Genetics in Medicine

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Hospital Internal Medicine

Noon Conference
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Mayo Clinic Internal Medicine Residency
Disclosures

- No conflicts of interest, except Mayo Clinic does offer various genetic tests and special coagulation testing.
- No off label uses of drugs
Family History in General Medicine

“Non-contributory”
Case

- 3 weeks of ‘dizzy spells’ and migraines
- Passed out after coming back from shopping
- No jerking movements, tongue biting, or incontinence

- Upon arrival at the ED
  - Pupils were fixed and dilated
  - Bradycardic; refractory to atropine
  - Temporary pacing and dopamine started
• Initial ECG
  • Sinus rhythm, RBBB, LAFB, 1st degree AV block

• Progressed to a wide complex rhythm

• Then PEA arrest.
  • She received 3 mins of CPR with ROSC
• LHC
  • clean coronaries
  • Severely dilated and hypokinetic LV
    • ? Apical ballooning
  • Balloon pump placed

• TTE
  • Moderate-severe RV enlargement
  • Severe decrease in RV systolic function
  • Estimated RVSP 37 mmHg (102 systolic)
  • Dilated IVC with no inspiratory collapse
• MAPs >65 mmHg
• But then…
  • Complete heart block
  • Followed by pulseless torsades
  • Pulse returned after defibrillation
• Emergent pacemaker placement
Labs

- Lactate 3.7
- TSH 0.2 (RR 0.3-4.2)
- Hb A1c 5.9 % (RR 4-6)
- Plts 128
- Iron studies normal
- Urine drug screen negative
So when I get to see her

- She is intubated and sedated
- Not obviously dysmorphic
- Hearing and neurologic exams not possible

- Lacking information about her-
  - Earlier health and growth
  - Exercise tolerance
  - Intellectual development
RV muscle biopsy

- Pathology did not see vacuolization

- EM requested
  - mild, non-specific degenerative changes noted. Diagnostic ultrastructural abnormalities of mitochondria are not seen.
Additional Clinical Information

• Calves not hypertrophic
• No cataract or balding
• Easy fatigability
• But her relative describes arm cramps where she needs to actively stretch her wrists out for relief.
Poor exercise tolerance
Worse ET
Severe intellectual disability

Maternal anticipation

Worse ET
Severe intellectual disability
SUMMARY INTERPRETATION

POSITIVE

The most significant finding in this panel of tests is a pathogenic mutation. This result is consistent with a diagnosis of, or a predisposition to develop, myotonic syndrome.

<table>
<thead>
<tr>
<th>Gene/Test</th>
<th>Technical Result</th>
<th>Mutation Type</th>
<th>Inheritance</th>
<th>Clinical Relevance</th>
<th>Reference</th>
<th>Pub Med ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPK</td>
<td>856 and 13 repeats</td>
<td>Repeat Expansion</td>
<td>Autosomal Dominant</td>
<td>Pathogenic</td>
<td>Normal (5-34) Premutation (35-49) Mildly Affected (50-99) Classic (100-1000) Congenital (&gt;1000)</td>
<td></td>
</tr>
</tbody>
</table>

All other analyzed segments were negative.

Recommendations: This individual’s family members are at risk for possessing or inheriting this mutation. Careful reconciliation of this molecular data with this individual’s clinical presentation, family history, and other laboratory results, in conjunction with genetic counseling, is highly recommended.
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Clinical Signs</th>
<th>CTG Repeat Size $^{1,2}$</th>
<th>Age of Onset</th>
<th>Average Age of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutable normal (premutation)</td>
<td>None</td>
<td>35-49</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mild</td>
<td>Cataracts</td>
<td>50-~150</td>
<td>20-70 yrs</td>
<td>60 yrs to normal life span</td>
</tr>
<tr>
<td></td>
<td>Mild myotonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic</td>
<td>Weakness</td>
<td>~100-~1000</td>
<td>10-30 yrs</td>
<td>48-55 yrs</td>
</tr>
<tr>
<td></td>
<td>Myotonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>Infantile hypotonia</td>
<td>$&gt;1000^3$</td>
<td>Birth to 10 yrs</td>
<td>45 yrs $^4$</td>
</tr>
<tr>
<td></td>
<td>Respiratory deficits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intellectual disability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Classic signs present in adults</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immediate Recommendations

