Hereditary Cancer Genetic Testing in Cancer Treatment, Detection, and Prevention

Amanda Eppolito, MS, CGC
Frederick Flynt, MD, FACP

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Clinical Co-Management of the Oncology Patient
Disclosures

We have no relevant financial relationships with any ACCME defined commercial interests.
Objectives

• List current guidelines for hereditary cancer genetic testing.

• Answer frequently asked questions about genetic testing.

• Examine genetic testing implications for cancer treatment, detection, and prevention.
Hereditary Cancer Red Flags

- **Young** age (≤ 50) at diagnosis
- **Multiple family members** with the same or related cancers
- **Multiple cancers** in the same person
- **“Rare”** cancer
- From a population at **higher risk** (e.g. Ashkenazi Jewish)
Guidelines keep expanding...

Young
- Diagnosed ≤ 50
  - Breast Cancer
  - Colorectal cancer
  - Endometrial cancer
- Triple negative breast cancer ≤ 60

“Rare”
- Ovarian cancer
- Pancreatic cancer
- Metastatic prostate cancer
- Male breast cancer
- Others (e.g. paraganglioma/pheochromocytoma)
**Guidelines keep expanding…**

### Multiple

- **Polyposis** (e.g. >10 adenomas, >1 hamartoma)

- **Breast Cancer OR Prostate Cancer (Gleason ≥7) &**
  - 2 breast primaries
  - 1 relative with breast ≤ 50, ovarian, male breast, pancreatic, HG/met prostate
  - 2 relatives with breast cancer or prostate cancer (any age)

- **Colon Cancer OR Endometrial Cancer &**
  - 1 other Lynch syndrome cancer* in the patient
  - 1 relative with Lynch syndrome cancer* ≤ 50
  - 2 relatives with Lynch syndrome cancers* (any age)

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*Lynch syndrome cancers = colorectal, endometrial, gastric, ovarian, pancreas, ureter & renal pelvic, brain, biliary tract, small intestine cancer, sebaceous adenomas/carcinomas*
Higher Risk Population

- Ashkenazi Jewish &
  - Breast cancer
  - Prostate cancer (high grade)

- Known gene mutation in the family

- Abnormal tumor studies:
  - Evidence of mismatch repair deficiency
    (e.g. microsatellite instability)
  - Mutation (e.g. BRCA1/2) on tumor profiling, regardless of tumor type

- Consider testing to determine eligibility for targeted treatment
  (e.g. metastatic breast cancer)
Rapid changes in testing technology

- **1996**: BRCA1/2 sequencing
- **2007**: BRCA1/2 del/dup “BART”
- **2012**: 1st cancer panels test ~15 genes
- **2019**: Testing up to 83 genes available
BRCA1
BRCA2
Newer genes
Moderate risk genes
Other high risk genes
Undiscovered genes

Hereditary
Familial
Sporadic
## Moderate risk genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>High Risk Genes</th>
<th>Moderate Risk Genes</th>
<th>Newer Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1, BRCA2, TP53, PTEN, CDH1, STK11</td>
<td>ATM, CHEK2, PALB2, NBN</td>
<td>BARD1, BRIP1, RAD51C, RAD51D</td>
<td></td>
</tr>
<tr>
<td>Lifetime Breast Cancer Risk</td>
<td>45-87%</td>
<td>20-55%</td>
<td>Not well defined</td>
</tr>
<tr>
<td>Medical Management</td>
<td>RR mastectomy or high risk breast screening</td>
<td>High risk breast screening (mammo &amp; MRI)</td>
<td>Not well established</td>
</tr>
</tbody>
</table>
Rapid changes in pricing

- **1996**: BRCA1/2 sequencing
- **2007**: BRCA1/2 del/dup “BART”
- **2012**: 1st cancer panels test ~15 genes
- **2019**: Testing up to 83 genes available

Test Cost $3,000-$4,000

Test Cost as low as $250, up to ?
Rapid changes in public knowledge, interest & policy

- **1996**: BRCA1 discovered
- **2007**: GINA passed
- **2008**: Supreme Court ruling
- **2012**: Testing up to 83 genes available
- **2013**: DT Consumer testing ↑
- **2019**: 1st cancer panels test ~15 genes

- **“Angelina Effect”**: 2013
- **Supreme Court ruling**: 2012
- **DT Consumer testing ↑**: 2019
- **BRCA1/2 sequencing**: 1996
- **BRCA1/2 del/dup “BART”**: 2007
Direct-to-Consumer Genetic Testing

Knowledge is power
$249 genetic test to understand your risk for hereditary breast & ovarian cancer. Genetic counseling included.

