Genetic Testing for Disease Prevention: Has the Era of Personalized Medicine Begun?

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In the last year, have you referred a patient to genetic counseling?
A. No
B. Yes, only for prenatal genetic counseling
C. Yes, for other types of genetic counseling

In the last year, have you ordered a genetic test?
A. No
B. Yes, only prenatal
C. Yes, for other types of genetic tests

In the last year, have you been asked to interpret a patient’s genetic test that you didn’t order?
A. No
B. Yes, only for prenatal test results
C. Yes, for other types of genetic tests
Relevance and Definitions

- Why is this important to medical providers?
  - Most consumers of genetic testing know more than their providers*
  - Providers are trained to order and interpret tests
  - Genetic data in isolation is not useful
- What is meant by genetic testing?
  - DNA analysis of tissue, blood, saliva
- What is meant by disease prevention?
  - Risk is complex
  - Does risk knowledge → prevention?
- Personalized Medicine?  
  *Nature Biotechnol. 26, 76; 2008

Personalized Medicine and Genetic Testing Evidence

- Hereditary Syndromes
  - Hereditary Breast and Ovarian Cancer--HBOC
  - Hereditary Hemochromatosis--HHC
  - Hereditary Thrombophilia
- SNP (Single Nucleotide Polymorphism) chips and genetic testing
- Whole Genome Sequencing

Ivana Test’s Family History

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

Three Generation Pedigree

- Breast ca 40, d45
- Breast ca 65
- Breast cancer
What would you do next?
A. Tell Ivana not to worry, her family history is not concerning
B. Perform a clinical breast exam and discuss pros and cons of breast imaging
C. Give her family history “homework”
D. Test for deleterious BRCA mutations
E. Refer for genetic counseling

Genetic Counselor’s Family History
- Extensive pedigree, including cousins
- Verify cause of death, ages of dx and death
- Ovarian and “female” cancers often not discussed
- Ethnic ancestry on all 4 grandparents
- Next step: test affected individual first, if able
- National Society of Genetic Counselors: nsgc.org

Three Generation Pedigree, Next Visit
Which of the following are true?

A. Most health insurance plans cover BRCA testing in appropriate individuals
B. Most health insurance plans cover screening and prevention in BRCA carriers.
C. US federal law prevents health insurance plans from ↑ premiums or dropping coverage based on genetic test results.
D. There are no legal protections for life insurance.
E. All of the above

Ivana Test, Conclusion

- Ivana’s father tested positive for a mutation common in the Jewish population
- Ivana then tested using the Jewish panel and was negative...true negative, known family mutation

**Bottom Lines:**

Men can be BRCA carriers

Start with affected individual (↑est prob of + test; ID family mutation)

Henry Chromatin and siblings

- Henry is 40 and healthy
- Henry’s 35 year old brother, Harold, was told he had hemochromatosis
- Henry also has 2 sisters, one with diabetes
- Henry’s mother and father are alive and well
- Henry has 2 children and 8 nieces/nephews
Classic Hereditary Hemochromatosis is Autosomal Recessive

Hereditary Hemochromatosis (HHC)
Autosomal Recessive
Genetic testing for 2 mutations in HFE gene
- C282Y: Carriers common
  - 10% of whites, 3% of Hispanics, 2% of African Americans, 0.1% of Asians
  - 1/200 whites are homozygotes (C282Y/C282Y)
- H63D: Carriers common
  - 25% of whites, 18% of Hispanics, 6% of African Americans, 9% of Asians

Phenotype vs. Genotype Testing
- Most people with HHC have a C282Y/C282Y genotype, but most C282Y/C282Y’s don’t develop HHC.
- Genotypes of HHC affecteds
  - C282Y/C282Y  ~ 60-90%
  - C282Y/H63D  3-8%
  - H63D/H63D  ~ 1%
- Diagnosis of HHC should not be made on genotype alone.

