Genetics in Oncology: Hereditary Cancer and Updates in Genetic Testing

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Objectives

- Understand the process of genetic counseling
- Identify patients appropriate for genetics referral
- Understand sporadic and hereditary cancer, as well as common syndromes
- Become familiar with guidelines for individuals with a hereditary cancer syndrome

What is a Genetic Counselor?

- A genetic counselor is a healthcare professional with specialized training in medical genetics and counseling.
- Master of Science in Genetic Counseling
- Board-certified by the American Board of Genetic Counseling
What is a Genetic Counselor?

• Hospitals, doctor’s offices
  – Pediatrics, prenatal, oncology, neurology, cardiology, etc.
• Genetic testing laboratories
• Research studies
• Public health
• Insurance companies
• Many other areas of health care

What is Genetic Counseling?

• Genetic counseling is a process to evaluate and understand a family’s risk of an inherited medical condition.
• Identify and inform patients of their genetic risks and their options for managing those risks.

Genetic Counseling is a Multistep Process
Genetic Counseling Process

- Personal health evaluation
  - Cancer pathology, age(s) of diagnosis
  - Non-cancerous clinical features
  - Screening history
- Family history evaluation
  - Full family structure (age of living and deceased)
  - Cancer history with details
  - Non-cancerous clinical features (polyps, etc)
  - Testing in family members

Genetic Counseling Process

- Personal risks of cancer based on personal and family history (risk assessment)
- Risk of hereditary syndrome in the family
- Cancer genetics concepts
- Appropriate genetic testing options
- Full informed consent prior to genetic testing
- Decision making/emotional support

Genetic Counseling Process

- Insurance authorization
- Patient direct contact for questions
- Results interpretation
  - Literature review
- Results disclosure to patient
Genetic Counseling Process

- Positive results (mutation identified)
- Review known risks and limited info
- Recommendations for surveillance/risk reduction (goal: early detection and prevention)
- Patient resources, references
- Family resources, references
- Research opportunities
- Annual follow-up

Which Patient Should See Genetics?

- Early-onset breast/colon cancer
- Multiple relatives on same side of family with same/related cancers
- More than one primary cancer in the same individual
- Rare type of cancer or tumor pathology
- Known genetic mutation in family
- Ethnicity associated with higher frequency of hereditary cancer syndrome

Which Patient Should See Genetics?

- Triple negative (ER-, PR-, HER2-) breast cancer ≥ 80 y
- From a population at increased risk
- Invasive ovarian cancer
- Male breast cancer
Which Patient Should See Genetics?

CRC in patient <50 y.o. Synchronous or metachronous CRC, or other LS-related cancer
CRC in patient with 1+ first-degree relative with LS-related cancer (one <50 y.o.)
CRC in patient with 2+ first- or second-degree relative with LS-related cancer

Challenges with current guidelines

• Complex
• NCCN familial/high risk guidelines specific to hereditary breast/ovarian and colon
• Specific to well-known hereditary cancer syndromes
  – Other hereditary types of cancer can include pancreatic, renal, thyroid, sarcomas, melanomas
• Limited direction regarding multigene panel testing
• Evidence-based vs clinical opinion decisions

Cancer Etiology

All cancer is genetic.

NOT ALL CANCER IS HEREDITARY

Hereditary cancer occurs when a genetic mutation was inherited from a parent increasing the risk of developing certain types of cancer
Cancer Etiology

- **Hereditary**
  - 5-10%

- **Familial**
  - 20-25%

- **Sporadic**
  - 70-75%

Cancer Etiology

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Cancer Etiology

• 25,000 genes
• Pairs: maternal and paternal copy for each
• Each gene encodes instructions for the cell to function and which traits to express

Cancer Etiology

• Tumor suppressor genes
• Proto-oncogenes
• DNA mismatch repair genes

What is a Mutation?

**MUTATION:** A CHANGE IN THE GENETIC CODE

Example: The hat is red.
Mutation type 1: The cat is red.
Mutation type 2: The hat is ___.

