Genetic Risk Assessment for Cancer
Jennifer Siettmann, MS CGC
Certified Genetic Counselor/Cancer Risk Counselor
Banner Good Samaritan Cancer Screening & Prevention Program

Banner University Medical Center Phoenix
Objectives

• Describe the role of genetic counseling and genetic testing in patient care
• List indications for referral for hereditary cancer genetic testing
• Describe features of common hereditary cancer syndromes
• Describe the genetic testing process and new testing advancements
Genetic Predisposition Testing is a Multistep Process

1. Identify at-risk patients
2. Provide pretest counseling
3. Provide informed consent
4. Select and offer test
5. Disclose results
6. Provide post-test counseling and follow-up

Banner University Medical Center Phoenix
Who is at High Risk for Hereditary Cancer?

- Hereditary cancers account for only a small portion of all cancer.
  - Only about 5-10%
- Important to elicit cancer family history to determine who might be at risk
  - Personal history of cancer
  - Family history of cancer
Distribution of Cancer

- **Hereditary**
  - Gene mutation is inherited in family
  - Significantly increased cancer risk

- **Familial**
  - Multiple genes & environmental factors may be involved
  - Some increase in cancer risk

- **Sporadic**
  - Cancer occurs by chance or related to environmental factors
  - General population cancer risk

Banner University Medical Center Phoenix
When to Expect a Hereditary Cancer Syndrome

- Cancer in two or more close relatives (on same side of family)
- Early age at diagnosis (<50)
- Multiple primary tumors in the same individual
- Bilaterality or multiple rare cancers
- Pattern of tumors consistent with specific cancer syndrome (e.g. breast and ovary)
- Evidence of autosomal dominant transmission
  - Multiple affected generations
- Presence of congenital anomalies or syndrome-associated benign lesions
Suspicious Genetic Cancers

Andrea Forman, Fox Chase Cancer Center
Rare Tumors That Warrant Genetic Evaluation

- Adrenocortical Carcinoma ($Tp53$)
- Carcinoid Tumors (specifically thymic gland) ($MEN1$)
- Diffuse Gastric Cancer ($CDH1$)
- Fallopian Tube/Primary Peritoneal Cancer ($BRCA1/BRCA2$)
- Leiomyosarcoma ($FH$)
- Medullary Thyroid Cancer ($RET$)
- Paraganglioma ($SDHA, SDHB, SDHC, SDHD, SDHAF2$)
- Pheochromocytoma ($SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, RET, NF1$)
- Chromophobe or Oncocytic Renal Cell Cancer ($FLCN$)
- Sebaceous Neoplasms/Carcinomas ($MLH1, MSH2, MSH6, PMS2, EPCAM$)
- Sex Cord Tumors with Annular Tubules ($STK11$)

*Banks, et al. 10 Rare Tumors that Warrant a Genetics Referral. Fam Cancer. Epub 2012, Nov 28.*
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoblastoma</td>
<td><em>RB1</em></td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td><em>P53</em></td>
<td>Breast, brain, bone</td>
</tr>
<tr>
<td>FAP</td>
<td><em>APC</em></td>
<td>Polyps, colon, thyroid</td>
</tr>
<tr>
<td>Lynch</td>
<td><em>MLH1, MSH2, MSH6, PMS2</em></td>
<td>Colon, uterine, ovarian, GI</td>
</tr>
<tr>
<td>Breast and Ovarian</td>
<td><em>BRCA1 and BRCA2</em></td>
<td>Breast, ovarian</td>
</tr>
<tr>
<td>Von Hippel Lindau</td>
<td><em>VHL</em></td>
<td>Renal, pheo</td>
</tr>
<tr>
<td>Cowden</td>
<td><em>PTEN</em></td>
<td>Breast, uterine, thyroid</td>
</tr>
<tr>
<td>HDGC</td>
<td><em>CDH1</em></td>
<td>Diffuse gastric, lobular breast</td>
</tr>
<tr>
<td>MEN2/FMTC</td>
<td><em>RET</em></td>
<td>Thyroid</td>
</tr>
<tr>
<td>Hereditary Melanoma</td>
<td><em>CDKN2, CDK4</em></td>
<td>Melanoma</td>
</tr>
<tr>
<td>Hereditary PGL/PCC</td>
<td><em>SDHB, SDHD</em></td>
<td>Pheo, paraganglioma</td>
</tr>
</tbody>
</table>
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

