What You Should Know About Genetic Testing: Healthcare Provider Update

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Associate Professor – Clinical Licensed Genetic Counselor

The James

Creating a cancer-free world. One person, one discovery at a time.
Disclosures

- No pertinent conflicts to disclose
Learning objectives

- Recognize common features of hereditary breast cancer syndromes
- Understand the current landscape of multi-gene panel testing
- Identify patients that could benefit from cancer genetic counseling and risk assessment
- Review ways to work with cancer genetics service providers
What is a genetic counselor?

- Healthcare professional with specialized training in molecular/clinical genetics and counseling
- Member of the healthcare team – can serve as a resource
- Interpret and provide clear and comprehensive information about gene-associated risks
- Ascertain the usefulness of genetic technologies for individual patients
Angelina Jolie Pitt: Diary of a Surgery

Angelina Jolie Pitt, 1945-1946

Los Angeles - Two years ago I made the decision to have a preventative double mastectomy. A simple blood test had revealed that I carried a mutation in the BRCA-1 gene, and gave me an estimated 85 percent risk of breast cancer and a 50 percent risk of ovarian cancer. I chose not to undergo prophylactic surgery after reviewing the available options and with the support of my family.

I wanted other women to know about the options. I wanted to help people understand the risk of breast and ovarian cancer, the results of genetic tests, the role of density, and the care of lymph nodes.

I have been sharing this story since then. It is a way to encourage women not to ignore the information, but to do what is right for them. My goal is to empower women physically and emotionally, helping them make the best decisions and navigate the challenges of treatment and recovery.
Let’s review...

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- Caused by mutations in \( BRCA1 \) or \( BRCA2 \)

**Classic features**

- Multiple cases of early onset breast cancer
- Ovarian cancer
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Male breast cancer
- Ashkenazi Jewish heritage
Cancer Risks Associated with HBOC

- Increased risk of multiple tumor types
  - Breast cancer (females): 50-85%
  - Breast cancer (males): 6-9%
  - Ovarian cancer: 20-40%
  - Rare tumors: pancreatic, melanoma, prostate

- There are published management guidelines for early detection and risk reduction
Goal: Personalize plan for risk management

- Breast cancer early detection/risk reduction
  - Clinical breast exam every 6-12 months starting age 25
  - MRI age 25-29y
  - MRI and mammography 30-75y
  - Consider prophylactic mastectomy

- Ovarian cancer risk reduction
  - BSO age 35-40y (could delay with BRCA2)
    - Special pathology protocol

- Possible screening for pancreatic cancer and melanoma

NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian v.2.2016
Management implications: now and later

Now
- Surgical management – might consider contralateral mastectomy at the time of initial diagnosis
- Chemotherapy/clinical trials

Later
- Risk-reducing mastectomy
- Bilateral Salpingo Oophorectomy (BSO)
- Increased surveillance
Prophylactic surgery

- **Mastectomy**
  - Reduces breast cancer risk by 90-95%
  - Occult cancers have been detected
  - Many reconstruction options

- **Oophorectomy**
  - Reduces ovarian/peritoneal risk by 80%
    - Residual risk of peritoneal cancer risk post BSO is 1-6%
  - Remove ovaries and fallopian tubes (+/- uterus)
    - Pelvic washings
    - Serial sectioning
  - Occult cancers –studies report 5-10% (often in tubes)

Manchanda et al. BJOG. 2011 Jun;118(7):814-24
Finch et al. JCO. 2014 May;32(15):1547-54.
Oophorectomy and breast cancer risk

- Early studies showed risk reduction if performed prior to age 50
- Recent study showed no reduction in breast cancer risk
- Still no reliable screening so recommended regardless of impact on breast cancer risk
- Investigations looking at feasibility of salpingectomy

Domchek et al. JAMA. 2010;304(9):967-975
Heemskerk-Gerritsen et al. JNCI. 2015;107(5):1-9
Is additional genetic testing warranted?

- No one-size-fits-all answer
- Need to see the report!
  
  You need to know
  
  1. What testing was already performed?
     - Was it actually germline genetic testing or tumor testing?
     - Did the lab look for all types of mutations?
     - If it was germline testing, what genes were included?