Cancer Etiology

- Tumor suppressor genes
  - Regulates cell division
  - Inhibits cell proliferation
  - Promotes apoptosis (programmed cell death)
  - Suppresses development of cancer
  - Absence can allow cancer to develop

Cancer Etiology: Sporadic

damage to genes are acquired within single cell

- 2 working copies
- 1 working copy
- 2 broken copies

Tumor Develops

Cancer Etiology

- Proto-oncogenes
  - Provide signals to regulate cell division and death
  - Can become altered by mutations → oncoproteins
    - ONCOGENES can cause a cell to divide in an unregulated manner
  - When altered, can contribute to cancer development
Cancer Etiology: Sporadic

Damage to genes are acquired within single cell

2 working copies → 1 working copy + 1 altered copy → Tumor Develops

Cancer Etiology

- DNA mismatch repair genes
  - Repair errors in DNA synthesis, ensures fidelity of genetic recombination, participates in initiating apoptosis in response to DNA damage
  - Maintain genomic stability
  - Failure to accomplish DNA mismatch repair may result in cancer development

Cancer Etiology: Sporadic

- Lung cancer
- Lymphoma
Cancer Etiology

Hereditary: 5-10%

Familial: 20-25%

Sporadic: 70-75%

Cancer
**Cancer Etiology: Hereditary**

HEREDITARY

- BRCA1, BRCA2
- MLH1, MSH2, MSH6, PMS2, EPCAM
- PTEN
- TP53
- CDH1
- STK11
- APC, MUTYH
- BMPR1A, SMAD4
- RET, MEN1
- CDKN2A

**Breast cancer**

- BRCA1, BRCA2: Hereditary Breast and Ovarian Cancer syndrome
  - Most common hereditary breast/ovarian cancer
  - Breast, ovarian, pancreatic, male breast, prostate
- PTEN: Cowden syndrome
  - Breast, uterine, thyroid
- TP53: Li Fraumeni syndrome
  - Breast, sarcomas, brain, adrenal cortical, colorectal, etc.
- CDH1: Hereditary Diffuse Gastric Cancer syndrome
  - Breast, diffuse gastric
Hereditary Cancer: Breast

- General Population: 12
- BRCA1, BRCA2: 45-87
- CDH1: 39-52
- PTEN: up to 50
- PALB2: 33-58
- TP53: Significantly Increased

HBOC Inheritance

- **BRCA1, BRCA2**: Tumor suppressor genes

**HEREDITARY CANCER**: one broken copy is inherited

- all cells
- 1 working copy
- 1 broken copy
- 2 broken copies
- Tumor Develops

HBOC Risks

- General Population
- With a BRCA1/2 gene mutation

- 12
- 2
- 1.1
- 1.5
- Increased

HBOC Management

• NCCN guidelines
• Breast cancer
  – High risk screening
    • 25 years: annual breast MRI
    • 30 years: annual breast MRI and mammogram
  – Prophylactic intervention
    • Prophylactic bilateral mastectomy
  – Annual screening no longer indicated
• Chemoprevention
  • Tamoxifen
  • Targeted therapies?

HBOC Management

• NCCN guidelines
• Ovarian cancer
  – Prophylactic intervention
    • 35-40 years: bilateral salpingo-oophorectomy
  – High risk screening
    • CA-125 and transvaginal ultrasound
    • May be considered in younger individuals
    • NOT A SUBSTITUTE FOR RRSO
  – Chemoprevention
    • Oral contraceptives
    • Targeted therapies?

