Genetic Counseling & the Woman’s Health Patient

MCW Women’s Health Conference
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Samantha Stachowiak, MS, CGC

At the conclusion of this presentation, participants should understand the following:

• How to recognize patients and families who may benefit from a prenatal or cancer genetics consult
• Understand how a patient’s family history may impact cancer screening recommendations
• Understand the benefits and limitations of cell free DNA testing

Family History is Important

• 5 – 10% of all cancers are HEREDITARY
• 15-20% of cancers are FAMILIAL
• 70-80% of cancers are SPORADIC
• Family history tailors cancer screening recommendations and reduces cancer risks

“The identification of at-risk individuals can facilitate individualized preventative care and surveillance, which could impact disease morbidity and mortality.”
Owens et al, 2011
Family History: The Basics

• Who?
  – Mom, dad, siblings, aunts, uncles, nieces, nephews, children,
    grandchildren, grandparents, and cousins
  – Maternal and paternal relatives

• What?
  – Cancer type
  – Age of diagnosis
  – Unusual pathological features
  – Multiple primaries

• "Are there other cancers?"

• Ancestry?
What is Genetic Counseling?

• Process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease
• Genetic Counselors are specially trained Advanced Practice Providers

What is the Role of a Cancer Genetic Counselor?

• Provide risk assessment based on family history
• Evaluate for possible hereditary cancer syndromes
• Determine appropriate genetic test and testing strategy
  – Genetic counseling does not always include genetic testing
• Aid in test interpretation
What is the Role of a Cancer Genetic Counselor?

- Explore the psychological impact of genetic testing
- Work closely with insurance companies
- Address genetic discrimination concerns
- Introduce medical management options
- Talk about implications for family members
- Discuss the option of DNA banking
- Acts as a resource for the patient and family

Laboratories offering genetic testing for hereditary cancer

...and many more.
Genetic Testing is Multifaceted

- Multiple genes for a syndrome
- Different testing methods
  - Tumor testing
  - Genetic testing
    - Single site analysis
    - Multisite analysis
    - Sequencing
    - Deletion/duplication testing
    - Next Generation sequencing technologies
- New genes become available for testing
- Determine most informative family member for testing
- Challenges in test interpretation and variants of uncertain significance

Movement away from single gene testing and toward Next Generation Sequencing (NGS) multi-gene panels

Why?
- Efficient sequencing of multiple genes
- Many genes implicated in each cancer
  - Testing multiple genes simultaneously can be more time efficient and more cost effective
  - Overlapping clinical presentation among different hereditary cancer syndromes
- Approximately 9-10% of BRCA-negative patients have a causative gene mutation identified via panel testing (Ambry Genetics data)

Genes Associate with Hereditary Breast and Ovarian Cancer
Next Generation Sequencing

- Massively parallel sequencing
- Create 100’s to 1000’s of reads per base pair
- Provided enhanced resolution, throughput and speed
- Generates large amounts of data quickly in a cost effective manner
- Sequence multiple genes simultaneously
- Possible to detect mosaicism

Sequencing Methodology

Sanger Sequencing
- Increased cost
- Longer read lengths
- Primer targeted full coverage of exons

Next Generation Sequencing
- Massively parallel sequencing

Breast cancer genes

<table>
<thead>
<tr>
<th></th>
<th>Rare</th>
<th>Common</th>
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<tbody>
<tr>
<td>High risk genes</td>
<td>Example: BRCA1, PTEN, 53BP1, CDH1, PALB2</td>
<td>increases risk 10x-20x Lifetime risk of breast cancer up to 80% Often involve family history of other cancers (e.g., ovarian cancer) Clinical testing available</td>
</tr>
<tr>
<td>Moderate risk genes</td>
<td>Examples: ATM, CHEK2, RAD50</td>
<td>increases risk 2x-4x Lifetime risk of breast cancer up to 10% Clinical testing available</td>
</tr>
<tr>
<td>Low risk genes</td>
<td></td>
<td>increases risk 1-2x Multiplicative effect May account for 13-16% of breast cancer Clinical testing not available</td>
</tr>
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</table>
Genetic Testing