• Extreme caution with statin use

• Neurology Evaluation
  • EMG
  • Audiometry
  • Eye exam

• Swallow evaluation

• Medic-Alert bracelet
Subsequent Recommendations

- Diabetes, hypothyroidism, and male hypogonadism surveillance
- PFT and sleep study
- PMR and speech therapy
- Extreme caution with anesthesia and muscle relaxants (eg vecuronium)
- Annual ECG and periodic echo surveillance for untested at-risk family members.
Genotype-Phenotype Correlation

• AKA genetic determinism

• But CTG repeats are inherently unstable
  • In mitosis as well as meiosis

→ Somatic mosaicism
  • Different tissues may have different sized expansions
Deciding to test

• A 35 year old man with a father who had Huntington disease that developed age 55 requests genetic testing.

• What would you do if you were the son?
  • Order the test
  • Recommend against testing as Huntington is an incurable condition that cannot be averted
  • Discuss potential risks to life insurance and employment, but order the test if he was not concerned
  • Refer to genetics

• What would you do if he was your patient?
  • Order the test

Pre-symptomatic Testing

• There is a material difference between a *fait accompli* and receiving a result you consciously volunteered for.
  
  • In the latter you may take ownership and integrate it differently (positively) into your life
  
  • Knowledge was acquired for a specific purpose
  
  • Even ‘bad news’ might be less demoralizing
Thrombosis Risk Factors

• Virchow’s Triad
  • **Hypercoagulability**
    • Medications (estrogen), inflammation/cancer, smoking
    • GENETIC
  • **Hemodynamics** (stasis, turbulence)
    • Travel, surgery, trauma, anomalous anatomy, obesity lines/instrumentation
  • **Endothelial injury/dysfunction**
    • Trauma, inflammation/smoking, lines/instrumentation, infection

Images taken from:
and
Blood August 6, 2009 vol. 114 no. 6 1138-1139
Inherited Thrombophilia - a quantitative trait

- We all know height is inherited
- Yet there is no pattern of having any given fraction of offspring tall/average/short. (exc Gaussian)
- It is merely a tendency for parents to have offspring of corresponding height
- This is due to there being many genes being inherited or not inherited, in parallel
- A random sampling of the parents height genes finds its way into each of the offspring, without any having exactly the same set
- And environment can render a child of short parents to be tall, and vice versa

Which single factor is *the* cause?
Moreover, if the difference between 2 people is 1 small angel/devil- Would that justify lifelong changes in Rx?

Surgery  Acquired Protein C def
FVL   FVL
Obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Normals</th>
<th>% VTE pts</th>
<th>RR of 1st DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden (heterozygous)</td>
<td>0.05-4.8*</td>
<td>18.8</td>
<td>7</td>
</tr>
<tr>
<td>Factor V Leiden (homozygous)</td>
<td>0.02</td>
<td>1.5</td>
<td>80</td>
</tr>
<tr>
<td>Factor V with R2 mutation (heterozygous)</td>
<td>0.06-0.12</td>
<td>10.0</td>
<td>10</td>
</tr>
<tr>
<td>Prothrombin G20210A allele</td>
<td>0.06-2.7*</td>
<td>7.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.2-0.4</td>
<td>3.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.2-0.4</td>
<td>2.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>0.02-0.2</td>
<td>1.9</td>
<td>20</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>&lt;0.01</td>
<td>0.8</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hyperhomocysteinemia**</td>
<td>5-7</td>
<td>10</td>
<td>2.95</td>
</tr>
<tr>
<td>Elevated factor VIII level</td>
<td>11</td>
<td>25</td>
<td>4.8</td>
</tr>
<tr>
<td>Elevated factor IX level</td>
<td>10</td>
<td>20</td>
<td>2.8</td>
</tr>
<tr>
<td>Elevated factor XI level</td>
<td>10</td>
<td>19</td>
<td>2.2</td>
</tr>
<tr>
<td>Elevated lipoprotein (a) level</td>
<td>7</td>
<td>20</td>
<td>3.2</td>
</tr>
<tr>
<td>Elevated thrombin-activatable fibrinolysis inhibitor (TAFI)</td>
<td>9</td>
<td>14</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*Percent lowest in Asian or African descent; highest in Caucasian descent

