Genetic Testing for Disease Predisposition

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The focus of this lecture is on genetic testing instead of an in-depth discussion of disease

Definitions

- “Genetic Testing”
  - Many types (full sequencing, single site, common mutations, chromosome analysis, etc.)
  - Many tissues (tumors, blood, buccal mucosa)
  - Not just a test, a process
  - Specialty labs

- “Disease Predisposition”
  - Risk is a complex issue, not “all or nothing”
  - Which diseases?
  - What to do with results?

“Explosion of genetic info”

www.genetests.org
1131 clinical genetic tests
~300 - 400 more/yr

CDC EGAPP project
“Explosion of genetic information is a public health issue”

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“Explosion of genetic information is a public health issue”
1. Ivana Test: 24 y/o, mother just diagnosed; aunt died of breast cancer. “I just want the test”

2. Cy Fibrosis: 28 y/o with male infertility. His genetic testing for cystic fibrosis is prompting his wife to consider testing.

3. Ima Clotter: Healthy 30 y/o whose sister was found to carry “blood clotting genes” after several miscarriages. Not sure she wants to test, “How would it change things for me?”

Ivana Test’s Family History

- Mother diagnosed last month with breast cancer
- Aunt with breast cancer was paternal, died at 45
- Eastern European
- Not close with paternal side
  - Only one cousin
  - Paternal grandmother died young

BRCA tests & insurance: What’s false?

- Health insurance won’t cover BRCA testing.
- Health insurance won’t cover appropriate screening and prevention in BRCA carriers.
- Health insurance plans can increase premiums or drop coverage based on BRCA results.
- There are no legal protections for life insurance.
- None of the above
- All of the above
- D only
Three Generation Pedigree

- **Diabetes**: d.82
- **MI**: d.71
- **Breast ca 40, d45**: 85

Three Generation Pedigree, Next Visit

- **Diabetes**: d.82
- **Ovarian**: d.40
- **Prostate ca 55, Now 66**: Breast ca 65
- **Breast 33**: 47

Misconceptions About Family History

- "Cancer on the father's side of the family doesn't count."
- "Ovarian cancer in the family history is not a factor in breast cancer risk."
- "The most important thing in the family history is the number of women with breast cancer."
- **Half of all women with hereditary risk inherited it from their father.**
- **Ovarian cancer is an important indicator of hereditary risk, although it is not always present.**
- **Age of onset of breast cancer is more important than the number of women with the disease.**
Genetic Counselor’s Family History

- Extensive pedigree, including cousins
- Verify cause of death, age of diagnosis and death
- Ovarian and “female” cancers often not discussed
- Ask about Jewish ancestry
- Next step is to test individual already affected with cancer
  - “Genetics is a family business”

Cells have Two Copies of BRCA1 and BRCA2

Autosomal Dominant Inheritance

Father with mutation on one chromosome

Each child has a 50% chance of inheriting an autosomal dominant disorder
**BRCA 1 / 2 Associated Cancers:**

**Lifetime Risk**

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>BRCA Population</th>
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</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>12%</td>
<td>60-85%</td>
</tr>
<tr>
<td>Second Primary Breast</td>
<td>&lt;1%</td>
<td>40-50%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>20-40%</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>10-20%</td>
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**Founder Mutations**

- In the general population
  - ~ 1/400 carry BRCA mutations
- Hundreds of different mutations identified
- In the Ashkenazi Jewish population
  - 1/40 carry one of 3 specific mutations
  - 2 in BRCA 1 and 1 in BRCA 2, explain 90%
- Other “founder” populations
  - French Canadians, Icelanders, Polish

**Testing Options**

- Comprehensive Analysis
- Single Site Analysis
- Multisite 3 Analysis (BRACANALYSIS ONLY)

**BRCA1**
- 1056delAG
- 592insC

**BRCA2**
- 615delT
Three Possible BRCA results

- **Positive**: Known deleterious mutation found
- **Negative**:
  - **Uninformative negative**: No mutation found, but family history is not explained
  - **True negative**: Known mutation in family and patient doesn’t have it
- **Variant of Undetermined Significance**: Change in DNA, but unsure whether it’s deleterious or benign

Are some “uninformative negatives” really positive?

King, JAMA 06

- 300 very high risk families with “uninformative negative” results AND 4 family members with breast or ovarian cancer
- 12% had duplications (extra chapter), deletions (missing chapter), or rearrangements (misplaced chapter) in BRCA1 or BRCA2, “false negatives”
- Unclear how common these duplications or rearrangements are in the larger population receiving BRCA testing

Ivana Test, Conclusion

- Ivana’s father tested positive for a mutation common in the Jewish population
- Men can carry mutations in BRCA1/2
- Start with an affected individual if possible
- Ivana then tested using the Jewish panel and was negative
- A negative result is only a “true negative” when there is a positive result in the family
Cy Fibrosis’s History

- Infertility work-up showed azoospermia.
- Congenital absence of vas deferens (1-2% of infertile men have this).
- Standard CF testing showed patient is a carrier of Delta F508.
- He wants to use ICSI (intracytoplasmic sperm injection).