Learn more
At-home testing ≠ Clinical testing

23andMe “Health” component is NOT certified to be used for clinical actionability

Note: Their “BRCA” testing includes only 3 specific (Jewish) mutations and still requires confirmation in a clinical lab prior to clinical action.

Third party data analysis is NOT reliable.
Genetic Testing FAQs

• How is testing performed?
  – Blood or saliva (same accuracy)

• Can I do 23andme testing instead?
  – No, 23andme testing has a very different purpose and quality.

• How many genes will be tested?
  – During a GC visit, we review level of testing indicated based on personal/family history, but patient also weighs in on how much they want to know.

• How much does testing cost?
  – List price varies, but usually well-covered by insurance if meet criteria for testing.
  – In many cases, $0 out-of-pocket under ACA. In other cases, falls to deductible/coinsurance. Financial assistance & grant programs are available, if needed.
  – Several labs have self-pay price as low as $250.

• Do I need to call my insurance company first?
  – If patient is seeing a GC, will confirm at appt that patient meets insurance criteria, discuss lab billing policy, and patient will be notified by testing lab re OOP cost.

• Will I be discriminated against if I get genetic testing?
  – Genetic Information Nondiscrimination Act (GINA) covers health insurance & employment (but not life, disability, or long-term care insurance)

• My family member is dying and we want to do genetic testing, but how?
  – Consider DNA banking (e.g. Prevention Genetics for $169, family can coordinate)
Cancer Treatment, Detection, and Prevention in Hereditary Cancer Families
Family #1

- (L) brca (triple neg) dx 55
- (R) brca (ER+) dx 60
- st IV, lung mets
- ovarian cancer dx 62

- d. 75
- d. 85
- 35  30
- 63  65
- 30  40
- d. 75  d. 85
Family #1

BRCA1 Cancer Risks:
- Female Breast  46-87%
- Ovarian  39-63%
- Male Breast  1-2%
- Prostate  9%
- Pancreatic  1-3%
BRCA: Management

Systemic therapy options

• For all patients with metastatic HER-2 negative breast cancer who are eligible for single agent therapy, strongly consider germline BRCA testing (NCCN guidelines 2019)

• PARP inhibitors, olaparib and talazoparib are both category 1 treatment options as single agent therapies for HER-2 negative metastatic disease in those with germline BRCA 1/2 mutations
BRCA: Management

PARP Inhibitors

- Inhibitors of polyadenosine diphosphate-ribose polymerase (PARP) useful in BRCA-mutated breast cancer and ovarian cancer (and potentially others).

- PARP is involved in molecular events leading to cell recovery from DNA damage.
  - When PARP1 (most abundant of PARP family) is inhibited, double-strand DNA breaks accumulate.
  - Under normal conditions, these are repaired via the BRCA pathway-dependent homologous recombination mechanism.
  - Inhibition of PARP renders tumors lacking BRCA function exquisitely sensitive to cell death.
DNA damage (SSBs)

PARP inhibition impairs base excision repair

DNA replication (DNA DSBs or replication fork collapse)

Normal cell with functional HR pathway

HR-mediated DNA repair
Cell survival

Tumor-selective cell death (synthetic lethality)

HR-deficient tumor cell (BRCA deficient)

Cell death
Impaired HR-mediated DNA repair
BRCA Management

PARP Inhibitors: Metastatic Breast Cancer

• **OlympiAD trial:**
  – Subset of 121 *BRCA* mutation carriers with metastatic triple-negative disease (all with prior treatment with anthracycline and a taxane in either the adjuvant or metastatic setting) tx with olaparib
  – Improved PFS relative to those receiving chemotherapy (hazard ratio [HR] for progression or death 0.43, 95% CI 0.29-0.63)

• **EMBRACA trial:**
  – Talozoparib improved PFS relative to single-agent chemotherapy (HR 0.60, 95% CI 0.41-0.87)
BRCA Management

PARP Inhibitors: Ovarian Cancer maintenance tx

- Maintenance olaparib after initial diagnosis and treatment with chemotherapy in BRCA-associated advanced ovarian cancer
  - SOLO1 trial: maintenance tx vs placebo
    - 400 pts with advanced ovarian CA with a BRCA 1/2 mutation with CR/PR to upfront chemo
    - At 41 mos of f/u, olaparib improved the three-year rate of freedom from disease progression or death (60 versus 27 percent)

- PARP inhibitors niraparib, olaparib, and rucabarib are approved for maintenance therapy b/c of improved PFS regardless of BRCA mutation status
  - Data on OS outcomes are pending
BRCA Management

PARP Inhibitors: Recurrent ovarian cancer tx

- **Olaparib** is approved for recurrent BRCA + (germline) ovarian cancer as single-agent therapy after \( \geq 3 \) lines of treatment.