**>18.5 μmol/L

Discovered 1965
Discovered 1990s
40% 1st VTE <50y

**Fig. 1.** Overall survival in individuals with thrombophilia and controls. The solid line represents individuals with thrombophilia, the dotted line the control group.
Delusions of Grandeur

- Do we suppose we have the insight to quantify the exact effect on thrombotic tendency of one, or even several, defects in such a complex system?
  - Not denying that in specific situations the thrombophilias do promote clotting

- Until science has uncovered all the variables, the best guide is biology
  - What their own and their family’s tendency suggests
Sure, but height is a continuum, how is VTE anything but dichotomous?

• The **strength** of the tendency to clot **is** being demonstrated when someone presents with a clot
  • It is seen by looking at:
    • What other precipitants there were
    • What age they are affected
    • How many episodes they (eventually) may have
    • Site
    • Resistance to anticoagulation/prophylaxis etc.
Genetic Versus Multifactorial disease

• ‘Hereditary’ hemochromatosis
  • Autosomal recessive
  • Yet affects men >> women
  • 1/9 Caucasians in N. America is a carrier of the C282Y mutation
    • 1/227 homozygous.
  • C282Y/C282Y is seen in >90% of typical patients;
    • However, with reduced penetrance, ~20% of male homozygotes and 50% of female homozygotes will have nl ferritin levels.
    • If the disease is defined based on symptoms, the prevalence would be much lower still.

• Should genotype be used to define disease or the presence of iron overload, INDEPENDENT of genotype.

Can J Gastroenterol. 2007 February; 21(2): 101–104.
'A Major Treatment Gap In Preventive Cardiology'

- 509 pts *under 60 yrs* admitted to CCU with symptomatic CAD
- 70% had insufficient data for FHx analysis
- In a subsequent cohort of 103 pts in the same unit, a NP recorded a 1st degree relative with CV disease <60y in 43%,
- 95% of these CCU pts had phenotypic familial hypercholesterolemia (FH).

→ <30% of these admissions, on whom you miss the FH dx.

Clues to a Genetic Etiology

• Severity
• Age of onset
• Frequency of recurrences
• Family history

• Severe illness is used to justify shortcuts
  • But this group is self-selecting for pathology and high pick-up rates
Differential Diagnosis

- Family history narrows the differential
  - Very few things in medicine clinch a diagnosis, in and of themselves.
    (And whole genome sequencing will be NO different)
  - ‘Autosomal dominant myopathy’ is much more useful to the neurologist than simply ‘positive family history’
Liability

• At what point do we become liable for writing ‘non-contributory’ when that is wrong?

• At what point can we safely stop drawing the pedigree?
  (One geneticist’s suggestion)
  • 1st degree relatives
  • Just get the ages and cause of death of parents.
    • If they had an MI, try to establish if it was truly ischemic Vs unexplained sudden death, and if it was their first.
  • Any other diseases that people had early....(<50y) ?
  • Any siblings/offspring die in childhood?
  • Infertility/miscarriages and developmental delay?
  • Additional will always depend on the condition.
    • You can refer to genetics (consulting is cheaper than ordering tests)
Patient-Provider Relationship

- Patients believe their family history is relevant (even fatalistically determinant) and are disoriented when we brush over it.

