CANCER GENETIC COUNSELING

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- No conflicts of interest to report
LEARNING OBJECTIVES

- Differentiate between sporadic, familial, and hereditary cancer and review genetics basics
- Review examples of hereditary cancer susceptibility syndromes
- Discuss pros and cons of multigene panels
- Explore the role of cancer genetic counselors
CANCER CATEGORIES
CANCER CATEGORIES

- Sporadic: 60-75%
- Familial: 20-30%
- Hereditary: 5-10%
SPORADIC CANCER

- Few family members with cancer
- Later age of onset
- Chance
- Environmental factors
FAMILIAL CANCER

- > 1 individual on the same side of the family with same type of cancer
- Typically later ages of onset
- Shared genes and environment

![Family Tree Diagram]

Br ca dx 63
Br ca dx 71
Br ca 73
HEREDITARY CANCER RED FLAGS

- Cancer at early ages
- Multiple primary cancers in one person
- Multiple cases of same or related cancers on the same side of the family
- Rare cancers
- Ethnic Background
CANCER GENETICS BASICS
TUMOR SUPPRESSOR GENES

Tumor Suppressor Gene(s)

PROTECTION AGAINST TUMOR DEVELOPMENT

Tumor Suppressor Gene(s) w/ mutation(s)

DECREASED PROTECTION AGAINST TUMOR DEVELOPMENT
Most hereditary cancer susceptibility syndromes are autosomal dominant.

Some syndromes have significant de novo mutation rate.

So lack of suspicious family history does not rule out condition.

Autosomal recessive conditions: MUTYH-associated polyposis (MAP), CMMR-D, Fanconi Anemia.
HEREDITARY CANCER SUSCEPTIBILITY SYNDROME EXAMPLES
HEREDITARY BREAST AND OVARIAN CANCER RED FLAGS

- Early-onset breast cancer (< 50 yo)
- Triple negative breast ca, especially < 60 yo
- Multiple breast cancer cases in family
- Invasive ovarian cancer
- Other assoc ca: pancreatic, prostate, melanoma
- Multiple primary HBOC-associated cancers in individual
- Male Breast Cancer
- Ashkenazi Jewish ancestry and HBOC

- Caused by mutations in BRCA1/2
<table>
<thead>
<tr>
<th>Cancer</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Gen. Pop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>46-63%</td>
<td>38-53%</td>
<td>12%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>34-44%</td>
<td>12-20%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>increased</td>
<td>20-30%</td>
<td>16%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>increased</td>
<td>7%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3-4%</td>
<td>2-5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>not increased</td>
<td>increased</td>
<td>2%</td>
</tr>
</tbody>
</table>

HBOC

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- BRCA
- Ovarian Ca
- BRCA2+
- HBOC
- BRCA2+
• Core cancers
  • Sarcomas of bone and soft tissue
  • Premenopausal breast cancer (can be very early onset)
  • Brain tumors
  • Adrenocortical carcinoma

• Non-core cancers – colon, uterine, esophageal, gonadal germ cell, leukemia and lymphoma, lung, melanoma, neuroblastoma, ovarian, pancreatic, prostate, gastric, thyroid, renal

• Caused by mutations in TP53 (p53) gene

• NCCN: TP53 testing should be considered for women diagnosed with breast cancer ≤ age 35, especially after negative BRCA testing

(Schneider, 2013)
• High risk of early-onset cancer
  • Risk of cancer ~50% by age 30, 90% by age 60 (~100% for women)
  • 0-10 yrs: soft tissue sarcomas, brain tumors, ACC
  • 11-20 yrs: bone sarcomas
  • >20 years: breast cancer, brain tumors

• Multiple primaries
  • Approximately 57% risk of second cancer
  • Approximately 38% risk for third cancer
  • 4th primaries have been reported
  • Survivors of childhood cancers at highest risk, likely related to treatment of previous cancers

(Schneider, 2013)
CHOMPRET LFS TESTING CRITERIA

• Any individual who has:
  • A tumor belonging to the LFS tumor spectrum before age 46 AND
  • At least one FDR or SDR with an LFS tumor (except breast if first individual has breast cancer) before age 56 or with multiple tumors; OR
  • An Individual with multiple tumors (except multiple breast tumors), 2 of which belong to LFS tumor spectrum, and the first of which occurred before age 46 years; OR
  • An individual who is diagnosed with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history
LYNCH SYNDROME

