Do Genetic Tests Make Sense for Prevention?

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Learning Objectives

• Participants will understand the clinical utility of genetic testing in cancer and other areas of medicine.

• Participants will be able to identify specific genetic variants that increase the risk for a medical condition, such as breast cancer.

• Participants will understand how using genetic testing can benefit family members.

Presentation Content

1. Inspiration for the Presentation
2. The Rapid Expansion of Genetic Testing
3. Next Generation Sequencing
4. Genetic Counseling
5. Case examples of genetic testing for prevention
   • Cardiology
   • Oncology
   • Neurology
   • Whole Exome Sequencing

“It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change.”

Charles Darwin
Inspiration for this presentation

The Rapid Expansion of Genetic Testing

An increase in Direct-To-Consumer testing

A review of Genetic Technology
Next Generation Sequencing (NGS)
NGS

Sequencing by Synthesis

Sequencing Data

Align to reference sequence
Determining the Pathogenicity of Genetic Variants

- **Pathogenic** — This variant directly contributes to the development of disease. Some pathogenic variants may not be fully penetrant. In the case of recessive or X-linked conditions, a single pathogenic variant may not be sufficient to cause disease on its own. Additional evidence is not expected to alter the classification of this variant.

- **Likely pathogenic** — This variant is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity, but we cannot fully rule out the possibility that new evidence may demonstrate that this variant has little or no clinical significance.

- **Uncertain significance** — There is not enough information at this time to support a more definitive classification of this variant.

- **Likely benign** — This variant is not expected to have a major effect on disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion, but we cannot fully rule out the possibility that new evidence may demonstrate that this variant can contribute to disease.

- **Benign** — This variant does not cause disease.

DTC testing

- Uses qualitative genotyping to detect clinically relevant variants in the genomic DNA of adults from saliva for the purpose of reporting and interpreting genetic health risks and reporting carrier status.

- It is not intended to diagnose any disease. Each genetic health risk report describes if a person has variants associated with a higher risk of developing a disease, but does not describe a person’s overall risk of developing the disease.

- These reports are not intended to tell you anything about your current state of health.

Single Nucleotide Polymorphisms (SNPs)

Sequence variations exist at defined positions within genomes and are responsible for individual phenotypic characteristics, including a person’s propensity toward complex disorders such as heart disease and cancer.

As tools for understanding human variation and molecular genetics, sequence variations can be used for gene mapping, definition of population structure, and performance of functional studies.

Genetic Counseling
Genetic Counseling is . . .

...a communication process, which aims to help individuals, couples and families understand and adapt to the medical, psychological, familial and reproductive implications of the genetic contribution to specific health conditions.

This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about the natural history of the condition, inheritance pattern, testing, management, prevention, support resources and research.
- Counseling to promote informed choices in view of risk assessment, family goals, ethical and religious values.
- Support to encourage the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.


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Genetic Counselors

Master’s Level training in Genetic Counseling

Board Certification by American Board of Genetic Counseling (ABGC)

Licensure by state

Recertification every 5 years by exam or continuing education

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Genetic Testing in Oncology

BRCA and the ‘Angelina Jolie effect’

“...But I am writing about it now because I hope that other women can benefit from my experience......today it is possible to find out through a blood test whether you are highly susceptible to breast and ovarian cancer, and then take action.......My chances of developing breast cancer have dropped from 87 percent to under 5 percent.”

15 working days following Jolie’s article, daily rates of testing for harmful mutations in BRCA1 and BRCA2 genes rose by 64%, compared with the 15 working days before. After six months, average monthly testing rates were still 37% higher than in the four months prior.

But the study revealed that while genetic testing rates increased, there was no change in average, overall mastectomy rates in the six months following the article’s publication — and showed a slight drop in mastectomy rates among those who had BRCA tests.
**Proportion of Hereditary Breast Cancer**

- Sporadic: 80%
- Familial: 10-15%
- Hereditary: 5-10%

**Characteristics of Hereditary Cancer syndromes**

- Apparently autosomal dominant transmission of specific cancer type(s)
- Earlier age of onset of cancers than is typical
- Multiple primary cancers in an individual
- Clustering of rare cancers
- Bilateral or multifocal cancers
- First degree relatives of mutation carriers are at 50% risk to have the same mutation
- Those who do not have the familial mutation have the general population risk for cancer

**Case Study**

- A 36-year-old female of Western European, non-Jewish ancestry presented to the genetic counselor with a personal history of early onset breast cancer and a family history of breast and colon cancer.
  - Family history was significant for a maternal aunt with breast cancer diagnosed at age 75. The patient’s father was diagnosed with colon cancer at age 45 and a paternal grandfather was diagnosed with colon cancer at age 73.
  - Ethnicity is Western European, non-Jewish.