- Family history is not some medically suspect ‘belief-system’

- Most clinicians are not lacking expertise
  - We mostly lack the raw pedigree information needed to speak intelligently to their concerns

- *Excluding* risk to themselves (or their offspring) based on simple history can be more ‘therapeutic’ than any prescription.
  - Hard to get >50% recurrence risk, but this is *not* intuitive. (Mitochondrial inheritance)
Mother with breast cancer and confirmed BRCA1 mutation

What test would you order for her 41 yo daughter?

Independent of experience, or specialty, physicians chose more comprehensive testing for healthy relatives than recommended.

• Only 20.4% correctly ordered the $475 test (known mutation) rather than $3340 (comprehensive)
• The correct test takes also takes 2 weeks, instead of 8
• Only 2% followed best-practice in all scenarios

The argument against referring to Genetics was ‘cost’ and ‘time’

Considerations about Genetic Testing

- Permanent result
  - Future understanding may add additional information to the same test result
- Pre-symptomatic, but predisposed to a disease
  - Life/disability insurance
- Cost
- Risk of negative and other non-informative results

Ensenauer et al. Mayo Clinic Proc. 2005. 80(1); 63-73.
Ethical considerations

- ALL states advise appropriate counseling prior to genetic tests

- Though few require written consent, you would be safest recording the discussion in the chart
  - CIM protocol includes seeing a genetic counselor

- If a result comes back positive, the ordering provider would be responsible for communicating the genetic implications - even if they do not warrant active intervention/testing

- You could open up issues of paternity assignment
Whole Genome Sequencing is here

- ‘Real’ gene testing

- Imagine you diagnose Marfan Syndrome while testing for somatic genetic targets in a pancreatic tumor…

- **Will you:**
  - Co-ordinate their annual eye exam and echo?
  - Counsel them about their recurrence risk?
  - Arrange for testing their blood relatives?

- (Medicine will have to find a way to document pedigrees scientifically if we are going to do this kind of testing)
ACMG Recommendations for Reporting Incidental Findings in Exome/Genome Sequencing

Gene Testing - a ‘procedure’, not a ‘test’

• ECG and LHC look for similar problems
  • But are different
  • Invasiveness carries additional risk

• Aren’t CBC and CFTR testing both mere blood draws?

• Gene testing is ‘invasive’
  • There are indications, benefits and risks
  • It requires counseling, consent, and follow up on results
Family History

- Does take time
- But, only needs to be constructed once
- Both clinician and patient can see whether there is a preponderance in relation to degrees of relationship, and proportion affected
  - Differential diagnosis
    - May not rule in, but can narrow possibilities
  - Directs investigation and therapy
  - This aids compliance - once the pt is convinced they really have a family history
  - Can identify others at risk

- Saves time and money in the long run

McKay MJ. Med J Aust 2010; 193(7); 429-30.
At what point do we become liable for writing ‘non-contributory’ when that is wrong?

• Or when can we safely stop drawing the pedigree?
  (One geneticist’s suggestion)

  • 1\textsuperscript{st} degree relatives
  • Ages and cause of death
    • If they had cancer of X, try to establish if it was truly primary ca of X, and the age at diagnosis
  • Any siblings/offspring die in childhood?
  • Any cancer or other diseases that anyone had early.....<50y ?
    • Extend further as necessary

• Referral to Genetics is cheaper than ordering tests
Pre-symptomatic Testing

• There is a material difference between a *fait accompli* and receiving a result you consciously volunteered for.

  • In the latter you may take ownership and integrate it differently (positively) into your life

  • Knowledge was acquired for a specific purpose

  • Even ‘bad news’ might be less demoralizing
Missed Diagnoses

- Referrals to Genetics commonly occur when all affected relatives are deceased

- Makes testing and risk assessment more difficult

- Reduces benefit from testing and prophylactic interventions

- Oncology and Palliative care have the first and last chance to refer.
3-2-1 Family History Rule

- 3 affected relatives with the same/associated cancers
- Across 2 generations
- With at least 1 affected <50 years
Could referral be improved using the 3-2-1 family history rule?

