Genetic Testing In Primary Care: Who do we Test and for What?
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UCSF Women’s Health & Cancer Risk Program

Your Patient’s Genetic Test is Positive: How do you Counsel your Patient?
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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”

Cases: What’s the PCP’s Role?
- Hereditary Breast and Ovarian Cancer
- Lynch Syndrome
- Hereditary Hemochromatosis (HHC)
- Hereditary Thrombophilia
- “Letting the Genome Out of the Bottle”
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

Where to start with Ivana?

- She’s 24 and has no medical problems
- Her clinical breast exam is normal
- At 24, no radiographic screening is recommended
- She can create a pedigree to share with family at http://familyhistory.hhs.gov/
- You begin her pedigree and refer to a genetic counselor specializing in cancer (www.nsgc.org)

Three Generation Pedigree

Three Generation Pedigree after seeing Genetic Counselor

UCSF Cancer Risk Program
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
- Ethnic ancestry on all 4 grandparents
- Next step: test affected individual first, if able

BRCA 1 / 2 Associated Cancers:

<table>
<thead>
<tr>
<th>Lifetime Risk</th>
<th>General Population</th>
<th>BRCA Population</th>
</tr>
</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>BRCA1 - 20-40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2 - 10-20%</td>
</tr>
</tbody>
</table>

Other cancers associated with BRCA:
prostate, male breast, melanoma, pancreas

How Much Breast Cancer Is Hereditary?

- Breast Cancer
  - Sporadic
  - Family clusters
  - Hereditary

Suggested Guidelines for BRCA Testing

- Breast cancer before 40 or so (or any age if Jewish)
- Ovarian cancer at any age
- Male breast cancer at any age
- Relatives of a BRCA mutation carrier
- Strong family history of breast, ovarian, and/or related cancers
- Bilateral breast cancer
- Prior probability of 5-10% for testing positive

An individual with multiple primary cancers should be referred to genetics for evaluation of other cancer syndromes
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.

Family History of Hereditary Breast and Ovarian Cancer

- Hereditary
  - Ov, 52
  - Br, 42
  - Br, 45
- Sporadic
  - Br, 63
  - Br, 71

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

Autosomal Dominant Inheritance

Father with mutation on one chromosome

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

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
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

Benefits, Risks, and Limitations of BRCA Testing

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks and Limitations</th>
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</thead>
<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>
</tr>
<tr>
<td>May relieve anxiety</td>
<td>May result in psychosocial or economic harm</td>
</tr>
</tbody>
</table>
**Insurance and Genetic Testing**
- Most health insurance plans cover BRCA testing in appropriate individuals.
- Most health insurance plans cover appropriate screening and prevention in BRCA carriers.
- Federal law prevents health insurance plans from increasing premiums or dropping coverage based on genetic test results.
- There are no legal protections for life insurance.

**Ivana Test, next steps**
- Ivana’s cousin tested positive for a mutation common in the Jewish population.
- Ivana’s father tested positive for this same mutation.
- Ivan then tested negative…true negative, known family mutation.

**Bottom Lines: Men can be BRCA carriers**
- Start with affected individual (↑est prob of + result)…can identify family mutation.

**What would the oncologist say…**
- For Ivana’s cousin who already has breast cancer:
  - Would BRCA+ results change her current rx?
  - Do BRCA+ results affect recurrence and/or second primary?
  - Screening and prevention recommendations?

**Managing Breast Cancer in BRCA Positive Women**
- Treatment of the primary breast cancer may be influenced:
  - Breast preservation may not be applicable: high risk of second primary breast cancers, though radiation may reduce the risk:
    - Lifetime risk in BRCA – women about 15%.
    - Lifetime risk in BRCA+ women at least twice that.
  - Fear of radiation-induced cancers: BRCA1 and 2 are both radiation-repair genes—no long term F/U yet.
  - BRCA1 cancers are more often ER/PR negative.
Managing Breast Cancer in BRCA Positive Women

- Choices for prevention in women with cancer
  - Oophorectomy:
    - Most often chosen by these women—over 50% do so
    - Usually are past reproductive years, though not always
    - Reduces risk of later new breast cancer; may help reduce risk of relapse of ER+ cancer
  - Mastectomy:
    - For the primary breast cancer
    - For the opposite breast
- Chemoprevention?
- Screening?

