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

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Director of Clinical Research, UCSF Cancer Risk Program
Director of Training, Center for Translational and Policy Research in Personalized Medicine (TRANSPERS)

Have you referred patients to have genetic counseling or testing for...

1. Hereditary Cancer Syndromes
2. Cystic fibrosis
3. Hereditary Hemochromatosis
4. Hereditary Thrombophilia
5. Other hereditary syndromes
6. More than one of the above
7. None of the above

Have you sent genetic tests for...

1. BRCA
2. Cystic Fibrosis
3. HFE (Hereditary Hemochromatosis)
4. Factor V Leiden and/or Prothrombin 20210
5. Other genetic tests
6. More than one of the above
7. None of the above

Have you seen patients who wanted your interpretation of genetic tests you didn’t order for...

1. Hereditary Cancer Syndromes
2. Cystic fibrosis
3. Hereditary Hemochromatosis
4. Hereditary Thrombophilia
5. “Whole genome” scans
6. More than one of the above
7. None of the above
Have you ever ordered or been asked to interpret results from a home genetic test kit?

1. Yes
2. No
3. Don’t know

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
  - 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

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

*Nature Biotechnol 26, 76; 2008
What would you do next?

1. Tell Ivana not to worry, her family history is not concerning
2. Perform a clinical breast exam and discuss pros and cons of breast imaging
3. Give her family history “homework”
4. Test for deleterious BRCA mutations
5. 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
Which of the following are true?

1. Most health insurance plans cover BRCA testing in appropriate individuals.
2. Most health insurance cover screening and prevention in BRCA carriers.
3. Federal law prevents health insurance plans from premiums or dropping coverage based on genetic test results.
4. There are no legal protections for life insurance.
5. 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 (↑ test prob of + test; ID family mutation)
Cyrus and Christy Fibrosis

- Cyrus had azoospermia and congenital absence of vas deferens (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)

What are the chances of Cyrus and Christy’s fetus having Cystic Fibrosis?

1. One in four
2. One in two
3. Unable to determine with current info

Screen Christy? If so, how?

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Incidence</th>
<th>Carrier Frequency F508</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1/3300</td>
<td>1/25</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/8500</td>
<td>1/46</td>
</tr>
<tr>
<td>AJ</td>
<td>1/4000</td>
<td>1/29</td>
</tr>
<tr>
<td>Black</td>
<td>1/15,300</td>
<td>1/65</td>
</tr>
<tr>
<td>Native American</td>
<td>1/20</td>
<td></td>
</tr>
<tr>
<td>Zuni</td>
<td>1/3970</td>
<td></td>
</tr>
<tr>
<td>Pueblo</td>
<td>1/1500</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1/32,100</td>
<td>1/90</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

Family Implications

- 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
**Henry Chromatin and siblings**

- Henry is 40 and healthy
- Henry’s 35 year old brother, Harry, 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

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**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

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**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.

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**HHC Penetrance: 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?

1. Order LFT’s on your patient, Henry
2. Order a transferrin sat on Henry
3. Send Henry for 2 mutation HFE testing
4. Send Harry for 2 mutation HFE testing
5. A combination of the above
6. 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
- Harry’s genotype is C282Y/C282Y
- The sister with diabetes has normal labs and her genotype is H63D/nl

**Bottom Lines:**

Genotype ≠ Phenotype
Penetrance can be a moving target

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*

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**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>

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**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>

Gerhardt, NEJM 2000

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**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?

1. Test for the thrombophilia panel (Factor V and PT20210)
2. Don’t test, but continue OCP’s
3. Don’t test, but stop OCP’s
4. 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 anticoagulation 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

Direct to Consumer

“As if we didn’t already know too much about ourselves, we’re having our DNA done.”
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

Letting the Genome Out, Conclusion
- No pre-test counseling
- Increased anxiety
- SNP-mania: research versus clinical use
  - Population prevalence depends on population
  - Penetrance: moving target, hard to interpret results
- Genome knowledge in isolation is not generally useful

**Bottom Line:** $999 would have been better spent on a gym membership

Genomic Profiles for Disease Risk: Predictive or Premature?
Kenneth Offit, MD, MPH, JAMA 2008
- 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