• Benefits
  – Provides more accurate risk of cancer moving forward for individuals and families
  – Provides information useful for medical management
  – Leads to cancer PREVENTION and EARLY detection of cancer
  – May actually relieve anxiety

• Risks
  – Emotional (increased fear/anxiety)
  – Insurance Discrimination

• Limitations
  – Genetic testing is not able to detect all causes of hereditary cancer
  – Continued risk for sporadic cancers
  – Some management strategies not proven effective

Genetic Information Nondiscrimination Act (GINA)

• GINA is a federal law passed in 2008 that protects individuals from genetic discrimination in health insurance and employment
  – GINA prohibits employers from discriminating against employees and applicants based on genetic tests and genetic information and prohibits health insurers from restricting enrollment or adjusting premiums for health insurance on the basis of genetic information

• For additional information: http://ginahelp.org/

Breast Cancer

• Most commonly diagnosed cancer in women
• 2nd leading cause of cancer death in women

• Risk Factors
  – Age
    • Risk increases with age
    • Median age at diagnosis is 61 years
  – Hormonal factors
    • Early menarche/Late menopause
    • Nulliparity
    • Hormone replacement therapy
  – Lifestyle
    • Alcohol consumption
    • Physical inactivity
    • Obesity
How much of breast cancer is hereditary

Breast Cancer Genetics

Genetic Evaluation Guidelines

Personal history:
- Premenopausal breast cancer (<50 yrs)
- Bilateral breast cancer
- Ovarian cancer
- Male breast cancer
- Postmenopausal breast cancer with a family history of any of the above

Family history:
Women who are not of Ashkenazi (Eastern European Jewish) heritage should be referred for genetic evaluation if they have any of the following:
- Male or female first-or second-degree relative with breast cancer
- Male or female first- or second-degree relative with ovarian cancer
- Male or female first-or second-degree relative who has been diagnosed with cancer in both breasts
- Female first-degree relative diagnosed with breast or ovarian cancer
- Female first-degree relative diagnosed with breast and ovarian cancer
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National Comprehensive Cancer Network and US Preventive Services Task Force
Breast Cancer Risk Models

- Risk assessment models can aid in patient management
- Chance of developing breast cancer
  - Gail model
  - Claus tables
  - BRCAPRO
  - Tyrer-Cuzick (IBIS)
  - BOADICEA
- Chance of having BRCA gene mutation
  - BRCAPRO
  - Tyrer-Cuzick (IBIS)
  - BOADICEA

Hereditary Breast and Ovarian Cancer (HBOC) Syndrome

- BRCA1 & BRCA2 gene mutations
- Autosomal dominant inheritance
- Breast cancer
  - 45-85% lifetime risk
  - Risk for a 2nd primary breast cancer
- Ovarian cancer
  - 15-45% lifetime risk
- Other increased cancer risk
  - Prostate, male breast, pancreatic, melanoma, ocular melanoma

HBOC Medical Management

- Change in screening recommendations
  - National Comprehensive Cancer Network
  - American Cancer Society
  - US Preventive Services Task Force
  - American College of Obstetrics and Gynecology
- High risk surveillance
  - Annual mammograms and breast MRI
  - Semi-annual transvaginal ultrasound and CA-125
  - Starting at age 30
- Risk reduction options
  - Tamoxifen for chemoprevention of breast cancer
  - Prophylactic mastectomy
  - Oral contraceptive use for chemoprevention of ovarian cancer
  - Prophylactic salpingo-oophorectomy
- Decision Tool from Women with BRCA Mutation, http://brcatool.stanford.edu/brca.html
- Information for family members
Patient Resources