HBOC Management

• NCCN guidelines
• Male breast cancer
  – 35 years: clinical breast exams
  – Limited evidence to support breast imaging
• Prostate cancer
  – 40 years: annual PSA (BRCA2)
• Pancreatic cancer
  – No specific screening guidelines exist
  – Can consider screening based on family history
Hereditary Cancer: Colorectal

- **MLH1, MSH2, MSH6, PMS2, EPCAM**: Lynch syndrome
  - Most common form of hereditary colorectal/uterine cancer
  - CRC, uterine, ovarian, gastric, small bowel, hepatobiliary, urinary tract, pancreatic, CNS

- **APC**: Familial Adenomatous Polyposis syndrome
  - 100-1,000s adenomatous colon polyps
  - >99% risk of CRC without intervention, thyroid, duodenal/periampullary, CNS

- **MUTYH**: MUTYH-associated Polyposis syndrome
  - Polyposis, CRC
  - Autosomal recessive

- **SMAD4, BMPR1A**: Juvenile Polyposis syndrome
  - CRC, gastrointestinal, pancreatic

**LS Inheritance**

- **MLH1, MSH2, MSH6, PMS2, EPCAM**: DNA mismatch repair

**HEREDITARY CANCER**: one broken copy is inherited

- All cells

- 1 working copy

- 1 broken copy

Tumor Develops
LS Risks

LS Management

- NCCN guidelines
- Colorectal cancer
  - 20-25 years: colonoscopy q. 1-2 years
  - Aspirin? Data not yet robust for standard use recommendations
- Uterine and ovarian cancers
  - After childbearing: hysterectomy and bilateral salpingo-oophorectomy
  - Data and evidence do not support screening for these cancers in women with LS

LS Management

- NCCN guidelines
- Gastric and small bowel cancers
  - No clear evidence to support screening
  - 30-35 years: consider EGD q. 3-5 years for select patients
- Urothelial cancer
  - 25-30 years: consider annual urinalysis
- Pancreatic cancer
  - No screening recommendation possible at this time
  - Consider screening based on family history
Management of Hereditary Cancers

TWO MAIN GOALS
1. Early detection
   - Earlier screenings
   - More frequent screenings
2. Prevention
   - Prophylactic surgery
   - Chemoprevention

Hereditary Cancer Gene Panel Testing

• Supreme Court overturns BRCA1/2 patent (June 13, 2013)

Your Genes Have Been Freed.

Hereditary Cancer Gene Panel Testing

• Supreme Court overturns BRCA1/2 patent (June 13, 2013)
  – Flood of commercial laboratories offering testing
• Next-generation sequencing technology
  – Simultaneous analysis of multiple genes (phenotype specific or pan-cancer)
  – Low cost
• Initially used for affected BRCA-negative
• Increasingly used as front-line testing
  – More than one gene could explain phenotype
**Hereditary Cancer Gene Panel Testing**

- Opportunity for more comprehensive hereditary cancer assessment
  - Mixed family cancer phenotype
  - Increased positive results yield
    - Increasing targeted treatment options
  - Re-testing patients who were previously single-gene negative

**Hereditary Cancer Gene Panel Testing**

- Time-efficiency
  - Surgical decision patients
- Cost-efficiency
- Decrease in testing fatigue

**Genetic Testing for Hereditary Cancer**

- **HEREDITARY 5-10%**
  - BRCA1, BRCA2
  - MLH1, MSH2, MSH6, PMS2, EPCAM
  - PTEN
  - TP53
  - CDH1
  - PALB2
  - CHEK2
  - ATM
  - STK11
  - APC, MUTYH
  - BMPR1A, SMAD4

- ALK, ATM, AKT1, BAP1, BARDO, BLM, BRR1, CASR, CDC73, CDK4, CDKN1B, CDKN1C, CEPPA, CHEK2, Dicer1, DKK1, EGR1, FH, FLCN, GATA2, GPC3, GREM1, HEDGE, HRAS, KIT, MAX, MET, MIF, NBN, NF1, NF2, PALB2, PDGFR, PHOX2B, POLO1, POLE, PRKAR1A, PTCH1, RAD50, RAD51C, RAD51D, RBL1, RECQ4, RET, RNF11, SDHA, SDHAF2, SDHAF4, SDHAF6, SDHAF7, SMARCD1, SMARCE1, TERT, TMEM127, TSC1, TSC2, VHL, WRN, WT1
Hereditary Cancer Gene Panel Testing