Cystic Fibrosis Genetics

- CF is caused by mutations in a single large gene on chromosome 7 (codes CFTR protein).
- CF is typically autosomal recessive.
- 250 kilobases, 1480 amino acid protein.
- Wide phenotypic variation of disease.
- 1998 consensus statement for screening:
  - Family history of CF or partner’s family hx of CF.
  - Whites of European or AJ descent planning pregnancy or seeking prenatal care.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Incidence</th>
<th>Carrier Frequency</th>
<th>F508</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1/3300</td>
<td>1/25</td>
<td>70%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/8500</td>
<td>1/46</td>
<td>46%</td>
</tr>
<tr>
<td>AJ</td>
<td>1/29</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Black</td>
<td>1/15,300</td>
<td>1/65</td>
<td>48%</td>
</tr>
<tr>
<td>Native American</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuni</td>
<td>1/3970</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Pueblo</td>
<td>1/1500</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Asian</td>
<td>1/32,100</td>
<td>1/90</td>
<td>30%</td>
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Cy’s wife has a “variant”

- “Variants of Undetermined Significance” (VUS) occur in about 5% of whites receiving full sequence testing, 20-40% of non-whites
- VUS are becoming more common
- Full sequence testing becoming more common technology
- Testing is becoming more accepted and available in non-white populations

What are the chances the fetus will have cystic fibrosis?

- One in 4
- One in 2
- One in 8
- Unknown

Ima Clotter’s Family History

- After 3 miscarriages, Ima’s older sister was found to have a “double defect”
- Ima is G1P1, on birth control pills, and healthy.
- A third sister is currently pregnant.
- Feels it’s “opened Pandora’s Box” and wonders “How will it change my care if I test?”
What is a “double defect?”

Two inherited thrombophilias

Factor V Leiden, nucleotide 1691 transition from guanine to adenine results in Arg506Gln protein
Prothrombin 20210, guanine to adenine, untranslated
MTHFR variant (C677T)
Protein C deficiency
Protein S deficiency
Antithrombin deficiency

Risks of first venous thrombosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>Annual Incidence</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>1.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>(MTHFR C677T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT 20210</td>
<td>2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>OCP's</td>
<td>4.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Factor V Leiden hetero</td>
<td>7.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Plus OCPs</td>
<td>35</td>
<td>0.29</td>
</tr>
<tr>
<td>Factor V Leiden homo</td>
<td>80</td>
<td>0.5-1.0</td>
</tr>
</tbody>
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Thromboembolism in Pregnant Women with Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Probability per pregnancy</th>
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<tbody>
<tr>
<td>None</td>
<td>0.03%</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>0.25%</td>
</tr>
<tr>
<td>PT 20210</td>
<td>0.5%</td>
</tr>
<tr>
<td>Factor V and PT 20210</td>
<td>4.6%</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.4%</td>
</tr>
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Gerhardt, NEJM 2000
Would testing change management?

- Indefinite anticoagulation recommended if
  - 2 or more spontaneous thromboses
  - 1 spontaneous thrombosis and
    - Antithrombin deficiency or antiphospholipid Ab
    - Life threatening or unusual site
    - "Double" or more defects
- Anticoagulate during pregnancy if
  - Antithrombin deficiency or "double defect"
  - Consider if personal or FH of thrombosis

Ima Clotter, Conclusion

- Ima is heterozygous for Factor V Leiden
  - She stops OCPs
- Ima’s pregnant sister carries a “double defect”
  - She is discussing anticoagulation with her OB
- Both defects are autosomal dominant
- Testing was fairly straightforward, as there were 2 genes with known mutations.

Which of the following principles apply to genetic testing?

- If possible, start with the affected individual
- Genotype does not always equal phenotype
- Discuss pros and cons of testing
- Knowledge of ethnic background is helpful
- Plan for the “next step” and consider all possible test outcomes
- All of the above
Why consider testing for predisposition genes?

- To identify patients at very high risk of disease
- To identify patients who are not at increased risk, despite family history
- To allow high risk patients to consider increased screening, chemoprevention, or preventive procedures
- To assist with prenatal counseling
- To possibly allow patient to enter screening/prevention trials
- To provide important health info to extended family

A Multi-Step Process: Pretest Genetic Counseling

 Assess
- Personal and family medical history
- Risk perception and motivation for testing

 Educate
- Basic genetics and inheritance
- Genotype/phenotype disparities and risk
- Genetic counselor resources: www.nsgc.org

 Discuss
- Risks, benefits, and limitations of testing
- Test procedure and alternatives to testing
- Management options

A Multi-Step Process: Post-test Genetic Counseling

 Review
- Educational concepts and family history
- Risk and prior probabilities

 Disclose
- Test results
- Interpretation of results

 Discuss
- Plans for prevention and treatment
- Sharing results with family members
- Potentially testing other family members
Family History of Hereditary Breast and Ovarian Cancer

Hereditary

- Ov, 32
- Br, 42
- Br, 45
- Two or more women with breast cancer before age 50 or ovarian cancer at any age
- One woman with breast cancer before age 50 or ovarian cancer at any age, plus Ashkenazi ancestry

Sporadic

- Br, 63
- Br, 71
- None of the breast cancer is diagnosed before age 60
- No ovarian cancer
- No clear pattern on one side of family or other

### Benefits, Risks, and Limitations of BRCA Testing

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks and Limitations</th>
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<tbody>
<tr>
<td>- Identifies high-risk individuals</td>
<td>- Does not detect <em>all</em> mutations (rearrangements, other genes)</td>
</tr>
<tr>
<td>- Identifies noncarriers (low-risk) in families with a known mutation</td>
<td>- Continued risk of sporadic cancer</td>
</tr>
<tr>
<td>- Allows early detection and prevention strategies</td>
<td>- Efficacy of some interventions unproven</td>
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<td>- May relieve anxiety</td>
<td>- May result in psychosocial or economic harm</td>
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