### Evidence Based
- **Available**
  - Yes
  - No

- **Evidence**
  - Yes
  - No
**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

 Nguy, Nature 09

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**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_

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

_Eric Topol_

**“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.”**

_Eric Topol_

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Female A</th>
<th>Female B</th>
<th>Female C</th>
<th>Male D</th>
<th>Male E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>↑↑</td>
<td>-↓</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>↓↑</td>
<td>↓↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓=</td>
</tr>
<tr>
<td>Heart attack</td>
<td>↓↓</td>
<td>=↓</td>
<td>=↓</td>
<td>=↓</td>
<td>↑↑</td>
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<tr>
<td>Lupus</td>
<td>↑↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑=</td>
<td>↑=</td>
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<tr>
<td>Macular degeneration</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑=</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>↑↑</td>
<td>↓↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>↓↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>=↓</td>
<td>↑↑</td>
<td>↓=</td>
<td>↓↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>↓↓</td>
<td>=↓</td>
<td>↓↓</td>
<td>↑↓</td>
<td>=↓</td>
</tr>
</tbody>
</table>
**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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**“Explosion of genetic info”**

www.genetests.org

CDC EGAPP project

“Explosion of genetic information is a public health issue”

Khoury M, Genet Med 09

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**Not a tsunami, a rising tide**

![Growth of Genetic Testing](chart.png)

**Growth of Genetic Testing**

- Genetic testing labs
- Diseases for which testing is available

Each child has a 50% chance of inheriting an autosomal dominant disorder.

**Autosomal Dominant Inheritance**

Father with mutation on one chromosome

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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
Open letter to Medical Community
23 and Me now $499

- We do not and will not provide medical advice to our customers.
- Information we provide is tailored to genotypes, not to individuals.
- We have no way of evaluating our customers' health or medical needs, and we make every effort to clarify this for our customers.
- Genes are far from the only determinant of health.
- The scientific understanding of how genetics may affect disease risk and other aspects of a person's health is changing and will continue to change as more research is done.
- Giving personalized genetic information to our customers can inspire them to take more responsibility for their own health and well-being.
- At the very least, we hope our product will stimulate conversation among doctors, patients and researchers about genes and their role in human health.

Framing Risk and DTC Marketing
Gray, Cancer Epi Biomarkers Prevention 2008

- 284 women with family histories of breast/ovarian cancer randomized to mock DTC website or same website that included info on risks of genetic testing online...risk info from expert sources, and unattributed
- Outcomes of survey—intent to test, testing site preference, beliefs about DTC testing
- Risk exposed women had lower intent (0.48*) and less positive beliefs about online testing
All but one of EGAPP’s reviews have been unfavorable or neutral, generally because the panel didn’t see evidence of a health benefit. For example, in January an EGAPP group recommended against routine testing for factor V Leiden and prothrombin gene variants in people with a history of deep-vein blood clots. Both genes influence clotting. People who have had such clots should be treated with anticoagulants anyway, regardless of genetic status, the panel concluded. And in a second group—relatives of people who have had clots but who themselves have not—the panel judged that it would be too risky to treat preemptively with anticoagulants (which can cause hemorrhaging) based on genetic status alone.

The exception to EGAPP’s general pattern was a decision in 2009 in favor of a test for mutations linked to an inherited type of colorectal cancer, called Lynch syndrome. The evidence, EGAPP concluded, justified testing colon tumors of newly diagnosed patients—not to help the patient but to alert relatives of those who test positive that they have a 20% risk of being affected.

A patient being treated with clopidogrel (Plavix), a drug given to prevent the formation of clots after a heart attack and placed in a coronary artery, Some versions of the gene for the enzyme CYPIA2 have been identified as a “major” risk factor in patients who metabolize clopidogrel poorly, increasing the risk of blood clots and death. This makes it high, says Topol, because the mutation is common and unaltered is widely prescribed. At March 2010, the U.S. Food and Drug Administration (FDA) noted a March

As an example, the researchers reported that the treatment of some cancers, and in screening couples before conception to find dangerous mutations. Based on recent studies of cancer cell genetics, many labs are developing therapies to target specific mutations. However, these are not yet practical. Most public health reviews of these techniques have not found a breakthrough.