- 508 random pts referred to a cancer genetics clinic
- 71% referrals were for unaffected persons
  - 22% of these had all affected family deceased
  - 24% of these had lost their last affected relative <1yr prior to appointment
- 59% met all 3-2-1 criteria
- 23% met 2 criteria
- 67% could have been referred earlier

Genetic Testing Paradigm

- Testing (living) affected relatives removes ambiguity of indirect testing
  - Consent and obtaining useful sample is much easier

- A negative result on an at-risk relative is NON-INFORMATIVE
  - It cannot confirm the individual is unaffected

- Variant of Uncertain significance (VUS) is INDETERMINATE
  - We try to correlate these with other indicators of pathogenicity
  - Very tricky to interpret with unaffected persons
Genetic Testing Paradigm

- A positive result in an affected person → TRUE POSITIVE
  → site-specific cascade testing of relatives

- A negative result in an individual from a family with a known mutation is a TRUE NEGATIVE
  - Allows reversion to screening recommendations for the average-risk population
  - Confirms no additional risk to that person’s offspring
DNA Banking

- Long-term storage of DNA
- Available commercially, $100-300
- Not usually covered by insurance
- Can allow deferral of counselling and financial costs to a less stressful time
- Need to specify which individuals can access specimen
- Ideally, the patient should specify those persons in their Will
- We use this to do follow on testing of active pts, but our lab strongly discourages promising very long term availability
Indications for Genetic Testing

• Confirm diagnosis
• Predict prognosis
  • Including genotype-phenotype correlations
• Determine (and justify) management
  • Eg support insurance claims for annual breast MRI
• Recurrence risk
• Investigate at-risk relatives (and pregnancies)
Mayo Medical School Course

  - myocardial infarction AND cholesterol
  - thrombosis AND stroke
  - breast cancer AND ovarian cancer

### $$$ List prices

- **Mayo Medical Laboratories**
  
  may not reflect actual prices billed and does not relate to how much is reimbursed to the patient, if any

<table>
<thead>
<tr>
<th>Service Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia profile (THRMP #83093)</td>
<td>$2246.80</td>
</tr>
<tr>
<td>Antithrombin activity (ATTF)</td>
<td>$219.80</td>
</tr>
<tr>
<td>Protein C activity (CFX)</td>
<td>$255.80</td>
</tr>
<tr>
<td>Protein S Ag, free (PSF)</td>
<td>$172.20</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation (PTNT)</td>
<td>$546.10</td>
</tr>
<tr>
<td>Activated Protein C resistance (APCRV)</td>
<td>$308.70</td>
</tr>
</tbody>
</table>

**Total** $1502.60
The Thrombophilias: “Well-Defined Risk Factors with Uncertain Therapeutic Implications”


• Experimental data was real, but not ‘real life’

• Clinical data from highly affected families only represented the tip of the iceberg.
  • It was wrong to extrapolate from these reports
  • Something as common as 10% of a population is extraordinarily unlikely to be highly lethal.
    • Natural selection would have reduced it.

• We have 10-15 years of experience now, the studies are done, the science is mature, and we need not go on making the same errors
Scale of our Problem (as a profession)

Example-

ACOG advise in “women with recurrent pregnancy loss (RPL) or placental abruption, IT testing is NOT recommended because it is unclear whether anticoagulation reduces recurrence (level B)”

Obstet Gynecol 2011; 118;730-40

• Yet <¾ of women with RPL have ‘thrombophilia panels’ ordered
  • Just became embedded in people’s minds as a basic part of ‘the work-up’

• And management is commonly modified on the basis of results

• Patients who have experienced RPL are more likely to request treatment once found to have a genetic “abnormality” that could ‘explain’ the losses.
  • Treatment risks may be readily accepted without full consideration by patients desperate for a pregnancy.

Genet Med 2012; 14, 39–50
Br J Haematol 2009;144:241–244
• We worry about missing ‘diagnoses’ and implications for treatment decisions

• But, pts worry about more basic facts
  • Life expectancy
    • And even if the risk of clot is marginally greater, the risk of sequelae is a fraction
  • Risk and burden and expense of Rx

R.M. Bertina, F.R. Rosendaal. Venous Thrombosis — The Interaction of Genes and Environment..
Self-Reflection

• We frequently order testing during active thrombosis or anticoagulation.
  • Are we more liable for ordering a test inappropriately and acting upon the result (inappropriately)?
  • Is it wrong to wait on a test because the result will be inaccurate because of an active situation out of our control?