• Caused by mutations in the \textit{BRCA1} and \textit{BRCA2} tumor suppressor genes

• Incidence: 1 in 4,000
  – 1 in 40 in Ashkenazi Jewish families

• Features:
  – Early onset breast cancer (under age 50)
  – Ovarian cancer
  – Bilateral breast cancer
  – Male breast cancer
  – Ashkenazi Jewish heritage
HBOC Lifetime Cancer Risks

Breast cancer: 50-85%
(often early age at onset)

Second primary breast cancer: 40-60%
(5%/yr vs. 1%/yr for sporadic BC)

Ovarian cancer: 15-45%

Absolute risk likely to be higher than 10%
*Prostate cancer
Absolute risk 10% or lower
*Male breast cancer
*Fallopian tube cancer
*Pancreatic cancer

Lynch Syndrome

- Caused by mutations in mismatch repair genes MLH1, MSH2, MSH6, and PMS2

- Features:
  - Early age of colon cancer diagnosis (~45 years)
  - Right-sided cancers
  - Cancers outside the colon:
    - Uterine/Endometrial
    - Ovarian
    - Stomach, small bowel, urinary tract, bile ducts, brain, pancreas
## Lynch Syndrome Lifetime Cancer Risks

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population</th>
<th>MLH1 and MSH2 Mutation</th>
<th>MSH6 Mutation</th>
<th>PMS2 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>40-80%</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>Stomach</td>
<td>&lt;1%</td>
<td>1-13%</td>
<td>&lt;=3%</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.6%</td>
<td>4-24%</td>
<td>1-11%</td>
<td></td>
</tr>
<tr>
<td>Bile Duct</td>
<td>&lt;1%</td>
<td>1.4-4%</td>
<td>Not reported</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</td>
<td>&lt;1%</td>
<td>3-6%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1-3%</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>
IHC Testing for Lynch Syndrome

MLHI

MSH2

MSH6

PMS2

Normal

Suspicious of Lynch
Genetic Predisposition Testing is a Multistep Process

- Identify at-risk patients
- Provide pretest counseling
- Provide informed consent
- Select and offer test
- Disclose results
- Provide post-test counseling and follow-up
Pretest Genetic Counseling

• Assess
  – Personal and family medical history
  – Risk perception and motivation for testing
• Educate
  – Basic genetics and inheritance
  – Cancer genetics and risk
• Discuss
  – Risks, benefits, and limitations of testing
  – Test procedure
  – Alternatives to testing
  – Management options

Pretest Genetic Counseling

• Anticipatory guidance
  – Cancer genetics professionals should walk the patient through “what if” scenarios

• Consideration of multiple motivations for testing
  – Why does the patient want to be tested?
  – What does he or she hope to accomplish?

• Informed consent discussion

Basic Genetics

Cell

Chromosomes
Each chromosome is composed of one large continuous DNA molecule.

Gene
A gene is a segment of DNA that encodes a protein product.

Protein
A protein is a complex organic compound composed of hundreds or thousands of amino acids.

DNA

Adenine
Thymine
Guanine
Cytosine

Banner University Medical Center
Phoenix
Inheritance: Typically Autosomal Dominant
Genetic Predisposition Testing is a Multistep Process

1. Identify at-risk patients
2. Provide pretest counseling
3. Provide informed consent
4. Select and offer test
5. Disclose results
6. Provide post-test counseling and follow-up
• Old method: test for one syndrome/gene, if negative, go on to next...

