Genetic Testing 101: Identifying High Risk Individuals
September 28, 2015
Webinar Objectives

• Understand how to identify individuals at increased risk for breast cancer

• Introduce some of the more common hereditary breast cancer syndromes

• Examine the different genetic tests available as well as ideal genetic testing strategies

• Explore management of women identified to be at high risk
Len Lichtenfeld, MD, MACP
American Cancer Society
Disclosure/Conflict of Interest

- I am an employee for GeneDx, Inc., a wholly-owned subsidiary of BioReference Laboratories, Inc., which is a wholly-owned subsidiary of OPKO Health Inc.
Breast Cancer – Risk Factors

- 1 in 8 (12%) women will develop breast cancer

  Not all risk is created equal

- Early age of menarche
- Late age at first child birth/nulliparity
- Breast density
- Breast biopsy history/atypia
- Lobular carcinoma in situ
- Family history
Breast Cancer – Sporadic vs. Hereditary

- Sporadic: 95%–90%
- Family clusters: 5%–10%
- Hereditary: 15%–20%

American Cancer Society
National Accreditation Program for Breast Centers
All Cancer Arises From Gene Mutations

**Germline mutations**
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

**Parent**
- Mutation in egg or sperm

**Child**
- All cells affected in offspring

**Somatic mutations**
- Occur in nongermline tissues
- Are nonheritable
- Sporadic cancer

**Somatic mutation** (e.g., breast)
Family History – Red Flags

- Early age of breast cancer onset (<45-50y)
- **Triple Negative** breast cancers (<60y)
- Multiple primary breast cancers
- Breast cancer & second non-breast primary cancer
- Many relatives affected; multiple generations
- Male breast cancer
- Breast cancer plus other cancers in the family (e.g. pancreas, ovarian, uterine, sarcomas)
- Ashkenazi Jewish (Eastern European) ancestry
Referral/Cancer Risk Assessment (CRA) Guidelines

- ACOG (Obstet Gynecol) – 2009
- ASBS – 2006
- NCCN (www.nccn.org) – yearly
- NSGC/ACMG (J Genet Counsel) – 2014
- SGO (Gyne Oncol) – 2014
- USPSTF (Ann Intern Med) – 2014 (2nd update)

The guidelines are recognized in the Affordable Care Act and pts who meet these guidelines should qualify for cancer risk assessment and genetic testing (BRCA1/2) at no cost.
Referral Guidelines - NCCN

NCCN Guidelines Version 2.2015
Breast and/or Ovarian Cancer Genetic Assessment

Criteria for Further Genetic Risk Evaluation

An individual with a personal history of cancer but with a family history of any of the following:

- A known mutation in a cancer susceptibility gene within the family
- Breast cancer
- Ovarian cancer
- A personal and/or family history of three or more of the following (especially if early onset): pancreatic cancer, prostate cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract, diffuse gastric cancer (can include multiple primary cancers in same individual)
- Male breast cancer

For populations at increased risk, requirements for inclusion may be modified (e.g., individuals of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Who Should Perform Cancer Risk Assessment

- **ACOG**
  - Conducted by a healthcare provider with expertise in cancer genetics

- **ASCO**
  - A qualified health professional

- **NCCN**
  - A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse or other health care professional with expertise and experience in cancer genetics

- **NSGC/ACMG**
  - Cancer genetics specialist
Family History Collection for CRA

- Using a questionnaire as a guide, an individual gathers detailed information on their personal/family history
  - Current ages
  - Ages at death
  - Causes of death
  - Site that cancer originated? (i.e. uterine vs ovarian cancer?)
  - Ethnicity
  - Other questions, depending on reason for referral
    - Have the women had hysterectomies?
    - Have the women been diagnosed with fibrocystic breast disease?
    - Skin biopsies – what was found?
Cancer Risk Assessment/Genetic Counseling

- Aid in information gathering
- Risk assessment
- Education
- Discuss the risks, benefits, and limitations to genetic testing
- Interpret genetic test results
- Determine screening and prevention options
- Facilitate decision making
- Identify resources for patients
Most Cancer Susceptibility Genes are **Dominant** with Incomplete Penetrance

- Penetrance is often incomplete
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene, not cancer (50% chance)
Causes of Hereditary Susceptibility to Breast Cancer