**Genetic Testing Results**

A pathogenic variant in the **PALB2** gene indicating a deletion of one nucleotide was detected in this patient.

The **PALB2** gene is called the partner and localizer of the **BRCA2** gene. It provides instructions to make a protein that works with the **BRCA2** protein to repair damaged DNA and stop tumor growth.

**NCCN Guidelines for Women with Mutations in PALB2:**

- Annual screening mammogram (consider 3D mammography) and annual MRI with contrast beginning at age 30, or earlier based on family breast cancer history
- Discussing the option of risk-reducing mastectomy based on family history of breast cancer
Diagnostic Implications of PALB2

Diagnostic Implications:
• Women with a PALB2 mutation who have a family history of early-onset breast cancer may have an increased breast cancer risk.
• Women with PALB2 mutations and breast cancer frequently have a high-grade in infiltrating ductal carcinoma.
• PALB2 mutation carriers are 6-fold more likely to have a family history of pancreatic cancer, 4-fold more likely to have a family history of male breast cancer, and 1.3-fold more likely to have a family history of ovarian cancer compared to non-mutation carriers.
• PALB2 mutations have also been identified in patients with ovarian cancer. The association between PALB2 mutations and pancreatic cancer has been replicated in additional studies.

Clinical Utility of Oncology Genetic Testing

Genetic testing for cancer risk helps clinicians:
Establish an accurate diagnosis
Better understand cancer risks for their patients
Guide medical management to the need of the individual patient

Genetic testing for cancer risk helps patients:
Explain the history of cancer in their family
Make informed healthcare decisions
Identify other family members who are and are not at risk
Prevent cancer related deaths by increased surveillance and early detection

Genetic Testing in Cardiology

Hypertrophic Cardiomyopathy (HCM)
• A healthy 32-year-old man presents for evaluation of exertional dyspnea and syncope. A murmur is noted, and echocardiography reveals marked septal hypertrophy.
• His father died of an MI at 38 years of age, and his paternal uncle died as the driver in a single-car accident at 30 years of age. His younger brother is thought to have “athlete’s heart”
• Genetic testing reveals a diagnosis of hypertrophic cardiomyopathy.
• He asks: “What will happen to my kids? Will I be able to feel well enough to exercise again?”

Carolyn Y. Ho Circulation. 2012;125:1432-1438
HCM

Most common genetic cardiovascular disease - 1:50 persons in the general population

Characterized by heterogeneity in its cause: genetics, medications, infection, “athlete’s heart”

HCM involves hypertrophy of the left ventricle with thickening of the interventricular septum and the LV posterior wall.

Severity of disease involves left ventricular outflow obstruction and ventricular arrhythmias.

Genetic testing results

- Genetic testing identified a pathogenic mutation in the MYH7 gene, also present in his brother and 1 of his children.
- Serial follow up is planned for his daughter with the mutation.
- If a pathogenic sarcomere mutation is identified in the family, predictive genetic testing provides a cost effective and definitive means of family screening because longitudinal evaluation can be focused on mutation carriers.
- HCM has lifelong implications for patients and families and often impacts young, otherwise healthy individuals. Therefore lifestyle considerations (particularly regarding physical activity), family screening, and genetic counseling are important facets of clinical management.

Adding the genetic information to the family history

The clinical heterogeneity of HCM calls for individualized treatment. Three key components are considered:

1) Symptom management
2) Risk stratification for SCD,
3) Counseling/screening including exercise and lifestyle recommendations, family screening, and genetic counseling.

Clinical Utility of Cardiology Genetic Testing

Genetic testing for cardiology risk helps clinicians:

- Establish an accurate diagnosis when it is unclear by conventional testing
- Inform and educate those at increased risk (children, siblings)
- Prevent sudden death by life-style changes, surveillance and early intervention
Genetic Testing in Neurology

Epilepsy testing

- Genetic testing in a person with epilepsy can help confirm a specific diagnosis and may give information about other associated neurologic or medical conditions that may arise over time.
- It may assist your neurologist with selecting an appropriate seizure medication and also with expectations regarding appropriate seizure control. Genetic information may also influence whether or not a specialized diet, such as the ketogenic diet is recommended.
- Genetic information may help to limit unnecessary or invasive testing.
- Genetic testing may assist with understanding the prognosis or outlook of a person’s epilepsy and provides a basis for further genetic counseling for families.

Clinical Utility of Genetic Results?