What would the oncologist say…

- For Ivana’s cousin who already has breast ca
  - Would BRCA+ results change her current rx?
  - Do BRCA+ results affect recurrence and/or second primary?
  - Screening and prevention recommendations?

Men in BRCA + Families

- Prostate cancer
  - Most common cancer in men
  - Increased in some but not all BRCA families
  - Screening recommended, start age 40 (or age affected minus ten years)
- Breast cancer: physical exam only
- Examine the family pedigree
  - What other cancers have appeared?
  - Are they screenable?

What would the oncologist say…

- For Ivana’s cousin who already has breast ca
  - Would BRCA+ results change her current rx?
  - Do BRCA+ results affect recurrence and/or second primary?
  - Screening and prevention recommendations?

- For Ivana’s father
  - Screening for BRCA+ men?

- For Ivana
  - Cancer screening recommendations?
Screening and Chemoprevention in BRCA Carriers

- Breast cancer
  - CBE q 6 months, mammo at 25 y/o
  - MRI controversial (false positive=20%)
  - Tamoxifen may be more effective for BRCA2 than BRCA1 (80% of BRCA2 is ER+ and 80% of BRCA1 is ER-)
    - Not for reproductive age women without birth control
    - Not for older women, thrombotic risk women

Screening and Chemoprevention in BRCA Carriers

- Ovarian cancer
  - Expert recommendations: CA125 blood test and vaginal ultrasound every six months, start at age 25
  - OCP's for 3-5 years: 50% ↓ ovarian cancer
    - Unfortunately, this risk reduction applies to the OCP's of the 60's and 70's that are KNOWN to increase the risk of breast cancer
    - May be a class effect of suppressing ovulation, in which case the high progesterone, non-cyclic forms of contraception may work well—but unknown!
  - Other cancers: check the pedigree

Surgical options for BRCA carriers

- Risk-reducing salpingo-oophorectomy (RRSO)
  - ↓ ovarian and tubal cancers by 95%
  - Fine sectioning detects “occult tumors” in about 10% of tubes/ovaries
  - If pre-menopausal, 50% ↓ in breast cancer
- Risk-reducing mastectomy (RRM)
  - ↓ breast cancer by 95%
  - Many reconstruction options

Maria Colon and her 4 Children

- Maria is 52 and has several relatives with cancer
- Her 29 y/o son Frank dx’d with colon cancer
- Her sister had uterine cancer at 41 and her brother died of colon cancer at 50
- Colonoscopy at 50 showed 2 polyps, recommended to re-scope in 2-3 years
**Pedigree: familyhistory.hhs.gov**

**Lynch Syndrome**
- AKA Hereditary Non-Polyposis Colon Cancer
- Several ways to identify families
  - Clinical criteria
  - Tumor testing for Micro-Satellite Instability (MSI)
  - Genetic testing for MSH1 and MLH6
- Predisposes to: colon 70-80% lifetime risk, endometrial 20-60%, ovarian 10-12%, gastric 5-13%
- Also to: pancreas, gall bladder, small bowel, kidney, ureter, glioblastoma

**Clinical Criteria**
- Amsterdam (Families): 3 rels with Lynch ca and
  - One is first degree relative of the other two
  - At least 2 successive generations affected
  - At least one colorectal cancer dx’d before 50
  - Familial Adenomatous Polyposis excluded
- Bethesda (Individuals): with 2 Lynch cancers, CRC or endometrial cancer <50, with CRC and 1st deg rel with Lynch ca <50, adenomas < 40
- Sensitivity and specificity 30-60% and ↑ 20-30% when combined with MSI and/or gene testing

**What cancer screening do you recommend for Maria?**
- Annual colonoscopy
- Transvaginal ultrasound annually
- CA-125 annually (expert opinion)

**Would you recommend MSI or genetic testing?**
- If so, for who and which test?
- How would it change family recommendations?
**Lynch Syndrome: Screening**

- Target of interest is adenomatous polyp
  - Occur earlier in life vs sporadic
  - Larger vs age matched controls
  - More likely to evolve to cancer vs sporadic
  - May be “flat”, on a stalk, or sessile
- Removal of polyps thought to be curative for that particular lesion
- When detected early, can be removed endoscopically—always check margins!