70-80%: BRCA1 and BRCA2

20-30%: Other High Risk Genes
Moderate Risk Genes
Newer Genes
Unknown Genes

Image: www.dailymail.co.uk
Increased risk of prostate, pancreas, CRC, uterine, melanoma (40%−85%)

Second primary breast cancer (40%-60%)

Ovarian cancer (10%−50%)

Male breast cancer (6%)

Increased risk of prostate, pancreas, CRC, uterine, melanoma

Hereditary Breast & Ovarian Cancer Syndrome (BRCA1/BRCA2)
BRCA1/2 Genetic Testing Criteria

NCCN Guidelines Version 2.2015
Hereditary Breast and/or Ovarian Cancer Syndrome

HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer + one or more of the following:
  - Diagnosed ≥45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary
    - ≥1 close blood relative with breast cancer at any age
    - ≥1 close relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - An unknown or limited family history
  - Diagnosed ≤60 y with a:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative with breast cancer diagnosed ≤50 y
    - ≥2 close blood relatives with breast cancer at any age
    - ≥1 close blood relative with invasive ovarian cancer
    - ≥2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - A close male blood relative with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required
    - Personal history of invasive ovarian cancer
    - Personal history of male breast cancer

- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative with breast (≤50 y) and/or invasive ovarian and/or pancreatic or prostate cancer (Gleason score ≥7) at any age

- Personal history of pancreatic cancer at any age with ≥1 close blood relative with breast (≤50 y) and/or invasive ovarian and/or pancreatic cancer at any age

- Personal history of pancreatic cancer, and Ashkenazi Jewish ancestry

- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative who has breast cancer and/or invasive ovarian cancer and who has ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or invasive ovarian cancer

See Follow-up (HBOC-2)

If HBOC testing criteria not met, consider testing for other hereditary syndromes

If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

For further details regarding the nuances of genetic counseling and testing, see BR/0V-A

For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

Close blood relatives include first-, second-, and third-degree relatives on same side of family.

Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial non-mucinous histology. Other cancer genetic syndromes may be associated with mucinous ovarian cancer. Non-epithelial ovarian cancer may be associated with FUP and possibly other cancer syndromes. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome, be attentive for clinical evidence of this syndrome. See NCCN Guidelines for Genetic Familial High-Risk Assessment: Colorectal.

Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other HBOC criteria are met. Founder mutations exist in other populations.
Li-Fraumeni Syndrome (TP53)

- Associated with germline mutations in TP53 gene
- Risk of cancer
  - 50% by age 40; 90% by age 60
- Cancer spectrum
  - Breast (most frequent cancer in women)
  - Osteosarcoma/sarcomas (except Ewing), adrenal cortical, hematologic, brain tumors, BAC lung cancers, many others
  - Childhood cancer risk
- Risk of multiple cancers
- Treatment Implications
  - Radiation treatment for cancers can increase the risk for second malignancies in the radiation field
**Li-Fraumeni Syndrome Testing Criteria**

- Individual from a family with a known TP53 mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:
  - Combination of an individual diagnosed age <45 y with a sarcoma
  - AND
  - A first-degree relative diagnosed age <45 y with cancer
  - AND
  - An additional first- or second-degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age
- Chompret criteria:
  - Individual with a tumor from LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age
  - OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years
  - OR
  - Individual with adrenocortical carcinoma or choroid plexus carcinoma at any age of onset, regardless of the family history
- Early-age-onset breast cancer:
  - Individual with breast cancer ≤35 y, TP53 testing can be ordered alone, concurrently with BRCA1/2 testing and/or other gene testing or as a follow-up test after negative BRCA1/2 testing

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For further details regarding the nuances of genetic counseling and testing, see the NCCN Guidelines Index.

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2. To date, there have been no reports of Ewing sarcoma, GIST, desmoid tumor, or osteosarcoma in families with Li-Fraumeni syndrome.
Cowden Syndrome (PTEN)

- Associated with mutations in PTEN
- Condition has both benign tumors/features as well as malignancy risk
- Cancer spectrum
  - Breast (25-50%, one study 80%)
  - Uterine, thyroid, melanoma, colon, renal cell
- Other features (not complete list)
  - Macrocephaly
  - Mucocutaneous lesions
    - trichilemmomas and oral papillomatosis
  - GI hamartomas/ganglioneuromas
  - Thyroid structural lesions
# Cowden Syndrome Testing Criteria