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome/Condition</th>
<th>Treatment Implications</th>
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<tbody>
<tr>
<td>ALG3M</td>
<td>Pyrophosphate-soap glycoprotein uropathy</td>
<td>Reacts to treatment with supplements vitamin D3 and folic acid</td>
</tr>
<tr>
<td>FPN1</td>
<td>Copper转运deficiency</td>
<td>Reacts to treatment with supplements vitamin D3 and folic acid</td>
</tr>
<tr>
<td>PPT1</td>
<td>Pyruvate-propionate-dependent epilepsy</td>
<td>Reacts to treatment with pyruvate-propionate-phosphate (PUP)</td>
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<tr>
<td>PGD</td>
<td>Pyruvate-kinase-positive and other PGD-related disorders</td>
<td>Reacts to treatment with pyruvate-propionate-phosphate (PUP)</td>
</tr>
<tr>
<td>SQMTA</td>
<td>DYT1, syndrome and other SQMTA-related disorders</td>
<td>Reacts to treatment with pyruvate-propionate-phosphate (PUP)</td>
</tr>
<tr>
<td>SLC2A1</td>
<td>Glucose transporter type 2 deficiency syndrome (GluD1)</td>
<td>Reacts to treatment with pyruvate-propionate-phosphate (PUP)</td>
</tr>
<tr>
<td>TBC1</td>
<td>Tuberculosis complex</td>
<td>Reacts to treatment with pyruvate-propionate-phosphate (PUP)</td>
</tr>
<tr>
<td>TBC2</td>
<td>Tuberculosis complex</td>
<td>Reacts to treatment with pyruvate-propionate-phosphate (PUP)</td>
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For families, an answer

We weren’t just looking for a diagnosis—we were looking for information that would help with his treatment, and, in the early years, to help us decide whether to have another child.

Having this diagnosis after 16 years has had an impact on us beyond what I could have imagined. We now have a better idea of what to expect, which helps to reassure us and our family. Knowing the diagnosis also means that we can be better prepared for future medical procedures and treatment options.

The joy in sorrow...
Whole Exome Sequencing (WES)

What is WES?

The exome refers to the portion of the human genome that contains functionally important sequences of DNA that direct the body to make proteins essential for the body to function properly.

Case study: KB

- 2 y/o girl with MRI showing cerebellar degeneration, ataxia, postural tremor, hypotonia and developmental regression
- No family history of similar problems
- Based on the MRI, the family was told that the diagnosis was infantile neuroaxonal dystrophy (INAD)
- INAD is a fatal childhood disease (life expectancy 5-10 years) with no treatment except “medication for pain and sedation.”
- Family was told to “go home and love your child. There's nothing that can be done.”

KB’s Testing Prior to Exome Sequencing

- PLA2G6 gene sequencing and del/dup
- SNP microarray
- Skin biopsy
- Lumbar puncture (under anesthesia)
- (muscle biopsy was recommended, but parents declined)
- The cost of these tests was $69,659.
- The biopsy and LP also are invasive
- have significant risks associated with them.
- Tests did not confirm the clinical suspicion.
Exome Sequencing?
After one year of trying to get a diagnosis, they met with a geneticist and genetic counselor.

Geneticist’s differential diagnosis:
- metabolic disorder
- inherited ataxia

Patient had whole exome sequencing and mitochondrial genome sequencing. Whole exome sequencing was performed on both parents, as this increases the detection rate of the test.

Diagnosis: Mitochondrial Complex 1 Deficiency due to NUBPL mutations
- Analysis showed that the patient inherited one mutation from the father and one mutation from the mother
  - There is no single gene test for NUBPL
  - NUBPL was first reported in a patient in 2010¹
  - NUBPL is very rare (fewer than 30 cases reported)
- Autosomal recessive inheritance means that KB’s parents have a 25% chance of having another similarly-affected child

“Everything changed once the correct diagnosis was made” – KB’s father
- Appropriate treatment could be started (“mito cocktail”)
- Patients with mitochondrial disorders must avoid certain medications that put them at risk.¹
- NUBPL disorder: patients can live into adulthood (not lethal in childhood, as with INAD)
  - Parents started planning for KB’s future
  - Enrolled her in school
  - “We have a daughter with a future”
- KB has been enrolled in a US-funded clinical trial for mitochondrial disorders
- Family has started a website to educate, learn from, and support others

So then, Do Genetic Tests Make Sense for Prevention?
Yes!
Caveats: Who do I test and for what?

Finding the right patients to test

What kind of testing to do?
Diagnostic? Predictive?

“But it won’t change anything!”

Insurance coverage can be an issue

Questions? Thank you!