  2. Will genetic testing help this patient and/or her family make informed decisions?
Germline vs. somatic?

- Germline genetic testing looks for inherited mutations (usually a blood/saliva test)
- Somatic genetic testing looks for mutations that occurred in the cancer cells (usually a tumor tissue test…but now there are “liquid biopsies!”)
- Sometimes these are confused in notes or via patient report – make no assumptions!
Did the lab look for all types of possible mutations in *BRCA1/2*?

Common for patients tested prior to 2006

**First genetic test**

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1</em> sequencing</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
<tr>
<td>5-site rearrangement panel</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
<tr>
<td><em>BRCA2</em> sequencing</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
</tbody>
</table>

**Possible result after re-test years later**

<table>
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<tr>
<th>Test Performed</th>
<th>Result</th>
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</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1</em> full gene rearrangement</td>
<td>del exons 21-24</td>
<td>Deleterious</td>
</tr>
<tr>
<td><em>BRCA2</em> full gene rearrangement</td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
</tbody>
</table>
Beyond \textit{BRCA1} and \textit{BRCA2}

- Since 2013, genetic testing has changed dramatically
- Next generation sequencing
  - Multigene panels
  - More labs and more options
- Some associated cancer risks are well-defined
- Very little known about risks associated with some gene mutations
  - Few have published management recommendations
What genes were included?

**GENES ANALYZED**

Unless otherwise noted sequencing and large rearrangement analyses were performed on the following genes:

APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM (large rearrangement only), MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53.

** Other genes not analyzed with this test may also be associated with cancer.

**Complete Results**

The following genes were evaluated for sequence changes and exonic deletions/duplications:

ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53

Results are negative unless otherwise indicated

Benign, Likely Benign, and silent and intronic variants with no evidence towards pathogenicity, are not included in this report but are available upon request.

Note: BROCA (HRv4, MH40) includes the following cancer susceptibility genes: ATM, ATR, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FAM175A, FANCM, GEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PIK3CA, PMS2, PPM1D, POLD1, POLE, PTEN, RAD51B, RAD51C, RAD51D, RBBP8, RINT1, SLX4, SMARCA4, TP53, XRCC2
Will multigene testing help patient?

- Somewhat controversial
  - Higher chance of uncertain variant result (VUS)
  - Possibility of “surprise” incidental finding
  - More genes is not always better
  - Management recommendations lacking in some instances

- But – you might positively impact patient and family
  - Same goal as BRCA testing: personalized risk assessment and risk reduction
17-gene French panel on 708 patients suspected to have HBOC

6.3% had mutations in other genes

109/708 (15.3%) had pathogenic mutations

9% had mutations in BRCA1 or BRCA2


Recommendations exist for mutations in some of the panel genes

- Breast MRI

- Discuss RRM

- Recommend/Consider RRSO

NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian v.2.2016
When to Order a Cancer Gene Panel

- Current NCCN recommendations:
  - When more than one syndrome suspected
    - Eg. Breast cancer under age 35 – Li-Fraumeni is in differential so use panel including TP53
  - When a person is negative for BRCA gene mutations but personal/family history still highly suggestive

- Pay careful attention to testing lab and offerings

- Ideally offered by person with genetics expertise in the context of pre- and post-test counseling

NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian v.2.2016
Variability in panel options – changing daily!

- Breast cancer panels (as of June 2016)
  - Prices range from $249 - $4,500
  - Number of genes included ranges from 2-51 (with options to customize)
  - Turn-around time ranges from 3-12 weeks

- We pay attention to
  - Variant reclassification programs
  - Mutation detection rates (including large rearrangements!)
  - Billing practices and financial assistance options
Informed consent for genetic testing

- Syndrome, genes to be tested, associated risks
- Possible results and implications (including VUS)
- Options to assess risk without testing
- Implications for family members – importance of sharing information
- Accuracy of testing
- Cost
- Psychological implications
- Genetic discrimination risks
- Confidentiality issues
- Future use
- Options and limitations of result-based management
- Importance of intra-familial sharing
- Follow up plan