## NCCN Guidelines Version 2.2015
### Cowden Syndrome/PHTS

#### COWDEN SYNDROME/PTEN HAMARTOMA TUMOR SYNDROME TESTING CRITERIA

- Individual from a family with a known PTEN mutation
- Individual meeting clinical diagnostic criteria for CS/PHTS
- Individual with a personal history of:
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS) or
  - Adult Lhermitte-Duclos disease (cerebellar tumors) or
  - Autism spectrum disorder and macrocephaly or
  - Two or more biopsy-proven trichilemmomas or
  - Two or more major criteria (one must be macrocephaly) or
  - Three major criteria, without macrocephaly or
  - One major and ≥3 minor criteria or
  - ≥4 minor criteria

#### Minor criteria:
- Thyroid structural lesions (e.g., adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

#### Major criteria:
- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macroadenoma (megacystocele) (i.e., ≥97%, 68 cm in adult women, 60 cm in adult men)
- Macular pigmentation of glans penis
- Mucocutaneous lesions
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

#### Minor criteria:
- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthomas
- Lipomas
- Intellectual disability (i.e., IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer

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**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Hereditary Diffuse Gastric Cancer (CDH1)

- Associated with mutations in CDH1 (E-Cadherin)
- Hereditary Diffuse Gastric Cancer (HDGC)
  - 1-3% of all gastric cancers
- Clinical presentation
  - poorly differentiated adenocarcinoma in the stomach wall without tumor mass formation
  - Linitis plastica
  - Avg age of onset – 38y, lifetime risk thought to be upwards of 80%
- Breast Cancer Risk
  - 39-52% lifetime risk
  - most of the cancers are infiltrating lobular
PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

Criteria for Further Risk Evaluation for High-Risk Syndromes:*

- Referral to cancer genetics professional is recommended for an affected individual with one or more of the following:
  - A known mutation in a gastric cancer susceptibility gene within the family
  - Gastric cancer in one family member before age 40, or
  - Gastric cancer in 2 first-/second-degree relatives with one diagnosis before age 50, or
  - Gastric cancer in 3 first-/second-degree relatives independent of age, or
  - Gastric cancer and breast cancer in one patient with one diagnosis before age 50, or
  - Gastric cancer in one patient and breast cancer in one first-/second-degree relative with one diagnosis before age 50

Risk Assessment/Genetic Counseling

- While most gastric cancers are considered sporadic, it is estimated that 5% to 10% have a familial component and 3% to 5% are associated with an inherited cancer predisposition syndrome. Risk assessment and genetic counseling should include:
  - Detailed family history
  - Detailed medical and surgical history
  - Directed examination for related manifestations
  - Psychosocial assessment and support
  - Risk counseling
  - Education support
  - Discussion of genetic testing
  - Informed consent

Peutz-Jeghers Syndrome (STK11)

- Associated gene is STK11
- Primarily known as a hereditary colorectal/colon polyp syndrome
  - develop Peutz-Jeghers type polyps (hamartomas) in the large and small intestine
  - risk for CRC (40%), pancreas (11-35%), gastric (30%), others
  - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, fingers and genitalia
    - Fade with age
- Breast cancer is on the spectrum
  - estimated 45-50% lifetime risk

Image: www.skincareguide.ca
• No real genetic testing criteria, more diagnostic

PJS definition:\textsuperscript{a,b}

- A clinical diagnosis of PJS can be made when an individual has two or more of the following features:
  - Two or more Peutz-Jeghers-type hamartomatous polyps of the small intestine
  - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - Family history of PJS
Moderate Risk Genes

- **ATM**
  - autosomal recessive (2 mutations) condition = Ataxia Telangiectasia
  - carriers (i.e., single mutation) **2-4 fold increase risk for breast cancer**
  - data indicating a genotype/phenotype correlation
  - other cancers: colon, gastric, likely more

- **CHEK2**
  - ~2 fold increase risk for breast cancer
  - other cancers: male breast, colon, likely others

- **PALB2**
  - autosomal recessive (2 mutations) condition = Fanconi Anemia
  - carriers (i.e., single mutation) ~ **40-60% risk of breast cancer depending on age and family history (high risk?)**
    - Antoniou et al. NEJM 371(6):497-506; 2014
  - other cancers: likely ovarian, possibly others
### NCCN Guidelines Version 2.2015
Genetic/Familial High-Risk Assessment: Breast and Ovarian