- Results interpretation uncertainty
  - Moderate penetrance and "limited evidence" genes
    • Degree of cancer risks, management
  - Variants of unknown significance
  - Incidental findings

"Other" Hereditary Breast Cancer Genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>HIGH RISK GENES</th>
<th>MODERATE RISK GENES</th>
<th>NEWLY DESCRIBED GENES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53</td>
<td>ATM, CHEK2, PALB2, NFI</td>
<td>BARD1, BHRP, MRE11A, MRE11B, NBN, RAD50, RAD51C, RAD51D</td>
</tr>
<tr>
<td>Lifetime Breast Cancer Risk</td>
<td>45-87%</td>
<td>20-58%</td>
<td>Increased, but not well defined</td>
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<tr>
<td>Medical Management</td>
<td>Established guidelines for screening and prevention</td>
<td>Limited screening and/or prevention guidelines, or guidelines not yet established</td>
<td>Screening and/or prevention guidelines not yet established; Management based on family history and estimated cancer risk</td>
</tr>
</tbody>
</table>

Hereditary Cancer Gene Panel Testing

- Consistency among providers offering genetic testing
- Insurance coverage and contracts
- Choice of laboratory and specific panel
  - Consensus of genes per cancer-panel
Hereditary Cancer Gene Panel Testing

- Choice of laboratory and specific panel

**Table 1** | Salk University Acute Leukemia Cytogenetics Panel Testing

<table>
<thead>
<tr>
<th>Test Company</th>
<th>Ambry Genetics</th>
<th>University of Washington Laboratory Medicine</th>
<th>Myriad Genetics</th>
<th>GeneDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of panel test</td>
<td>BRCAln</td>
<td>Breast/Prostate</td>
<td>BRCA2 Cancer risk panel</td>
<td>myRisk</td>
</tr>
<tr>
<td>Number of genes</td>
<td>8</td>
<td>18</td>
<td>51</td>
<td>21</td>
</tr>
<tr>
<td>Price</td>
<td>$1,000</td>
<td>$1,000</td>
<td>$1,200</td>
<td>$700</td>
</tr>
<tr>
<td>Interpretation time</td>
<td>3 weeks</td>
<td>6-10 weeks</td>
<td>12 weeks</td>
<td>3 weeks</td>
</tr>
</tbody>
</table>

For laboratories that offer a breast cancer-specific panel, the information is included. For laboratories that offer one common panel that includes hereditary breast cancer gene, the common panel is included. All labs listed report that they offer insurance certificates. Laboratories did not disclose cost of testing.

Genetic Counseling is a Multistep Process

- Provide risk assessment
- Identify hereditary risk patients
- Provide informed consent
- Select and offer test
- Discuss results
- Provide post-test counseling and follow-up
Pre-test Genetic Counseling

• Traditional cancer genetic counseling
  — Genetic education, specific gene risk, management recommendations, potential risks
• New approaches to genetic counseling and informed consent
  — Single syndrome → multi-gene
  — Tiered-binned counseling
  — Style/approach not necessarily consistent among practices or even genetic counselors

Pre-test Genetic Counseling

• Specific information for each gene not discussed
  — Tiered information: genes can identify risk
  — High-risk genes vs moderate penetrance
  — Provide patients with reading materials regarding the genes analyzed/risks associated
• Binned discussion of management
  — Breast, colorectal, gynecologic, etc.
  — Screening vs prophylactic surgery
  — Possible gene-specific discussion?