What are the chances that Henry will get hemochromatosis?
A. One in four
B. One in two
C. Unable to determine with current info

A 61%, 14%, and 25% bar graph is shown.
HHC Penetration: Moving Target
- Depends on age & sex (Bulaj NEJM 00)

<table>
<thead>
<tr>
<th>C282Y/ C282Y</th>
<th>No iron overload</th>
<th>Iron overload only</th>
<th>Iron overload + dz related condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men &lt;40</td>
<td>20%</td>
<td>54%</td>
<td>26%</td>
</tr>
<tr>
<td>Men &gt;40</td>
<td>10%</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Women &lt;50</td>
<td>47%</td>
<td>48%</td>
<td>5%</td>
</tr>
<tr>
<td>Women &gt;50</td>
<td>12%</td>
<td>72%</td>
<td>16%</td>
</tr>
</tbody>
</table>
- Australian cohort: 28% of men and 1% of women with C282Y/C282Y developed iron overload over 12 years, current mean age 65 (Allen NEJM 08)

What would you do next?
A. Order LFT’s on your patient, Henry
B. Order a transferrin sat on Henry
C. Send Henry for 2 mutation HFE testing
D. Send Harold for 2 mutation HFE testing
E. A combination of the above
F. None of the above

Back to the Chromatosis Family
- Your patient Henry has an elevated transferrin sat at 46%
- Henry doesn’t want or need genetic testing for his individual care
- Harold’s genotype is C282Y/C282Y
- The sister with diabetes has normal labs and her genotype is H63D/nl

Bottom Lines:
Genotype ≠ Phenotype
Penetration can be a moving target

Family Implications

The Bad News, Mr. Piglet, is that your stuttering is genetic... The good news is all that DNA testing helped us determine who your father is...
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, younger, 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 G → A results in Arg506Gln protein
- Prothrombin 20210, G → A, untranslated
- MTHFR variant (C677T)
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency

**Bottom Line:**
Get sister’s actual results

“Double Defect” Results and Implications

- Ima’s sister carries the factor V Leiden and PT 20210 mutations
- Factor V + OCP’s = RR of 35.0 for VTE and annual incidence of 0.3%

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Relative Risk</th>
<th>Annual Incidence</th>
<th>Probability per Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT 20210</td>
<td>2.8</td>
<td>0.02%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>7.0</td>
<td>0.06%</td>
<td>0.25%</td>
</tr>
<tr>
<td>Both</td>
<td>20.0</td>
<td>0.15%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

Has this “opened Pandora’s box”?

- Ima’s sister wanted to know why she had recurrent pregnancy loss....but, is the “double defect” the reason?
- Ima is healthy, had a normal pregnancy and birth, and no problems on OCP’s
- As Ima’s PCP, discuss whether it’s a good time to test and how you’ll use results

**Bottom line:** Genetics is a “family business”
What would you recommend for Ima?

A. Test for the thrombophilia panel (Factor V and PT20210)
B. Don’t test, but continue OCP’s
C. Don’t test, but stop OCP’s
D. It depends

How might testing change care for Ima? For her sisters?

- For Ima
  - Discuss risks of OCP use and all possible test results
  - Review her birth control options and her plans for another pregnancy

- For her younger sister
  - How far along? Consult OB and/or hematologist

- For her older sister (known “double defect”)
  - Recommendations for “double defect” is to begin anti-coagulation with lovonox after → pregnant

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
- Testing was fairly straightforward
  - 2 known point mutations (Single Nucleotide Polymorphisms, or SNP’s)
- Counseling: risk, gene-environment interaction, values, psychosocial factors, family planning

Since the cloning, Professor Kane’s workload has eased up considerably.
Letting the genome out of the bottle  
(Hunter NEJM 08)

- 50 year old woman, overweight, mild HTN  
- $999 genome scan birthday present  
- ↑ risk for CHD and diabetes  
- 600,000 SNP chip for “informational” (not medical) purposes

Do Personal Genetic Tests Change Anxiety and/or Behavior?