**Colonoscopy for Lynch Syndrome**

- Onset: age 25 or 10 years younger than youngest cancer affected family member, whichever comes first
- Frequency: every one to two years, NOT longer even if a negative exam. Yearly if new polyps present on an exam.
- No data for use of CT colonoscopy: drawbacks are same prep, inability to see “flat” lesions, inability to remove at same sitting
- NO: sigmoidoscopy, +/- stool hemoccult
- Recommendations for FAP are quite different!

**Other Screens for Lynch Syndrome**

- Endometrial cancer
  - Especially if family history or MSH6 mutation
  - Endometrial biopsy (aspirate) or TVUS every 1-2 years, starting age 25-35, depending on family history
  - Some cohorts have ovarian cancer: consider screen
- Upper GI cancers
  - Endoscopy every 2 y starting age 30-35
  - Eradicate H. pylori if found
- Less data: ultrasound screening for GU tumors; head CT’s for families with Turcot’s syndrome; LFT’s for biliary tumors

**Surgery for Lynch Syndrome?**

- Total colectomy would be curative
- Subtotal colectomy would offer flex sig as a screening tool
- Surgery may be necessary to completely remove a large polyp, to treat Ca
- Hysterectomy would be curative for endometrial ca; might be reasonable if dysplasia found on biopsy; oophorectomy for families with ovarian...
The Colon Family, Test Results

- Frank’s tumor was MSI high
- The MLH1 genetic test showed a Variant of Undetermined Significance

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

- What does the oncologist recommend for Frank? For Maria? For other family members?

Henry Chromatin and siblings

- Henry is 40 and healthy
- Henry’s 35 year old Brother, Harry, was told he had hemochromatosis (found via abnl LFT’s on routine labs) and will need regular phlebotomy
- Harry doesn’t have Hep B, C, or alcoholism
- Henry’s 45 year old sister has diabetes, dx’d 1 yr ago
- Henry’s mother and father are both alive and well
- Henry has 2 children and 8 nieces/nephews (2-24 y/o)

Classic Hereditary Hemochromatosis is Autosomal Recessive

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Hereditary Hemochromatosis (HHC)

**Targeted Mutation Analysis of HFE gene**

1. C282Y: 10% of whites are carriers (heterozygotes) 3% Hispanics, 2% African Americans, 0.1% Asian 1/200 whites are homozygotes (C282Y/C282Y)
2. H63D: 25% of whites are carriers (heterozygotes) 18% Hispanics, 6% African Americans, 9% Asian

In individuals with HHC, what is detection rate?

- C282Y/C282Y ~ 60-90%
- C282Y/H63D 3-8%
- H63D/H63D ~ 1%
HHC Penetrance: Moving Target

- Depends on age & sex (Bulaj NEJM 00)

<table>
<thead>
<tr>
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<th>No iron overload</th>
<th>Iron overload Only</th>
<th>Iron overload + dz related condition</th>
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<tbody>
<tr>
<td>C282Y/ C282Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 median age 65 (Allen NEJM 08)

Phenotype vs. Genotype Testing

- Most people with HHC have a C282Y/C282Y genotype, but most C282Y/C282Y genotypes do not develop HHC.
- Diagnosis of HHC should not be made on genotype alone.
- Several very rare causes of disease (juvenile, transferrin receptor deficiency)

Mitigating Features for HHC penetrance?