• An irresistible urge to intervene can lead to fatal consequences.
  • 3% annual risk of major bleeding from anticoagulation
    • <8% in the elderly

• Indeed, are we obliged to test at all, if the result is not going to CHANGE management

  “ONLY ORDER A TEST IF YOU KNOW WHAT TO DO WITH THE RESULT”

- Anon
Practical Considerations for Testing

- Needs to be at least 2-3 mths after an acute event
- Off warfarin 2-4 weeks prior
- Caution with functional or antigenic tests
  - Normal ranges vary by age, race and gender
  - AT deficiency should always be confirmed with a 2nd sample
  - Also consider exogenous hormonal effects

<table>
<thead>
<tr>
<th>Test</th>
<th>Positivity</th>
<th>Fraction of positives which also had INR&gt;1.3</th>
<th>Median Age</th>
<th>% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein S Functional</td>
<td>17.7%</td>
<td>21.2%</td>
<td>46</td>
<td>65.7%</td>
</tr>
<tr>
<td>Protein S Total Ag</td>
<td>4.8%</td>
<td>40.5%</td>
<td>47</td>
<td>63.0%</td>
</tr>
<tr>
<td>Protein S Free Ag</td>
<td>18.5%</td>
<td>25.0%</td>
<td>39</td>
<td>67.4%</td>
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<tr>
<td>Protein C Functional</td>
<td>13.7%</td>
<td>53.8%</td>
<td>46</td>
<td>65.4%</td>
</tr>
<tr>
<td>Protein C Total Ag</td>
<td>12.9%</td>
<td>33.3%</td>
<td>47</td>
<td>62.9%</td>
</tr>
<tr>
<td>Antithrombin Functional</td>
<td>7.5%</td>
<td>N/A</td>
<td>46</td>
<td>65.8%</td>
</tr>
<tr>
<td>Antithrombin Antigen</td>
<td>14.3%</td>
<td>N/A</td>
<td>46</td>
<td>65.3%</td>
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<tr>
<td>APC resistance</td>
<td>17.7%</td>
<td>N/A</td>
<td>46</td>
<td>65.7%</td>
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<tr>
<td>V Leiden mutation</td>
<td>12.3%</td>
<td>N/A</td>
<td>47</td>
<td>64.1%</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>4.9%</td>
<td>N/A</td>
<td>46</td>
<td>64.1%</td>
</tr>
</tbody>
</table>

*Positivity for V Leiden and prothrombin mutations includes both heterozygotes and homozygotes; for the remaining assays it includes all results falling below the lower limit of the reported reference interval.*
• No need to know genotype (or even non-inherited thrombophilies)
Asymptomatic Screening

• Population screening requires:
  • Prevalent condition +
  • Safe, effective intervention +/-
  • Cost effective testing +/-
  • Clinical validity (high sens/spec) --
    • Poor positive (low penetrance) and negative predictive values (unknown unknowns)

• Screening unselected, asymptomatic people for IT is NOT indicated

Suggested Adult Testing Indications

- VTE before age 50
- ‘Unprovoked’ VTE at any age
- Recurrent VTE
- Unusual site (cerebral, mesenteric/PV, hepatic v.)
- VTE at any age if 1\textsuperscript{st} degree relative with VTE <50 yrs

If somehow identified as being a carrier of any single mutation, complete testing may be considered to elicit additional contributors

- This would NOT include testing all 1\textsuperscript{st} degree relatives (at 50% risk of being carriers), in absence of a clear biologic tendency
Ethical considerations

- ALL states advise appropriate counseling prior to genetic tests
  - Though few require written consent for IT
  - You would be safest recording the discussion in the chart