- Early-onset Lynch-associated cancers (< 50 yo)
- Multiple cases of CRC on the same side of the family
- Combination of related cancers in family
  - CRC
  - Endometrial, Ovarian
  - Gastric, Small Bowel
  - Renal, Urinary Tract
  - Brain
- Two primary cancers
- Rare: sebaceous adenomas/ carcinomas
- Caused by mutations in MMR genes: MLH1, MSH2, MSH6, PMS2, and EPCAM
LYNCH SYNDROME

AMSTERDAM II CRITERIA FOR CLINICAL DIAGNOSIS

- ≥ 3 family members (one of whom is a FDR of the other two) with Lynch-related cancers
- 2 successive affected generations
- ≥ 1 of the Lynch-related cancers diagnosed < 50 yo
- Exclusion of FAP

BETHESDA GUIDELINES FOR TUMOR TESTING

- CRC < 50 yo
- Presence of synch/metachronous Lynch-related cancers
- CRC with MSI-H histology and < 60 yo
- CRC and ≥1 FDR with Lynch-related cancer (one cancers < 50 yo)
- CRC and ≥2 FDRs or SDRs with Lynch-associated cancers regardless of age
<table>
<thead>
<tr>
<th>Cancer</th>
<th>MLH1/MSH2 Risk</th>
<th>MSH6 Risk</th>
<th>PMS2 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>40-80%</td>
<td>10-22%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>25-60%</td>
<td>16-26%</td>
<td>15%</td>
</tr>
<tr>
<td>Stomach</td>
<td>1-13%</td>
<td>&lt; 3%</td>
<td>*</td>
</tr>
<tr>
<td>Ovary</td>
<td>4-24%</td>
<td>1-11%</td>
<td>*</td>
</tr>
<tr>
<td>Hepatobil. tract</td>
<td>1-4%</td>
<td>Not reported</td>
<td>*</td>
</tr>
<tr>
<td>Urin. tract</td>
<td>1-4%</td>
<td>&lt;1%</td>
<td>*</td>
</tr>
<tr>
<td>Small bowel</td>
<td>3-6%</td>
<td>Not reported</td>
<td>*</td>
</tr>
<tr>
<td>CNS</td>
<td>1-3%</td>
<td>Not reported</td>
<td>*</td>
</tr>
<tr>
<td>Sebac. Neop.</td>
<td>1-9%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1-6%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

* Combined risk 6%
LYNCH TUMOR TESTING

- NCCN guidelines recommend colorectal tumor (MSI/IHC) testing:
  - Universal colorectal tumor testing OR
  - Testing for all individuals < 70 and those > 70 that meet Bethesda guidelines

- Tumor Testing Methods:
  - Microsatellite Instability (MSI)
    - MSI-High
  - Immunohistochemistry (IHC)
    - MMR deficient (which protein[s] missing can guide molecular testing)
  - BRAF
    - BRAF Negative
  - MLH1 Promoter Methylation
    - Negative for methylation
d. 65
CRC dx 48

CRC dx 51
Endo ca
dx 52
MLH1+

MLH1-

MLH1+

MLH1-

MLH1+
Biallelic MMR mutations cause CMMR-D, an AR syndrome with childhood onset

- Hematologic cancers (~30%)
- Brain tumors (~50%)
- GI cancers (~50% risk)
- GI polyps (~30% with 10 or more)
- Café-au-lait macules
- Lynch-associated cancers can be seen
- 40% risk of second primary cancers
FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

