What You’ve Always Wanted to Know about Genetics and Genomics in Cancer Prevention and Early Detection

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Disclosures

- Scientific advisory boards:
  - InVitae Genetics
  - Genome Medical
  - Promega

- Stock/Stock Options
  - Genome Medical
  - GI OnDemand
Normal Male Karyotype

1  2  3  4  5
6  7  8  9  10
11 12
13 14 15
16 17 18
19 20
21 22

Sex chromosomes
Sporadic

• Later age at onset (>60)
• Little or no family history of cancer
• Single or unilateral tumors

Inherited

• Early age at onset (<50)
• Multiple generations with cancer
• Bilateral multiple primary cancers
• Clustering of certain cancers (i.e. breast/ovarian)
Autosomal Dominant Inheritance

Carrier Parent

Non-carrier Parent

Aa 1/2  aa 1/2

Aa 1/2  aa

Aa 1/2  aa

Aa

Carrier

Carrier

Non-carrier

Non-carrier

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When to Suspect Hereditary Cancer Syndrome

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (eg, breast and ovary)
- Evidence of autosomal dominant transmission
The Most Common Hereditary Cancer Syndromes

- Hereditary Breast-Ovarian Cancer Syndrome
  - Due to mutations in the BRCA1 and BRCA2 genes

- Lynch Syndrome
  - Due to mutations in MLH1, MSH2, MSH6, PMS2, and EPCAM genes

- Considered Tier One Genetic Diseases by CDC along with Familial Hypercholesterolemia
  - Common
  - Easy to test for
  - Actionable

- Geisinger MyCode assessed for Tier 1 conditions in 50,000 health plan participants
  - 1.32% (1 in 76 individuals) had one of these conditions
  - Compare to the 1 in 800 positive rate in newborn screening programs
How Much Breast and Ovarian Cancer Is Hereditary?

Breast Cancer
- Hereditary: 15%
- Sporadic: 75%
- Familial: 10%

Ovarian Cancer
- Hereditary: 29%
- Sporadic: 76%
Hereditary Breast-Ovarian Cancer Syndrome (HBOC)

BRCA2

BRCA1
## Hereditary Breast Ovarian Cancer Risks (to 80)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>General Public</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>72%</td>
<td>69%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>39-58%</td>
<td>13-29%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>12.5-29%</td>
<td>27-60%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>≤5%</td>
<td>5-10%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
Relevance of Ashkenazi Jewish Descent

- 1 in 40 (2.5%) Ashkenazi Jews (males and females) carry a *BRCA1* or *BRCA2* founder mutation
- 1 in 400 (0.25%) in non-Jewish populations
- 3 mutations account for 95% of HBOC in Jewish individuals:
  - *BRCA1*: 185delAG, 5382insC
  - *BRCA2*: 6174delT
- Other founder examples: Iceland, Denmark, Finland: *BRCA2*: 999del5
HBOC Breast Cancer Management
NCCN Guidelines v2.2021

- Breast awareness starting at age 18 y.
- Clinical breast exam, every 6–12 months starting at age 25 y.
- Age 25–29 y, annual breast MRI screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
- Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast.
- Age >75 y, management should be considered on an individual basis.
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks.
  - Prophylactic mastectomy has been shown to reduce the risk for developing breast cancer by about 90%.
- Discuss options for risk reduction agents (e.g. chemoprevention with Tamoxifen) including risks and benefits of each medication.
Risk-reducing bilateral salpingo-oophorectomy between the ages of 35-40, or after child bearing is complete. Because ovarian cancer in women with BRCA2 mutations occurs later than in BRCA1, it is reasonable to delay risk-reducing BSO until age 40-45 unless family history warrants earlier age of prophylactic surgery.

Some evidence of slight increased risk for serous uterine cancer among BRCA1 mutation carriers – discuss consideration of hysterectomy with BSO.

If delaying BSO: transvaginal ultrasound with color Doppler imaging at age 30-35 with concurrent serum CA-125 - not been shown to be sufficiently sensitive to support a positive NCCN recommendation.

Consider oral contraceptives – discussion of risk/benefit.

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Cancer Screening in Males
NCCN Guidelines v2.2021

- Breast self-examination training and education beginning at age 35.
- Clinical breast examination every 12 months beginning at age 35.
- (BRCA2) Recommend prostate cancer screening including annual digital rectal examination and PSA test beginning at age 40.
- (BRCA1) Consider prostate cancer screening including annual digital rectal examination and PSA test beginning at age 40.
Screening for other cancers

- Melanoma: No specific screening guidelines but general melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure.

- Pancreatic cancer: Individuals with BRCA1/2, ATM, PALB2, TP53, or Lynch genes (except PMS2) with a FDR or SDR with pancreatic cancer:
  - Consider pancreatic cancer screening beginning at age 50 or 10 years younger than the earliest dx in family.
  - Annual contrast-enhanced MRI/MRCP and/or EUS with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening.
  - Most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any intervention.