#### Breast and Ovarian Management Based on Genetic Test Results

<table>
<thead>
<tr>
<th>Intervention Warranted Based on Gene and/or Risk Level</th>
<th>Recommend MRI (≥ 20% risk of breast cancer)</th>
<th>Recommend RRSO</th>
<th>Discuss Option of RRM</th>
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<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, Lynch syndrome</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53</td>
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<tr>
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<td>BARD1, BRIP1, PALB2, RAD51C, RAD51D</td>
<td>ATM, BARD1, CHEK2, PALB2, STK11</td>
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</tr>
</tbody>
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**a** Other genes may be included in multi-gene testing.

**b** Intervention may still be warranted based on family history or other clinical factors.

**c** See NCCN Guidelines for Breast Cancer Screening and Diagnosis.

**d** May be modified based on family history or specific gene mutation.

**e** See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
Newer Genes

- Case reports to handful of studies
- Cancer risk/spectrum not fully established
- Medical management unknown
- Is there a true link to breast cancer?
  - Million dollar question – what is the clinical utility?

<table>
<thead>
<tr>
<th>AKT1</th>
<th>BARD1</th>
<th>BRIP1</th>
<th>FAM175A</th>
<th>FANCC</th>
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<tr>
<td>GEN1</td>
<td>MRE11A</td>
<td>NBN</td>
<td>NF1</td>
<td>PIK3CA</td>
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<tr>
<td>RAD50</td>
<td>RAD51C/RAD51D</td>
<td>RECQL</td>
<td>RINT1</td>
<td>XRCC2</td>
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</table>
Genetic Testing for Hereditary Breast Cancer

• Single gene tests (Sanger sequencing) vs. Multigene Panels (Next Generation Sequencing)

**Single Gene (Sanger)**
- One read of the gene sequence
- Can detect single base pair change and deletion/duplications of ~100bp
- Need other technology to detect larger mutations

**Multigene Panel (NGS)**
- 1000s of reads of the gene sequence
- Can detect single base pair change and deletion/duplications of ~20-40bp
- Need other technology to detect larger mutations
- Can identify pts who are mosaic
  - Ability to identified somatic mutations from cancer in the blood
Genetic Testing for Hereditary Breast Cancer

- Single gene tests (Sanger sequencing) vs. Multigene Panels (Next Generation Sequencing [NGS])

**Single Gene (Sanger)**
- Labor Intensive
- Expensive
- One gene at a time
  - Time consuming
- *Gold Standard*
- Insurance generally will cover

**Multigene Panel (NGS)**
- Multiple genes and patients at one time
- More cost effective/faster
- Generates HUGE amount of data
  - Increase likelihood of VUS results
- Bioinformatically challenging
- May miss mutations single gene test could identify
- Insurance may or may not cover
MULTI-GENE TESTING

Overview of multi-gene testing

- The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.

- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, than multi-gene testing, may be more efficient and/or cost-effective.

- There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.

As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.

- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene tests are necessarily clinically actionable. As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives. In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.

- There is an increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes.

- It is for these and other reasons that multigene testing are ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

References (GENE-2)
Multigene Panels

- ASCO updated their policy on Genetic and Genomic Testing for Cancer Susceptibility (DOI:10.1200/JCO.2015.63.0996)
- ASCO recognizes that concurrent multigene testing may be efficient in circumstances that require multiple high-penetrance genes of established clinical utility as possible explanations for a patient’s personal and family history of cancer.
- ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient’s personal and/or family history.
- 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 multigene panels that include genes of uncertain clinical utility and genes not suggested by the patients’ personal and/or family history.
Genetic Test Results

- Positive (Deleterious Mutation/Pathogenic Variant)
- Negative
- Variant of Uncertain Significance
- Likely Pathogenic Variant/Suspected Deleterious
- Likely Benign Variant
Positive (Deleterious Mutation/Pathogenic Variant)

- A change was identified in a gene that is associated with an increased risk of breast and other cancers
- Medical management for the pt will need to include high risk breast cancer screening +/- breast cancer prevention
  - guidelines exist for the high and moderate risk genes
- Genetic testing for the mutation/variant is recommended for at-risk relatives who are 18+y/o (parents, siblings, adult offspring)
  - genetic testing of minors is rarely indicated and not recommended
  - exceptions = childhood cancer risk, FHx very early onset cancer (teens)
- Do not need to order a full gene test/multigene panel
  - exception = bilineal risk
Genetic Test Results - Negative