- 100s-1000s of adenomatous colon polyps
- Multiple cases of polyposis/CRC in family, especially at early ages
- Combination of polyposis and related cancers in family
  - CRC, small bowel
  - Pancreatic
  - Thyroid
  - CNS
  - Liver, bile ducts
  - Gastric
- Two primary cancers
- Associated extracolonic findings (osteomas, dental anomalies, CHRPE, soft tissue tumors, desmoid tumors)
- Caused by mutations in APC gene
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Gen. Pop.</th>
<th>FAP</th>
<th>Avg. Age Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>~100%</td>
<td>39 yrs</td>
</tr>
<tr>
<td>Small bowel: duodenum or periampulla</td>
<td>&lt; 1%</td>
<td>4-12%</td>
<td>45-52 yrs</td>
</tr>
<tr>
<td>Small bowel: distal to duodenum</td>
<td>&lt; 1%</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt; 1%</td>
<td>~2%</td>
<td></td>
</tr>
<tr>
<td>Thyroid (often papillary)</td>
<td>&lt; 1%</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>CNS (medulloblastoma)</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
<td></td>
</tr>
<tr>
<td>Liver (hepatoblastoma)</td>
<td>&lt; 1%</td>
<td>1.6%</td>
<td>&lt; 5 yrs (hepatoblastoma)</td>
</tr>
<tr>
<td>Bile ducts</td>
<td>&lt; 1%</td>
<td>Low, but increased</td>
<td></td>
</tr>
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</table>
ATTENUATED FAP (AFAP)

- Adenomatous colon polyps (avg: 30)
- Multiple cases of polyposis in family
- Combination of polyposis and related cancers in family (same as FAP)
- Polyposis and AFAP-related cancer in one individual
- Associated extracolonic findings seen less frequently in AFAP

- Caused by mutations in APC gene, much lower detection rate than in FAP
CRC @ 44
Innumerable colon polyps
Gastric polyps

CRC @ 42
~300 polyps

APC-

APC+
COWDEN SYNDROME

- Associated cancers: breast, thyroid, endometrial, renal, colon, melanoma

- Multiple benign findings:
  - Characteristic skin findings
  - Macrocephaly (larger head circumference)
  - GI polyps
  - Thyroid lesions (ex: goiter, nodules)
  - Autism, ID

- Rare: Lhermitte Duclos dis. (brain lesion)

- Caused by mutations in the *PTEN* gene

(Eng, 2012)
# Cowden Cancer Risks

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>General Population</th>
<th>Cowden Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast</td>
<td>12%</td>
<td>50-85%</td>
</tr>
<tr>
<td>Male breast</td>
<td>&lt;1%</td>
<td>increased</td>
</tr>
<tr>
<td>Thyroid (non-med.)</td>
<td>1%</td>
<td>10-35%</td>
</tr>
<tr>
<td>Uterine</td>
<td>3%</td>
<td>10-28%</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>2%</td>
<td>34%</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Eng, 2012; NSGC CA SIG, 2013)
MULTIGENE PANELS
<table>
<thead>
<tr>
<th>High Risk Genes</th>
<th>Moderate Risk Genes</th>
<th>Newer Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2 (HBOC: breast, ovary, prostate, pancreatic)</td>
<td>ATM (breast, colon, pancreatic)</td>
<td>AXIN2 (breast, colon)</td>
</tr>
<tr>
<td>MLH1/MSH2/MSH6/PMS2/EPCAM (Lynch: colon, endometrial, ovary, etc.)</td>
<td>CHEK2 (breast, colon, prostate, ovary)</td>
<td>BARD1/BRIP1 (breast, ovary)</td>
</tr>
<tr>
<td>APC/MUTYH (FAP/MAP: colon, gastric, breast, etc.)</td>
<td>PALB2 (breast, ovary, pancreatic)</td>
<td>RAD51C/RAD51D (breast, ovary)</td>
</tr>
<tr>
<td>SMAD4/BMPR1A (JPS: colon, gastric, pancreatic)</td>
<td></td>
<td>CDK4 (breast, pancreatic, skin)</td>
</tr>
<tr>
<td>CDH1 (HDGC: breast, gastric, colon)</td>
<td></td>
<td>FANCC (breast, pancreatic)</td>
</tr>
<tr>
<td>PTEN (Cowden: breast, thyroid, endometrial)</td>
<td></td>
<td>NBN (breast, melanoma, NH-lymphoma, colon)</td>
</tr>
<tr>
<td>STK11 (PJS: colon, breast, pancreatic, gastric, etc.)</td>
<td></td>
<td>XRCC2 (breast, colon, pancreatic)</td>
</tr>
<tr>
<td>TP53 (LFS: breast, ovary, sarcoma, brain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A (FAMMM: melanoma, pancreatic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VHL (VHL: neuroendocrine, renal)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### BENEFITS

- More cost-effective and efficient if considering multiple syndromes. Insurance may only allow one genetic test per lifetime.
- May identify rarer genetic causes of cancer in an individual/family.
- May identify genetic causes in “non-textbook” cases of well known cancer syndromes.