- Follow American Cancer Society guidelines for other cancer surveillance
Lynch Syndrome

- **MLH1**
- **MSH2**
- **MSH6**
- **PMS2**
Lynch Syndrome

- Over *1.2 million* individuals in the United States have Lynch syndrome
- Inherited condition that causes high risks for colorectal cancer, endometrial cancer, and other cancers
- Preventable cancers with early and more frequent screening
- 95% of affected individuals do not know they have Lynch syndrome
## Lynch Syndrome Cancer Risks (to 80)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>MLH1 and MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
<th>General Public</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>33-61%</td>
<td>10-44%</td>
<td>9-20%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>21-57%</td>
<td>16-49%</td>
<td>13-26%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.2-9%</td>
<td>≤1-8%</td>
<td>?</td>
<td>0.9%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>4-38%</td>
<td>1-13%</td>
<td>3%</td>
<td>1.3%</td>
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</table>
# Lynch Syndrome Surveillance Options

## NCCN v1.2020

<table>
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<tr>
<th>Intervention</th>
<th>Recommendation</th>
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<tr>
<td>Colon Cancer</td>
<td><strong>MLH1 &amp; MSH2:</strong> Colonoscopy every 1-2 y beginning at age 20-25 (or 2-5 years younger than earliest diagnosis if &lt;25)<strong>&lt;br&gt;</strong>&lt;br&gt;<strong>MSH6 &amp; PMS2:</strong> Colonoscopy every 1-2 y beginning at age 30-35 (or 2-5 years younger than earliest diagnosis if &lt;25)</td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td><strong>Education regarding symptoms</strong>&lt;br&gt;<strong>Consideration of hysterectomy after childbearing</strong>&lt;br&gt;<strong>Endometrial biopsy every 1-2 y beginning at age 30-35 can be considered</strong></td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td><strong>Education regarding symptoms</strong>&lt;br&gt;<strong>TVUS and CA-125 surveillance could be considered by no evidence of efficacy</strong>&lt;br&gt;<strong>BSO can be considered after childbearing</strong></td>
</tr>
<tr>
<td>Gastric &amp; Small Bowel Cancer</td>
<td><strong>Risk factors:</strong> male sex, older age, MLH1 or MSH2 pathogenic variants, FDR with gastric cancer, Asian ethnicity, chronic autoimmune gastritis, gastric intestinal metaplasia and gastric adenomas.&lt;br&gt;<strong>Consider EGD with random biopsy of the proximal and distal stomach for H.pylori, autoimmune gastritis, and intestinal metaplasia beginning at age 40 and surveillance EGD every 3-5 y in those with the above risk factors.</strong></td>
</tr>
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## Lynch Syndrome Surveillance Options

**NCCN v1.2020**

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<td><strong>Urothelial cancer</strong></td>
<td>No clear evidence to support. Consider in select individuals with a family history of urothelial cancer and individuals with <em>MSH2</em> pathogenic variants (especially males). Annual urinalysis starting at age 30-35</td>
</tr>
<tr>
<td><strong>Pancreatic Cancer</strong></td>
<td>Consider pancreatic cancer screening beginning at age 50 or 10 years younger than the earliest dx in family. Annual contrast-enhanced MRI/MRCP and/or EUS with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. Most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any intervention.</td>
</tr>
<tr>
<td><strong>Prostate Cancer</strong></td>
<td>General population screening</td>
</tr>
<tr>
<td><strong>Breast Cancer</strong></td>
<td>General population screening</td>
</tr>
<tr>
<td><strong>Brain Cancer</strong></td>
<td>Annual physical/neurologic examination starting at age 25-30y</td>
</tr>
<tr>
<td><strong>Reproductive Risks</strong></td>
<td>Advise about prenatal diagnosis and assisted reproduction including preimplantation genetic testing. Advise about risk of rare recessive syndrome called CMMR deficiency if both partners are carriers of pathogenic variants in the same MMR gene</td>
</tr>
</tbody>
</table>
Aspirin as chemoprevention for CRC

- Numerous studies have demonstrated benefit of aspirin and COX-2 inhibition in adenoma and CRC prevention
  - USPSTF recommends ASA 81mg for adults age 50-59 for primary CRC prevention (and CV disease prevention)
- CaPP2 study
  - Patients with Lynch syndrome randomized 2x2 factorial to ASA 600 mg/day and resistant starch (or placebo)
  - Early adenoma outcomes = no difference
  - At >4 years follow-up, those who took ASA for at least 2 years experienced reduction in CRC (Incidence rate ratio/IRR 0.37) and non-CRC LS cancers (IRR 0.49)
- Expert groups have awaited follow-up confirmatory studies before endorsing these data (CaPP3)
  - Also concern for toxicities associated with this dose of ASA


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GINA

- Prevents **health insurers** from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information.
  - Group and self-insured policies

- Insurers may not request that an individual undergo a genetic test.

- **Employers** cannot use genetic information to make hiring, firing, compensation, or promotion decisions.

- Sharply limits a health insurer's or employer's right to request, require, or purchase someone's genetic information.
Take Home Messages

- All cancer is genetic, but NOT all cancer is hereditary (inherited)

- In risk assessment:
  - Age at dx more important than # of cases
  - Ancestry critical
  - More rare tumors (ov ca) make a bigger impact to risk

- Identification of high risk families allows for:
  - proper cancer screening
  - education about testing options
A CANCER-FREE WORLD BEGINS HERE