.6%.
10 year population risk is 1.4%.
Lifetime risk is 39.7%.
Lifetime population risk is 13%.
Probability of a BRCA1 gene is 0%.
Probability of a BRCA2 gene is 0%.
Social considerations of genetic testing

Because no one lives in a black hole!
Risks – Testing a patient who...

• Will not comply with increased screening/management
• Is 18y, but too young to begin screening
• May make reproductive decisions
• May implicate a parent as “positive by default”
• Guilt and survivors guilt
• Some people don’t want to know!
When in doubt...
Referral to UTMC Oncology Genetic Counseling

Fill out the physician referral form:

Phone: (865) 305-2DNA (2362)
Fax: (865) 305-6362