Pre-test Genetic Counseling

• Limitations of genetic testing
  — Uninformative results
  — Inconclusive results / variants of unknown significance
  — Incidental findings
• Risks of testing
  — Psychological / social risks
• More specific and comprehensive information discussed at results
• Testing is voluntary
Genetic Counseling is a Multistep Process

- Provide risk assessment
- Identify hereditary risk patients
- Provide informed consent
- Select an offer test
- Disclose results
- Provide post-test counseling and follow-up

Post-test Genetic Counseling

- Discussion of moderate-penetration genes
  - Risks and management
  - Recommendations for family members to test single-site?
- Discussion of incidental or unexpected high-penetration genes in families lacking features of syndrome

Post-test Genetic Counseling

- Resources for patients
  - Limited data → limited support resources
- PCP/oncologist/surgeon/etc. education for care
  - Prevent inappropriate screening (patient anxiety)
  - Prevent inappropriate ‘risk-reducing’ surgery
- Annual patient follow-up/updating
Hereditary Cancer Gene Panel Testing

NCCN Guidelines Version 2.2015 – Overview of multi-gene testing

“…multigene testing are ideally offered in the context of professional genetic expertise for pre- and post-test counseling”

Rainville and Rana (2014)

“Given the complexity of testing and results interpretation, we recommend testing in centers where genetic counseling is provided to enable family history assessment and where patients can be followed and managed over a long term”


“Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multi-gene panels that include genes of uncertain clinical utility and genes not suggested by the patient’s personal and/or family history”

Legislation on Genetic Discrimination

GINA

Prohibits employment and health insurance discrimination

Legal protection against discrimination based on genetic information

Case Presentations
BRCaplus: Analysis of 5 High-Risk Hereditary Breast Cancer Genes

**Panel Results**
- **CDH1**: Pathogenic Mutation: c.1078dupT

**Summary**
- **POSITIVE: Pathogenic Mutation Detected**

**Interpretation**
- This individual is heterozygous for the c.1078dupT pathogenic mutation in the CDH1 gene.
- This result is consistent with a diagnosis of hereditary diffuse gastric cancer (HDGC).

- **Cancer Risk estimates:**
  - Lifetime risk of 87.4% for diffuse gastric cancer and 34.8% for Hereditary Breast Cancer (females only)
  - The expression and severity of the individual cannot be predicted.

- Genetic counseling is recommended for all patients undergoing genetic testing.

No pathogenic mutations, variants of uncertain significance, or gene deletions or duplications were detected in the other genes analyzed. In total, 5 genes were analyzed as part of this panel: BRCA1, BRCA2, CDH1, PTEN, and TP53.

The c.1078dupT pathogenic mutation, located in coding exon 13 of the CDH1 gene, results from a duplication of 7T pyrimidines 191 bp downstream from the translational start site, yielding a 71 bp frameshift and a premature stop codon. Since homozygotes and hemizygotes inactivate the abnormal allele, the alteration is interpreted as a pathogenic variant (c.1078dupT). Recommendations for Standards for Interpretation and Reporting of Sequence Variants. Practice 2017. Genet Med 2017;19:940–926.
**BreastNext: Analysis of 15 Genes Associated with Hereditary Breast Cancer**

<table>
<thead>
<tr>
<th>PANEL RESULTS</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic Mutation</td>
<td>p.R273H</td>
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</table>

**SUMMARY**

**POSSIBLE PATHOGENIC MUTATION DETECTED**

- This result is associated with an increase in risk for breast cancer.

- Cancer Risk Estimate: Male breast cancer risk up to 30%.

- The expression and severity for this condition cannot be predicted.

- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

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No pathogenic variants, variants of unknown significance, or gene deletions or duplications were detected in the other genes evaluated. In total, 10 genes were analyzed as part of this panel: TP53, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MSH2, MSH6, PALB2, PTEN, RAD51C, RAD51D, STK11, and WAP.

The p.R273H pathogenic mutation also known as c.818G>A is located in coding exon 5 of the TP53 gene. The alteration results from a C to T substitution at nucleotide position 818. The original c.818G allele was replaced by an allele with the C t replacement at nucleotide position 818, resulting in an alteration of the encoded amino acid (R to H).