- Alcohol: strong historical association
  - Alcohol does lower hepcidin, raise iron absorption
  - However, may not matter much for homozygotes
- Metabolic syndrome:
  - Increases ferritin levels, increases hepatic iron
  - May be confused with clinical disease
- Diet:
  - Increased iron intake???? Weak predictor at best
  - Vitamin C intake : does enhance iron absorption
- Sources of Iron Loss
  - Menstruation, childbirth
  - Chronic gastritis, H pylori, NSAIDS: little or no effect
- Inflammation
  - Lowers transferrin saturation, raise ferritin
  - Chronic active hepatitis will also increase hepatic iron---vaccinate
Back to the Chromatosis Family

- **Harry**
  - LFT's were ~ 1.5-2 times the upper limit of nl
  - Transferrin sat 50%, ferritin 1500
  - Liver biopsy consistent with hemochromatosis
  - No genetic testing to date
- **Henry**
  - Transferrin sat 46%, ferritin 100
- **Sister with diabetes**
  - Sat 40%, ferritin 30
- **Other sister**
  - Sat 50%, ferritin 250

French Staging of HHC

- **Stage 0**: Known homozygous, no biochemical abnormality: normal transferrin sat and ferritin
- **Stage 1**: Increased saturation (>45%) but normal ferritin and no symptoms
- **Stage 2**: Increased transferrin saturation AND abnormal ferritin (>300 for men, >200 for women) and no symptoms
- **Stage 3**: The above plus symptoms affecting quality of life (impotence, arthropathy, fatigue)
- **Stage 4**: The above with major organ disease: diabetes, cardiomyopathy, cirrhosis

Treatment of HHC—by phenotype

- If Stage 3 or 4: phlebotomy up to 7mL/kg or 550 mL—may give to blood bank
  - Weekly at first, hold only if Hgb <11 or symptoms
  - Target is Ferritin ≤50, then maintenance
  - May have iron deficiency symptoms; joints may not get better rapidly or at all
- **Stage 2**: phlebotomy, same parameters
  - May do less frequently, maintenance
- **Stage 0, 1**: Monitor only

Henry Chromatosis, Conclusion

- **Harry**
  - Targeted mutation testing: C282Y/C282Y
- **Henry**
  - C282Y/H63D
- **Sister with diabetes**
  - H63D/nl
- **Sister without diabetes**
  - C282Y/H63D
- **Mother**
  - C282Y/H63D
- **Father**
  - C282Y/nl

**Bottom Lines**: Genotype ≠ Phenotype
Penetrance can be a moving target
What does the hematologist recommend?

- Did genetic test results change care for any family members?

- Harry still gets treated
- Diabetic sister does not have the disease
- Brother: no evidence of disease; might monitor transferrin saturation every few years
- Sister: High saturation and high ferritin: consider phlebotomy program—at the very least watch closely

What does the hematologist recommend?

- With all the nieces and nephews, what screening and testing is recommended for the next generation? When to start?

- Test Harry’s partner: if she has no gene, then kids are NOT at risk
- Consider testing the mixed homozygotes’ partners
- You can wait until the children are adults
  - No family history of the juvenile form
  - Highly unlikely to manifest until over 18
Why do genotyping?
- Expensive, and genotype does not predict phenotype for most persons
- Could argue for transferrin saturation only
- However, majority of people in these families do NOT need saturation screening at all!
- Question of cost-effectiveness hasn’t been addressed

Do tested family members comply?
- HEIRS study—primary care based screening, notification by letter
  - Only 47% of those with homozygous genotype correctly understood their situation; 29% had no accurate recollection
  - Those who were negative had the best grasp
  - Iron overload vastly misunderstood, both + and –
  - Those who received a recommendation for action understood it; those with no recommendation were confused
  - Most did understand HHC is preventable, treatable
- Australian screening study followup: good compliance in pts recommended for phlebotomy

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, causes activated Protein C resistance
- Prothrombin 20210, Protein C resistance
- MTHFR variant (C677T), homocysteinemia
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency

Bottom Line: Get sister’s actual results
## Risks of first venous thrombosis

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<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>Annual Incidence</th>
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</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>0.02</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>
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<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>

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 with her whether it’s a good time to test and how you’ll use results

**Bottom line: Genetics is a “family business”**

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## 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 LMWH after becoming preg
Hematologist Weighs In