- **BrightPink** – a national non-profit focused on prevention and early detection in young women
- **FORCE** – a national non-profit devoted to hereditary breast and ovarian cancer
- **American Cancer Society**
- **National Cancer Institute**

Impact on Your Practice

- 9% of patients in a primary care practice have a considerable family history of breast or ovarian cancer
  - 63% of these patients (6% of all patients) were likely to be at especially high risk and warranted intensive evaluation
- 6.2% of a screening mammography population are considered to be at high risk of a BRCA gene mutation

Case Example
Case Example

- Lifetime risk of developing breast cancer
  - 26% based on BRCAPRO Model
  - 35% based on Tyrer-Cuzick Model
- Include annual breast MRI in medical management recommendations

Case Example

- Patient is now a TRUE NEGATIVE
- No increased risk for breast or ovarian cancer
- Medical management should include only annual mammogram

Prenatal Genetics

Samantha Stachowiak, MS, CGC
Who should be referred for prenatal genetic counseling?

Indications

- Advanced maternal age
  - 35 years or older at delivery for singleton pregnancy
  - 33 years or older for multiples
- Fetal ultrasound findings indicating an increased risk for aneuploidy
- Positive screening result for aneuploidy
- Pregnancy history
  - Multiple miscarriages
  - Prior pregnancy with a trisomy
- Personal history
  - Carrier of genetic condition
  - Translocation carrier
- Family history
  - Genetic condition
  - Congenital anomaly
- Ancestry/Ethnicity
  - Carrier screening

Benefits of Seeing A Prenatal Genetic Counselor

- Assess individual risk of having a child with birth defects or a genetic condition
  - Learn more about birth defect or genetic condition
- Have a conversation about testing options
- What to expect and to prepare for the birth of a child with special needs and/or genetic condition
- Discuss pregnancy options, such as continuation of pregnancy, termination or adoption
Referrals

Cell free DNA screening

- Also referred to as noninvasive prenatal screening (or testing)
- Screening method to identify pregnancies at increased risk for the common trisomies and sex chromosome aneuploidies
- Measures circulating cell-free DNA from maternal serum
- Cell-free DNA from the fetus is primarily derived from the placenta

Benefits

- Can be done anytime after 10 weeks gestation
- Noninvasive
- Higher detection rates and lower false positive rates than traditional serum screening
The NEXT Study

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<th>Variable</th>
<th>Standard Sensitivity</th>
<th>Go Diễn DNA Sensitivity</th>
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<td>80% (95% CI: 70-89)</td>
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Limitations

- Non-reportable results

- False positives
  - Positive Predictive Value (PPV)

The NEXT Study

Table 1. Cell-free DNA Test Performance Characteristics in Patients Who Receive an Interpretable Result

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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<td>Trisomy 16</td>
<td>96.3</td>
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<td>Trisomy 18</td>
<td>3.8</td>
<td>98.8</td>
<td>66.9</td>
<td>98.8</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>11.6</td>
<td>98.8</td>
<td>9.7</td>
<td>98.8</td>
</tr>
<tr>
<td>Sex chromosome aneuploidy</td>
<td>71.0</td>
<td>98.8</td>
<td>1.0</td>
<td>98.8</td>
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Table 2. Next-Generation Sequencing

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Note: Data from Norton, ME, et al., (2015) NEJM.
Updates in cell free DNA screening

Timeline of cell free DNA screening

Microdeletion syndromes

- Missing piece of chromosome
- Common deletions screened:
  - 22q11.2 deletion syndrome (DiGeorge)
  - 1p36 deletion syndrome
  - Cri-du-chat syndrome
  - Prader-Willi/Angelman syndrome
  - Wolf-Hirschhorn syndrome
- Often have wide range of symptoms
- Rare in general population
- Most occur sporadically
MaterniT Genome

- Most advanced information available from NIPT
- Looking at all chromosomes
- Identifies > 95% of genome-wide deletions or duplications ≥ 7 Mb
  — Resolution of a karyotype

Who should get this testing?