The TP53 gene is involved in the regulation of the cell cycle and apoptosis. Germline alterations in TP53 have been associated with hereditary breast cancer, especially in the context of Li-Fraumeni syndrome, which is characterized by a high risk of developing various types of cancer at an early age. The p.R273H mutation has been associated with an increased risk of breast cancer in several studies. For example, studies by Su et al. (2003) and Bosse et al. (2002) have highlighted the importance of this mutation in breast cancer susceptibility.

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**Beaumont**

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Summary
Positive result: Heterozygous Pathogenic variant identified in CDKN2A.

Clinical Summary
- A heterozygous, pathogenic variant, c.443-1G>A (p.Glu151Stop), was identified in CDKN2A.
- The CDKN2A gene is associated with autosomal-dominant cutaneous melanoma (OMIM: 168700).
- This result is consistent with a predisposition to, or diagnosis of, CDKN2A-related conditions.
- Hereditary cutaneous melanoma is characterized by multiple nevi that are a hereditary cancer syndrome that increases an individual's lifetime risk of developing cutaneous melanoma. CDKN2A sequence changes have also been associated with increased risk for pancreatic cancers, and some studies have reported increased incidence of breast cancer (PMIDs: 16864383, 16964381, 17549862, 17594932, 17989188, 20560463, 20560477). Individuals who are heterozygous for pathogenic variants in CDKN2A are uncommon, but have been reported in the literature (PMIDs: 16964381, 17989188). Individuals who are homozygous for pathogenic variants in CDKN2A are extremely rare, but have been reported in the literature (PMIDs: 168700) and are at high risk of developing cutaneous melanoma at a young age.
- It is likely that one copy of this pathogenic variant was inherited from each parent. All children of this individual have a 50% chance to inherit a pathogenic variant. More distant relatives may also be carriers. Testing for this variant is available.
OvaNext: Analyses of 22 Genes Associated with Hereditary Ovarian Cancer

| PANEL RESULTS | PALE1 | Pathogenic Mutation(s): p.Glu91

**SUMMARY**

**POSITIVE: Pathogenic Mutation Detected**

- This individual is heterozygous for the p.Glu91 pathogenic mutation in the PALE1 gene.
- Cancer Risk estimator: 23-50%. Increased risk for breast cancer (females only) and increased risk for pancreatic cancer risk.
- The expression and severity for this individual cannot be predicted.
- Genetic counseling is recommended for all individuals undergoing genetic testing.

No pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected in the other genes analyzed. In total, 21 genes were analyzed as part of this panel: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHK2, PALB2, PTEN, RAD51, RAD52, RAD54L, STK11, and TP53.

This p.Glu91 pathogenic mutation (also known as c.272G>A) is located in coding exon 3 of the PALE1 gene. Results from a 5' to 3' substitution at nucleotide position 190. This changes the amino acid from a glutamic acid to a stop codon within coding exon 3. This mutation has been identified in multiple families of ovarian and breast cancer patients. (Cancer Res. 2011 Mar;71(5):2225-30; Wang M, Breast Cancer Res. Treat. 2011 Jan;121(1):155-6; Jiang J, Hum Genet (2012 Mar;131(3):212-6; Tan LS, Breast Cancer Res. 2011:13(3):R87; Antoniou AC, N Engl J Med. 2014 Aug;371(7):697-704). Since premature ovarian failure may occur with this mutation, consideration for gonoroadenectomy for standards for interpretation and reporting of sequence variations. Revised 2007 - Consen Med. 2009 - 27(1).
Thank you

questions?

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Cancer Genetics Center
248-551-3388
www.cancer.beaumont.edu/genetics

References

- National Comprehensive Cancer Network Guidelines Version 2.2015; Genetic/Familial High-Risk Assessment: Breast and Ovarian
- National Comprehensive Cancer Network Guidelines Version 2.2015; Genetic/Familial High-Risk Assessment: Colorectal