• New method: genetic testing panels
  – Test for multiple hereditary syndromes/genes at one time
  – Lower costs
  – Results can be much more difficult and confusing to interpret

• Options for cancer specific panels (i.e. breast vs colon vs gynecologic) and varying sizes within those panels

• The difficulty comes from knowing which panel to order for which patient’s history, how many genes we want to test, and what the clinical efficacy is of each of the genes on the panel
  – Some genes are high risk genes, whereas others are moderate risk genes
# Example of a Breast Cancer Panel

<table>
<thead>
<tr>
<th>Genes</th>
<th>High Risk Genes</th>
<th>Moderate Risk Genes</th>
<th>Newer Moderate Risk Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>BRCA1, BRCA2, CDH1, PTEN, STK11, TP53</em></td>
<td><em>ATM, CHEK2, PALB2, NF1</em></td>
<td><em>BARD1, BRIP1, MRE11A, MUTYH, NBN, RAD50, RAD51C, RAD51D</em></td>
</tr>
<tr>
<td>Lifetime Breast Cancer Risk</td>
<td>50-85%</td>
<td>20-50%</td>
<td>20-40% (not well defined)</td>
</tr>
</tbody>
</table>
Genetic Predisposition Testing is a Multistep Process

- Identify at-risk patients
- Provide pretest counseling
- Provide informed consent
- Select and offer test
- Disclose results
- Provide post-test counseling and follow-up
Understanding Possible Test Results

- **Positive Result**
  - Known Family Mutation
  - No Known Family Mutation
  - Variant of Uncertain Significance

- **Negative Result**
  - Increased Cancer Risk
  - No Increased Cancer Risk
  - Cancer Risk Not Fully Defined

- **Unknown Cancer Risk**
High-Risk Clinical Management

Cancer Detection & Risk Reduction Options

- Notifying at-risk relatives
- Lifestyle Changes
- Increased Surveillance
- Chemoprevention
- Risk Reduction Surgery
Cost and Insurance

• Average test costs between $1500 to $4400 (depending on the panel and the lab)
• Insurance coverage pretty good if patient meets National Comprehensive Cancer Network (NCCN) guidelines
• Each insurance carrier has their own criteria, some are publicly available (Aetna, UHC, Medicare, BC/BS) some are not (Medicaid, Banner)
• Coverage of panel testing has been reliable so far so long as the patient meets criteria for Lynch or BRCA testing
In 2008, a federal law called the Genetic Information Nondiscrimination Act (GINA) was passed – Prevents health insurance and employers from discriminating based on genetic test results – Doesn’t apply to life insurance or long-term disability – Doesn’t apply to the military

Quick Guide to GINA

What GINA does
Prohibits group and individual health insurers from using a person’s genetic information in determining eligibility or premiums
Prohibits an insurer from requesting or requiring that a person undergo a genetic test
Prohibits employers from using a person’s genetic information in making employment decisions such as hiring, firing, job assignments, or any other terms of employment
Prohibits employers from requesting, requiring, or purchasing genetic information about persons or their family members
Will be enforced by the Department of Health and Human Services, the Department of Labor, and the Department of Treasury, along with the Equal Opportunity Employment Commission; remedies for violations include corrective action and monetary penalties

What GINA does not do
Does not prevent health care providers from recommending genetic tests to their patients
Does not mandate coverage for any particular test or treatment
Does not prohibit medical underwriting based on current health status
Does not cover life, disability, or long-term care insurance
Does not apply to members of the military

Key terms
“Genetic information” includes information about:
- A person’s genetic tests
- Genetic tests of a person’s family members (up to and including fourth-degree relatives)
- Any manifestation of a disease or disorder in a family member
- Participation of a person or family member in research that includes genetic testing, counseling, or education
“Genetic tests” refers to tests that assess genotypes, mutations, or chromosomal changes

Examples of protected tests are:
- Tests for BRCA1/BRCA2 (breast cancer) or HNPPC (colon cancer) mutations
- Classifications of genetic properties of an existing tumor to help determine therapy
- Tests for Huntington’s disease mutations
- Carrier screening for disorders such as cystic fibrosis, sickle cell anemia, spinal muscular atrophy, and the fragile X syndrome
- Routine tests such as complete blood counts, cholesterol tests, and liver function tests are not protected under GINA
Case Example 1: KM

• KM breast cancer @ 47
  – Mother: Br.Ca @ 28
    Died of Ov. Ca. @ 37
  – Maternal Aunt: Br. Ca @ 50
  – Maternal Aunt: Br. Ca. @ 58
  – Maternal Grandma: Br. Ca died in 50s
  – Father: Lung Ca @ 73