- ACOG and SMFM do not recommend routine screening for deletions or duplications
- Clinical validation needed

Carrier screening
Carrier Screening

- Identifying couples at risk for passing on genetic conditions to their offspring
- Depends on prevalence of condition, ancestry
- Most conditions are inherited in an autosomal recessive, or X-linked manner

Ethnicity-Based Carrier Screening

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>CHURCH</th>
<th>CARRIER FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>Cystic Fibrosis 1:12</td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>Tay-Sachs 1:16</td>
<td></td>
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<tr>
<td>Ashkenazi Jewish</td>
<td>Lipid Storage Disease 1:16</td>
<td></td>
</tr>
<tr>
<td>Arabic</td>
<td>Cystic Fibrosis 1:16</td>
<td></td>
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<tr>
<td>Baran</td>
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</tr>
<tr>
<td>Fragile X Syndrome</td>
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<td></td>
</tr>
<tr>
<td>Mediterranean</td>
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</tr>
</tbody>
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Guidelines: Carrier Screening

- Cystic Fibrosis (CF): offer to all women of reproductive age/preconception
- Spinal Muscular Atrophy (SMA)
  - ACOG: only when family history is present
  - ACMG: offer screening regardless of family history
- Fragile X syndrome: not recommended for population carrier screening
  - All recommend based on family history
  - ACOG adds: unexplained ID, developmental delay, autism, or primary ovarian insufficiency
Guidelines: Carrier Screening

- Hemoglobinopathies
  - ACOG: African-American, Mediterranean, Southeast Asian

- Ashkenazi Jewish:
  - ACOG: Tay-Sachs disease, CF, Canavan disease, familial dysautonomia
  - ACMG: same as ACOG as well as Niemann-Pick disease (type A), Bloom syndrome, Fanconi anemia group C, Mucolipidosis IV, and Gaucher disease

- French Canadian/Cajun: offer screening for Tay-Sachs disease (ACOG)

Expanded Carrier Screening

- More comprehensive screening
  - Advancements in technology allows screening of a large number of conditions simultaneously

- Same conditions offered to everyone (regardless of race or ethnicity)

- Ideally should be offered before conception
  - Provides couples with information for reproductive decision-making

Expand Carrier Screening

- In a study of 23,453 people, 24% were found to be a carrier of at least one non-mild condition
  - 5.2% were found to be carriers of two or more conditions
  - 127 “carrier couples” were identified
Expanded Carrier Screening

- Take away points from this study:
  - ACOG & ACMG guidelines would have missed 70% of carriers that were identified
  - Several severe diseases had higher carrier frequencies than expected
    - Smith Lemli-Opitz syndrome carrier frequency was 1 in 68 vs 1 in 123
  - Several conditions were present outside their characteristic ethnic group
    - 26.3% of familial dysautonomia carriers did not report Jewish ancestry

Limitations/Considerations

- Conditions screened for range in severity
- Many are rare
- Screen negative results reduce likelihood of being a carrier but does not eliminate it
- MANY labs to choose from
  - Different conditions
  - Detection rates
    - Genotyping vs Sequencing

How to Find Us

- Main GC phone line: 414-955-5899
  - Morgan Depas: 414-805-9036, mdepas@mcw.edu
- Email: genetic.counseling@mcw.edu
- Website: [http://www.mcw.edu/Human-and-Molecular-Genetics-Center-HMGC/Genetic-Counseling.htm](http://www.mcw.edu/Human-and-Molecular-Genetics-Center-HMGC/Genetic-Counseling.htm)
How to Find a Genetic Counselor

- The Wisconsin Genetics Website: [http://www.slh.wisc.edu/genetics/index.dot](http://www.slh.wisc.edu/genetics/index.dot)
- Contact State Genetic Coordinator
  - 608-267-7148
  - Contact Us tab of Wisconsin Genetics Website

References


Acknowledgements

- Wisconsin Cancer Risk Program Network (WiCRPN)