Robson et al. JCO. August 2015 ePub
Components of informed consent and pretest education in clinical cancer genetics

<table>
<thead>
<tr>
<th>Table 1. Components of Informed Consent and Pretest Education in Clinical Cancer Genetics</th>
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<tbody>
<tr>
<td><strong>Traditional Pretest Counseling for Susceptibility Testing (purpose of testing)</strong></td>
</tr>
<tr>
<td>Information on specific genetic mutations or genomic variants being tested, including whether range of risk associated with variant will affect medical care</td>
</tr>
<tr>
<td><strong>Pretest Counseling for Multigene Panel Testing (same general components as traditional counseling, with the following special considerations)</strong></td>
</tr>
<tr>
<td>Discussion of specific genotypes because a variant may not be individually high-penetrant, evaluated alone, or be detected in breast-ovary, Lynch, hereditary breast-ovary, or other familial or personal history, uncertain clinical utility more generally</td>
</tr>
<tr>
<td>Implications of positive mutation confirmed to be deleterious, negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result</td>
</tr>
<tr>
<td>Possibility test will not be informative</td>
</tr>
<tr>
<td><strong>Pretest Education for Somatic Mutation Profiling With Potential for Incidental Findings</strong></td>
</tr>
<tr>
<td>Attention should be paid to variants of uncertain significance</td>
</tr>
<tr>
<td>Risk that children and/or other family members may have inherited genetic condition</td>
</tr>
<tr>
<td>Fees involved in testing and counseling for DTC testing, whether counselor is employed by testing company</td>
</tr>
<tr>
<td>Psychological implications of test results (benefits and risks)</td>
</tr>
<tr>
<td>Risks and protections against genetic discrimination by employers or insurers</td>
</tr>
<tr>
<td>Confidentiality issues, including DTC testing companies and policies related to privacy and data security</td>
</tr>
<tr>
<td>Possible use of DNA samples for future research</td>
</tr>
<tr>
<td>Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing</td>
</tr>
<tr>
<td>Importance of sharing genetic and genomic test results with at-risk relatives so they may benefit from this information</td>
</tr>
<tr>
<td>Plans for disclosing test results and providing follow-up</td>
</tr>
<tr>
<td>Abbreviation: DTC, direct to consumer.</td>
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</tbody>
</table>

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Multigene panels require emphasis during informed consent

- **VUS rate**
  - With single genes the rate is often 2-3% but can approach 50% with some panels
  - Should not change management or recommend predictive testing for family members for VUS

- **Possible reproductive risks for recessive disorders**
  - For instance, *BRCA2* or *FANCC* mutations could cause Fanconi Anemia if biallelic mutations

- **Possibility of “surprise” results**
  - A mutation was found that doesn’t explain breast cancer diagnosis but introduces new risk
May help clarify risk assessment

- Varying possibilities
  A) Family has HBOC and unaffected daughters have risk-associated mutation
  B) Family has HBOC and daughters are true negatives
  C) Family does not have HBOC and daughters have familial risk
  D) Moderate risk gene mutation in family – may affect risk
  E) Etc.
Questions always remain

- Pretest counseling helps anticipate uncertainty
  - VUS and incidental findings
- What about anxiety?
  - Different for each individual
  - Studies show mostly neutral/positive feelings
  - Some increase in anxiety right at the time of testing but a normalization after time
    - For positive and negative!

Aktan-Collan et al. IJC. August 2001:93(4)608-611
Lynch et al. Ca Gen and Cyto. March 2006:165(2)91-97
Genetic counseling ≠ Genetic testing

- Genetic testing is optional
- Important to ascertain patient motivations and reservations
  - Including psychological issues
- Reservations or motivations may reflect misconceptions
  - Helplessness – “it’s inevitable anyway”
  - “I only have sons – it can’t affect them”
  - “My daughters are being proactive with screening”
Finding the best testing option for the patient