• European descent both sides
Case 1: KM Test Results and Plan

• **Test Result:** Positive for a *BRCA2* mutation
  – Up to 85% risk for breast cancer
    • 60% Risk for second primary
  – Up to 40% risk for ovarian/fallopian tube cancer
  – 6% risk for Male breast cancer

• **Prevention Method**
  – Bilateral salpingo-oophorectomy
  – Bilateral mastectomy

• **Family Prevention**
  – Offer testing and high risk prevention options to all close family members
Case Example 2: PA

• PA is a 65 y.o. woman diagnosed with uterine cancer @ 61 and bladder cancer @ 65
  – Sister: pancreatic @ 64
  – Mom: colon @ 56
  – Maternal aunt: colon @ 89
  – Maternal aunt: ovarian
  – Maternal cousin: colon in 40s
• European descent on both sides
Case 2: PA Test Results and Plan

- Ordered a panel for 32 cancer genes
- Test Result
  - Positive for a *MSH6* mutation
    - Up to 22% risk for colon cancer
    - Up to 26% risk for uterine cancer
    - Up to 11% risk for ovarian cancer
    - Increased risk for stomach, urinary tract, and possibly breast cancers
  - Variant of uncertain significance (VUS) in *NBN*
    - True mutations associated with moderately increased risk for breast and ovarian cancer
- Prevention Method:
  - Colonoscopy every 1-2 years beginning age 25-30
  - Patient already had hysterectomy and bilateral salpingo-oophorectomy
  - No screening is recommended for the *NBN* VUS as it is an inconclusive result and we cannot make recommendations for an inconclusive result
- Family Prevention:
  - Offer testing and high risk prevention options to all close family members
Case Example 3: BB

- BB diagnosed with breast cancer @ 49
  - Mother: breast @ 76
  - Maternal aunt: breast @ 44
  - 2 maternal uncles: brain @ 56 and 64
  - Paternal aunt: breast
  - Paternal cousin: breast @ 44
  - Paternal grandma: breast @ 31

- European descent on both sides
Case 3: CD Test Results and Plan

• Ordered a panel for 17 breast cancer genes

  **Test Result:**
  - Positive for a *Tp53* mutation, responsible for Li Fraumeni Syndrome
    • 50% risk for any type of cancer by age 40
    • 90% risk for any type of cancer by age 60

![Tumor Types Bar Chart]

- **Breast**, 24%
- **Bone**, 12.6%
- **Brain**, 12%
- **Sarcoma**, 11.6%
- **GI**, 7%
- **Gynecologic**, 5.3%
- **Hematologic**, 4.2%
- **Adrenal**, 3.6%
- **Other**, 14.1%
### Prevention Method

<table>
<thead>
<tr>
<th>Cancer</th>
<th>0-1 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td>Biannual physical exam (neurological, thyroid)</td>
</tr>
<tr>
<td></td>
<td>Avoid radiation treatment when possible</td>
</tr>
<tr>
<td><strong>Adrenocortical and Sarcoma</strong></td>
<td>Annual Testosterone levels</td>
</tr>
<tr>
<td></td>
<td>Annual WB-MRI*</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td>Annual brain MRI*</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td>Annual CBC, Erythrocyte labs</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td>Annual dermatologic exam</td>
</tr>
<tr>
<td><strong>Breast (begin at 25)</strong></td>
<td>Biannual clinical breast exam</td>
</tr>
<tr>
<td></td>
<td>Annual MRI and mammogram</td>
</tr>
<tr>
<td></td>
<td>Consider prophylactic mastectomy</td>
</tr>
<tr>
<td><strong>Colon (begin at 25)</strong></td>
<td>Colonoscopy and upper endoscopy every 2-5 years</td>
</tr>
<tr>
<td><strong>Ovarian (begin at 35)</strong></td>
<td>Biannual CA-125 and transvaginal U/S</td>
</tr>
<tr>
<td></td>
<td>Consider removing ovaries and uterus</td>
</tr>
</tbody>
</table>