Negative
No changes are identified in the gene(s) tested

Hx of Breast Cancer
• No hereditary cause in the family
• Hereditary cause in the family, but
  – Causative gene not tested
  – Unidentifiable mutation
  – Wrong person tested and need to test another affected family member (phenocopy)
• Unaffected family members may not need
• Management based on personal/family history

Unaffected
• The genetic test is uninformative
  – No hereditary cause in the family
  – Wrong gene(s) tested
  – Right gene(s), unidentifiable mutation
  – True negative, but do not know this because affected family member not shown to be positive
• Test affected family member (if possible) to clarify results
• Management based on personal/family history (MRI/Risk Models)
Variant of Uncertain Significance (VUS)
a change was identified in a gene that currently it is not known whether or not the change causes an increased risk for cancer

Hx of Breast Cancer
- Uninformative
  - Not sure if this is the cause of the cancer
  - Lab may or may not recontact you in the future with a reclassification
- Testing not recommended for unaffected family members
- Contact lab to see if family is eligible for variant study
- Management based on personal/family history not results

Unaffected
- Even more uninformative
  - No hereditary cause in the family
  - Wrong gene(s) tested
  - Right gene(s), unidentifiable mutation
  - Is the VUS on the side of the family with the cancer history
- Test affected family member (if possible) to clarify results (not just the VUS)
- Contact lab to see if family is eligible for variant study
- Management based on personal/family history not results (MRI/Risk Models)
Genetic Test Results – VLP & VLB

• **Variant Likely Pathogenic/Suspected Deleterious (VLP)**
  -A change was identified in a gene that is LIKLEY or SUSPECTED to be associated with an increased risk of breast and other cancers
  -Not enough evidence to call it a Positive, but all of the evidence is pointing in that direction
  -Management – follow guidelines but many are more conservative with prevention recommendations
  -Testing other family members generally indicated

• **Variant Likely Benign**
  -A change was identified in a gene that is NOT LIKLEY or NOT SUSPECTED to be associated with an increased risk of breast and other cancers
  -Essentially manage as a negative result
Who to Offer Testing to?

- Follow published guidelines
- Start with an individual in the family who has had breast cancer
  - IDEAL SITUATION
  - this will ultimately provide the most informative results for the family
  - want to select someone who looks ‘most genetic’ (youngest age of onset, bilateral disease, breast & another cancer)
- If all affecteds are deceased, start with relative who is closest degree of relationship to deceased affected relative
  - e.g., pt is 25, maternal grandmother died from breast cancer at 35, mother is living at 50
  - recommend testing the mother first
Management Considerations for Unaffected Women

- Can consider for women who have undergone genetic testing and have negative for VUS results
- Can consider for women who have strong family history of breast cancer and do not wish to undergo genetic testing
- 2 main options
  - Chemoprevention
  - Increased breast cancer screening
Management Considerations for Unaffected Women - Chemoprevention

- Tamoxifen/Raloxifene
  - Recommended for women with a 5 year breast cancer risk of ≥1.7% based on the Gail model
  - USPSTF gave grade B recommendation for women at increased risk

www.cancer.gov/bcrisktool/
Management Considerations for Unaffected Women – Increased Screening

- American Cancer Society and NCCN recommend annual breast MRI for women with a lifetime risk of ≥20-25%
  -based on personal history of LCIS or atypical hyperplasia OR
  -previous thoracic radiation OR
  -as calculated by models that are largely dependent on family history
    -e.g., Claus, Tyrer-Cuzick (IBIS), BRCAPRO, BOADICEA
  -per ACS guidelines: Gail model should NOT be used as it is not family history based model
How to Find a Genetics Provider

- NSGC
  - nsgc.org/p/cm/ld/fid=164

- NCI
  - www.cancer.gov/about-cancer/causes-prevention/genetics/directory

- American Nurses Credentialing Center
  - www.nursecredentialing.org
American Cancer Society Resources

• **American Cancer Society Breast Cancer Videos** - this video series for patients includes 2 patient videos on Breast Cancer Screening and Genetic Testing

• **Genetic Testing: What You Need to Know** – basic information on genetic testing for patients
Thank You!

QUESTIONS?
smweissman10@gmail.com