- The OB and OCP situations are an extreme of DVT risk that make prevention workable
- Other risk factors: cancer, antiphospholipid antibodies, hospitalization/immobility/surgery
- Because the annual risk of significant bleeding on anticoagulation is 1%, the benefit must exceed 1% to justify anticoagulation
- Screening in the population as a whole is not justified, nor is routine screening for every person with DVT

Does Testing Influence Treatment? Testing VTE Patients

- Might consider lifetime anticoagulation:
  - Antithrombin III deficiency is rare, but has highest case risk of recurrent VTE
  - Combinations of risk factors also high risk
- Common, variable penetrance, would treat only if recurrent:
  - Proteins S/C (except don’t start coumadin “bare”)
  - Prothrombin, Factor V mutations, MTHFR
- Circumstantial: unusual visceral site at high risk if recurrence, Doppler evidence of lack of clot resolution at 6-12 months, or persistent positive D-dimers

Risks for Carriers

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Surgery, Trauma</th>
<th>Pregnancy</th>
<th>Oral Contraceptives</th>
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<tbody>
<tr>
<td>Antithrombin III deficiency</td>
<td>0.04%/year</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>FVL</td>
<td>0.02%/year</td>
<td>0.1%</td>
<td>0.3%</td>
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<td>Prothrombin</td>
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<td>0.1%</td>
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</tr>
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<td>Factor V</td>
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<td>0.1%</td>
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</tr>
<tr>
<td>MTHFR</td>
<td>0.02%/year</td>
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<tr>
<td>Protein S/C</td>
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<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Protein C</td>
<td>0.02%/year</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Protein S/C + C</td>
<td>0.02%/year</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Protein S/C + C + Protein C</td>
<td>0.02%/year</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Preventive Treatment of Carriers

- Avoid: Estrogen treatment in any form—OCP’s, HRT, Tamoxifen, Raloxifene
- Prophylaxis for surgery, immobilization, long plane rides—use LMWH preferentially, duration after surgery should be more prolonged?
- Pregnancy: treatment with LMWH during pregnancy and the puerperium
Testing Unaffected Family Members

- Reproductive risks, as in this case
- Known possible double mutations
- Pedigree suggests very high penetrance or early onset of disease
- Counseling:
  - High risk situations: advise physicians, follow common sense rules to avoid risk

Whom to Screen?

- Women with ≥ 3 episodes fetal loss
- Recurrent VTE without “cause”--? lifetime anticoag?
- Young women with VTE on OCP’s or post partum?
- Risk factors that render screening moot: VTE with clear risk; antiphospholipid syndrome; cancer; intolerable risks for lifetime anticoagulation
- SCREENING DOES NOT DETERMINE WHO NEEDS LIFETIME ANTICOAGULATION—only patients with recurrent DVT need to be considered, and majority of these do not have a mutation

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

Letting the genome out of the bottle (Hunter NEJM 08)

- 50 year old man, 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

General Principles of Genetic Testing for Disease Predisposition

- Genetics is a “family business”
- Team approach: specialists and genetic counselors
- If possible, start with the affected individual
- Genotype does not always equal phenotype
- Penetrance can be a moving target
- Discuss pros and cons of testing
- Knowledge of ethnic background is helpful
- Plan for the “next step” and consider all possible test outcomes

Summary: 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

Summary: Role of PCP

- Pre- and post-test counseling
- Assembling and coordinating team of experts
- Acting as patient advocate and understanding patient’s values
- Considering patient, family, as well as genotype
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

Discuss
- Test results
- Interpretation of results

Discuss
- Plans for prevention and treatment
- Sharing results with family members
- Potentially testing other family members
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

Screen Cy’s wife? 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>1/29</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Black</td>
<td>1/15,300</td>
<td>1/65</td>
<td>48%</td>
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<tr>
<td>Native American</td>
<td></td>
<td></td>
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</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>
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<tr>
<td>Asian</td>
<td>1/32,100</td>
<td>1/90</td>
<td>30%</td>
</tr>
</tbody>
</table>

Bottom Line: Ethnicity matters

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 → more common technology
  - Testing → more accepted and available in non-whites
**Genetic Possibilities for Fetus**

- Normal / Normal
- Delta F508 / Normal
- Variant / Normal
- 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