- **Rucaparib** is approved for recurrent BRCA+ (germline or somatic) ovarian cancer as a single agent after \( \geq 2 \) lines of treatment.

- Single-agent niraparib, rucaparib, and olaparib are approved for recurrent ovarian cancer after CR/PR to platinum-based chemotherapy retreatment as maintenance tx (regardless of BRCA mutation status).
Family #2

- d. 78 (prostate ca dx 74)
- d. 80
- 72 (pancreatic ca dx 72, non-smoker)
- 65 (prostate ca dx 60, Gleason = 8)
- 70
- 30s

slide 25
Family #2

BRCA2
Cancer Risks:

- Female Breast 38-84%
- Ovarian 16-27%
- Male Breast 5-10%
- Prostate 20%
- Pancreatic 2-7%
- Melanoma elevated
PARP Inhibitors: Prostate Cancer

- Preliminary results have shown that men with metastatic prostate cancer and BRCA mutations may respond to treatment PARP inhibitors
- Other DNA repair gene mutations may also be more frequent in men with aggressive prostate cancer, and these may also respond to PARP inhibitors
Breast Cancer risk

- Refer to breast specialist/surgeon

- Annual mammo (consider 3D) & breast MRI
  - When to start?*
    - BRCA1/2: age 25
      *Modify based on family history

- Risk-reducing mastectomy

- Risk-reducing agents (i.e. Tamoxifen)
Ovarian Cancer Risk

- Consider referral to GYN oncologist
- Risk-reducing bilateral salpingo-oophorectomy
  - When?
    - BRCA1: age 35-40 & completed family
    - BRCA2: age 40-45
BRCA: Management

Male Carriers

BRCA1/2:

• Breast self-exam training and education

• Clinical breast exam (annual, begin @ age 35)

• Prostate cancer screening (annual, begin @ age 45)
Family #3

MSH6 Cancer Risks:

- Colon 10-22%
- Endometrium 16-26%
- Increased: stomach, ovary, prostate, hepatobiliary, urinary, small bowel, brain, sebaceous neoplasms, pancreas
Lynch Syndrome

Genetic background

- Lynch syndrome is an **autosomal dominant disorder**
  - Caused by a germline mutation in a **DNA mismatch repair gene** *(MLH1, MSH2, MSH6, and PMS2)*
  - Or loss of expression of *MSH2* due to deletion in the *EPCAM* gene
  - Causes **Microsatellite instability (MSI-H)**
    - MSI is not specific for Lynch syndrome
    - Up to 15% of sporadic cancers also demonstrate MSI
Lynch Syndrome: Management

Screening

• Annual CSP (start 20-25yo or 2-5 yrs prior to earliest age in family)

• Annual screening for endometrial and ovarian cancer (age 30-35yo or 3-5 yrs prior to earliest age in family)
  – Prophylactic TAH/BSO at the end of childbearing or at age 40

• EGD every 3-5 yrs (start 30-35yo)

• Annual urinalysis (start 30-35yo)

• Annual physical exam including skin and neuro exam (start 25-30yo)
Immunotherapy

- Immunotherapy has shown promising results in various cancers

- Checkpoint inhibitors
  - Approved for multiple advanced stage cancers: melanoma, non-small cell lung cancer, renal cell carcinoma, bladder, refractory Hodgkin lymphoma, and others

  - **Programmed cell death (PD1) inhibitors:**
    - PD-1 is a transmembrane protein inhibitory molecule
    - Interaction with PD ligand directly inhibits apoptosis of the tumor cell
    - Acts as a **physiologic brake** on unrestrained cytotoxic T effector function
    - PD1 inhibitors remove this brake
Lynch Syndrome: Management

Immunotherapy

• In 2017, the FDA approved pembrolizumab for treatment of any cancer with metastatic disease with MSI-H or mismatch repair-deficient solid tumors.

• This is the FIRST TIME a cancer treatment has been approved based on a common biomarker rather than organ-based approach.

• MSI-H causes a build up of somatic mutations in tumor cells and leads to:
  – High tumor mutational burden
  – Increased expression of neoantigens
  – Abundant tumor-infiltrating lymphocytes

• These changes have been linked to increased sensitivity to checkpoint inhibitor drugs.
Genetic Counseling and Testing

• IMPORTANT for patient care
  – Finding a genetic cancer predisposition syndrome can lead to:
    • Increased surveillance, hopefully leading to early detection
    • Increased prevention, through prophylactic surgery and systemic therapies
    • Increased progression free survival in the advanced cancer setting (and likely improved overall survival), by offering additional systemic therapeutic options
Thank you, and Questions?

Piedmont Cancer Genetics Program
(404) 425-7300

Referral via:
-Epic Ambulatory Referral to Cancer Genetics
Or faxed referral form