- Once you determine which laboratories have a technically robust test/test process
  - Review options for billing
    - Insurance pay
    - Institutional billing
    - Self pay
  - Review patient’s insurance requirements for coverage of testing
    - Meet certain personal/family history criteria
    - Genetic counseling requirement
    - Determine if there are limitations to coverage based on test ordered (no panels?)
Financial Aid

- Laboratories often have financial assistance programs
  - Differ with regard to qualifications
    - Some for uninsured only
    - Some provide assistance to underinsured
    - Some provide discount for self-pay patients
  - Differ with regard to documentation requirements
  - Differ with regard to review process
Provision of cancer genetics services

- Multiple service delivery models
  - Genetics professional on-site
  - Collaborative agreement with a genetics professional
    - Telemedicine
    - Phone counseling
    - Consult agreement (as needed)

- Typically involves multidisciplinary collaborative approach
Accreditation standards

- **2014 NAPBC:**
  - Standard 2.16 Cancer risk assessment, genetic counseling and genetic testing services are provided or referred.

- **2016 CoC**
  - STANDARD 2.3 Genetic Counseling and Risk Assessment Cancer risk assessment, genetic counseling, and genetic testing services are provided to patients either on-site or by referral to a qualified genetics professional.

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2016 Commission on Cancer: Cancer Program Standards: Ensuring Patient-Centered Care
2014 National Accreditation Program for Breast Centers Program Standards
How to find genetics professionals

- NSGC website - www.findageneticcounselor.org
  - Can search for telemedicine services
- Consider collaboration!
- Set up a referral mechanism/consult routine
Resources

- NCCN: Genetic/Familial High-Risk Assessment: Breast and Ovarian 2016

- Living Beyond Breast Cancer: Guide to Understanding Genetics and Family Risk Assessment
THANK YOU

- Leigha.senter@osumc.edu
What You Should Know About Genetic Testing: Healthcare Provider Update
ACA & Coverage of Genetic Testing

Lisa Schlager
Vice President, Community Affairs & Public Policy
FORCE's Mission is: To improve the lives of individuals and families affected by hereditary breast, ovarian, and related cancers.
Patient Protection and Affordable Care Act (PPACA)

✧ Access to health insurance for all Americans
✧ Elimination of pre-existing conditions as barrier to coverage
✧ **Coverage for screening and preventative services without copay or deductible**
✧ Coverage of young adults up to the age of 26 on parent’s plan
✧ Abolishment of annual and lifetime caps
✧ Capping out-of-pocket healthcare expenditures
✧ Coverage for those enrolled in clinical trials
## PPACA, USPSTF and Detection/Prevention for High Risk Women

**U.S. Preventive Services Task Force**

### Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women

**Clinical Summary of U.S. Preventive Services Task Force Recommendation**

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic women who have not been diagnosed with BRCA-related cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Screen women whose family history may be associated with an increased risk for potentially harmful BRCA mutations. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.</td>
</tr>
<tr>
<td>Grade: B</td>
<td>Do not routinely recommend genetic counseling or BRCA testing to women whose family history is not associated with an increased risk for potentially harmful BRCA mutations.</td>
</tr>
<tr>
<td>Grade: D</td>
<td></td>
</tr>
</tbody>
</table>

### Treatment

Interventions in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy).
Genetic Testing Under PPACA

- Under PPACA, health insurers are required to pay for both genetic counseling and BRCA testing for women who meet certain personal or family medical history criteria.

- For these patients, insurance companies must cover the entire cost of genetic counseling and BRCA testing with no out-of-pocket costs to the individual.
  - Initially interpreted to apply only to women who have never had cancer (aka unaffected carriers or previvors).
  - 2015 - In response to advocacy efforts, CCIIO and DOL issued a clarification that the guidelines also apply to women who have been previously diagnosed with cancer but are not in treatment and are asymptomatic.
Current Gaps in Services for High-Risk Women

USPSTF Guidelines Do Not Address

✧ Increased screening and preventive options for high-risk women (other than chemoprevention for certain women)
✧ Genetic counseling and testing for cancer survivors currently in treatment
✧ Genetic counseling and testing for Lynch and other hereditary cancer syndromes - single gene or multigene panel
✧ Second genetic test for women who previously tested negative