### CHALLENGES

- More expensive than single gene testing.
- May identify mutation in gene for which there is limited info/guidance:
  - Tumor Spectrum
  - Cancer risk estimates
  - Management recommendations
- Inconclusive test results more likely.
GENETIC COUNSELING
Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- **Interpretation** of family and medical histories
- **Education** about inheritance, testing, management, prevention, resources and research
- **Counseling** to promote informed choices

(NSGC, 2006)
WHEN TO CONSIDER TESTING

- American Society of Clinical Oncology: “Genetic counseling and testing should be offered if…”
  - An individual has personal or family history features suggestive of cancer predisposition
  - The test can be adequately interpreted
  - The test will influence medical management

(ASCO, 2003)
GENETIC COUNSELING GOALS

- Contracting
- Risk assessment
- Education
- Informed consent
- Results
- Medical Management Recommendations
- Support
• Motivations—Patients often want to gain a better understanding of:
  • Personal cancer risks
  • Options and considerations for participation in genetic testing or research
  • Screening and cancer prevention
  • Implications/recommendations for family members

• What can we offer?
PT CONCERNS REGARDING TESTING

- Cost
- Timing/Impact on treatment
- Childbearing considerations
  - Age at hysterectomy/oophorectomy
  - Risk to current/future children
- Quality of life
  - Perceived cancer risk
  - Body image; self-esteem
  - Surgery impact on quality of life
  - Management of surgical menopause
- Discrimination
• Methods
  • Medical and family history analysis
  • Risk models

• Challenges
  • Limited information
  • Family structure
  • Variability
- Testing Options

- Informed Consent
  - Benefits
  - Limitations
  - Possible outcomes
  - Risks

- Result Interpretation

- Result Explanation
POSSIBLE RESULTS

- Positive
- Negative
  - True negative
  - Uninformative negative
    - Unaffected pt
    - Detection rate
- Variant of Uncertain Significance (VUS)
  - VUS
  - Favors polymorphism (suspected benign)
  - Suspected deleterious
NEG RESULT INTERPRETATION

Diagnosis

- BRCA-
- Br ca dx 67
- Br dx 45
- d. 25 MVA
- d. 65
- Br ca dx 67
- d. 80
NEG RESULT INTERPRETATION

- Br ca dx 67
- MVA d.25
- BRCA -
- Br dx 45
- d.80
- d.65
NEG RESULT INTERPRETATION

- BRCA +
  - Br dx 45
  - BRCA -
  - Br ca dx 67

- MVA
  - d. 25

- BRCA +
  - d. 80

- BRCA -
  - d. 65
Recommendations for patient and family

- NCCN guidelines if exist
- Customize based on studies and medical/family history otherwise
- Take limitations into account (insurance coverage, location, etc.)
• Facilitate decision-making
  • Discuss how each test option and potential results might affect patient
  • Identify what is most important to patient
  • Listen to concerns and help them come to a decision

• Psychosocial counseling

• Provide support/resources
TELEGENETICS

- Patients complete medical/family history intake paperwork
- GC forwards test kits/packaging materials to referring provider
- **Patient has session through GoToMeeting with GC**
- Samples taken at cancer center with results coming to both referring provider and GC. Lab performs insurance preverification.
- GC forwards clinic note to referring provider and patient
- GC calls patient with test results and recommendations and forwards result letter to patient and referring provider
- Allows patients access to genetic counseling without cost/time of travel
- Can see patients for any cancer genetics indication

- **Multidisciplinary Gyn onc/Genetics Telemedicine Clinic to come!**
TAKE HOME MESSAGE

- 5-10% of cancers are due to underlying hereditary cause
- 20-30% cancers are due to combination of genetic and environmental factors. Increased surveillance may still be appropriate!
- A genetic counselor can review medical and family histories to determine:
  - whether testing is appropriate
  - who the best person is to test in a family
  - what testing is indicated
  - how test results and family history may affect medical management for patient and family
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