- Scripps Genomic Health Initiative (SGHI)  
  - 2037/3639 healthy participants completed survey  
  - Received genome scan for 23 conditions (diabetes, obesity, MI, cancer, Chron’s, psoriasis)  
  - Follow up 5-6 months after receiving results  
  - Further F/U planned for up to 20 years  
- 90% showed no distress related to results  
- No effect on diet/exercise  
- 26.5% shared results with physician

Topol et al, NEJM, 1/11/11

Letting the Genome Out, Conclusion

- No pre-test counseling  
- Increased anxiety  
- SNP-mania: research (Genome Wide Association Studies), entertainment, clinical  
- Genome knowledge in isolation is not generally useful

**Bottom Line:** $999 would have been better spent on a gym membership  
(Now $99 plus $9/month subscription service over a year)

Direct to Consumer

"As if we didn't already know too much about ourselves, we're having our DNA done."
Genomewide Association Studies and Risk Assessment

- “Care is needed in evaluating genetic predictive models, since they are often specific to the population in which they were developed, and their value can vary with genotypic frequencies, effect sizes, and disease incidence.”
- “Patients...should be advised that at present the results of such testing have no value in predicting risk and are not clinically directive.”

Manolio NEJM 2010

Evidence Based

<table>
<thead>
<tr>
<th>Available</th>
<th>Evidence Based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Offitt JAMA 2008

“Explosion of genetic info”

www.genetests.org

CDC EGAPP project

“Explosion of genetic information is a public health issue”

Khoury M, Genet Med 09

Not a tsunami, a rising tide

Growth of Genetic Testing

Khoury M, Genet Med 09
“Whole Genome Sequencing”

- 6.4 Billion Nucleotides
- May break the $1000 barrier in 2012 (Steve Jobs paid $100,000 for his WGS)
- Potential for oncology and identifying “novel cryptic variants”
- However, concern about “too much information” and unclear, incidental findings

JAMA Link et al 2011

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Bottom Lines

- Genetics is a family business
- Start with affected individual if possible
- Geneotype ≠ Phenotype
- Consider all possible results and their implications before testing
- Get help if needed

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Personal genomes: Misdirected Precautions

- Personal-genome tests are blurring the boundary between experts and lay people.
- Models of regulation are outdated—rethink

Prainsack, Nature 08

Agenda for Personalized Medicine

- Companies should communicate high risks better and test for drug response markers
- Community should study markers in all ethnicities and look at behavior after tests

Ng, Nature 09
Cyrus and Christy Fibrosis

- Cyrus had azoospermia and congenital absence of vas defrens (1-2% of infertile men have this)
- Standard CF testing showed Cyrus is a carrier of Delta F508
- He wants to use ICSI (intracytoplasmic sperm injection)

Screen Christy? If so, how?

<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>1/4000</td>
<td>1/29</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>1/20</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>
</tr>
</tbody>
</table>

Bottom Line: Ethnicity matters
Christy 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 → more common technology
  - Testing → more accepted and available in non-whites

Genetic Possibilities for Fetus
- Normal / Normal
- Delta F508 / Normal
- Normal / Variant
- Delta F508 / Variant
- Prenatal Genetic “Diagnosis”?

Bottom Line:
Consider all possible results and their implications before testing

Cy Fibrosis, Conclusion
- Infertility group involved genetic counseling after Cy was found to carry Delta F508
- Values of Cy and his wife
  - Having a child that biologically has their DNA
  - Leaving no stone unturned
  - Risk averse
- ICSI and Prenatal Genetic Diagnosis were both used, and the outcome is a healthy son
Risks of first venous thrombosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>Annual Incidence</th>
</tr>
</thead>
<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>1.0</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 PT20210</td>
<td>20</td>
<td>0.15</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>
</table>

Thromboembolism in Pregnant Women with Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Probability per pregnancy</th>
</tr>
</thead>
<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>
</tbody>
</table>

These data are informative for the potential of targeted screening, rather than the current mass medicine approach—screening based on specific individual risk.

As just one example, early detection is a critical factor in preventing many diseases, yet a lot of us don’t get our health screenings as recommended. For instance, only about half of the people who should get colonoscopies actually do.

Genomic Profiles for Disease Risk: Predictive or Premature?

- Explosion of commercial availability of genomic “tests”
  - For diseases, conditions, traits, ancestry
  - DTC Advertising
- Conditions range from
  - earwax (wet vs dry) to
  - risk for significant adult-onset diseases

Eric Topol

Kenneth Offit, MD, MPH, JAMA 2008

Gerhardt, NEJM 2000