- Provider and pt need to be aware there may be familial implications
  - If a result comes back positive, the ordering provider would be responsible for communicating the genetic implications - even if they do not warrant active intervention/testing
  - Theoretically you could open up issues of paternity assignment

- Legally pts will be required to report this in life and disability insurance applications
  - Medically covered under ‘GINA’
Family History

• Empiric risk from the SAME mutation differs between families
  • But can be estimated from the number of affected members
  • Median age at onset
    • 45yrs unselected FVL or PCD
    • 30yrs in members of affected families

Blood, Vol 94, No 8 (October 15), 1999: pp 2590-2594

• Women **without I.T.** from families with known defects have more risk than general population
  • A negative test would be false reassurance
  • Families share environment and behavioral risk factors, in addition to genes.
  • Indeed, FHx may be as/more useful than testing.
    • Face time required for testing would not be quicker than FHx, if done with the appropriate counseling.
    • In case of a positive, the pt would quickly be discussing family implications, and having a pedigree would shorten this discussion

Arch Intern Med. 2009;169(6):610-615
Routine Practice

• The general prevalence of IT, enriched in VTE (<50%), tells us that this is not a small, high-risk subset, but very much the *mainstream*
  • Liable to benefit from treatment guidelines drawn up for unselected cases (based on studies that would have inadvertently included similar pts)
  • Testing won’t affect your decision tree

• IT is considered ‘high-risk’ and warrants perioperative subcutaneous UFH / LMW heparin
  • Routine practice has again subsumed what is indicated for IT
  • Empiric thromboprophylaxis addresses IT-related risk
Clinical Judgment

- Do we give lifelong therapy with confirmed IT in the following situations?
  
  - 2 or more ‘provoked’ thromboses
  
  - 1 *life-threatening* thrombosis (PE, cerebral, mesenteric/PV)
  
  - 1 spontaneous thrombosis at an *unusual site* (cerebral or mesenteric vein)
  
  - 1 spontaneous thrombosis with >1 genetic risk factor
Contraception with IT

- 2-6x risk of VTE with pill Vs non-users.

- Relative risk Vs controls also on OCP:
  - FVL heterozygotes 6-40x (→ 0.35% excess abs risk)
  - PGM heterozygotes 10-15x
  - ATD, PCD, PSD <10x

- VTE risk in 1st year is 10x subsequent years!

- Estrogen now contained in combined pills, td patches & vaginal ring.

- Smoking may be synergistic for risk
Estimated number of asymptomatic thrombophilic women who should use LMWH prophylaxis during pregnancy and/or the postpartum period to prevent pregnancy-related VTE, and estimated number needed to test

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>N of female relatives to be tested to prevent VTE during pregnancy(^a)</th>
<th>N of female relatives to be tested to prevent VTE postpartum(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin, protein C, or protein S deficiency</td>
<td>83</td>
<td>33</td>
</tr>
<tr>
<td>Factor V Leiden or prothrombin mutation, heterozygous</td>
<td>250</td>
<td>60</td>
</tr>
<tr>
<td>Factor V Leiden, homozygous</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^a\) Based on family studies as outlined in Table 1

These estimates apply to women with a positive family history of VTE and assume a 100% efficacy of prophylaxis with LMWH

Estimated number of asymptomatic thrombophilic women who should avoid using oral contraceptives to prevent one VTE, and estimated number needed to test

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Risk on OC per year (%)</th>
<th>Risk difference per 100 women</th>
<th>N not taking OC to prevent 1 VT</th>
<th>N of female relatives to be tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin, protein C, or protein S deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient relatives</td>
<td>4.3(^a)</td>
<td>3.6</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>Non-deficient relatives</td>
<td>0.7(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden or prothrombin mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatives with the mutation</td>
<td>0.5(^a)</td>
<td>0.3</td>
<td>333</td>
<td>666</td>
</tr>
<tr>
<td>Relatives without the mutation</td>
<td>0.2(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population, no family history</td>
<td>0.03(^b)</td>
<td>0.02</td>
<td>5000</td>
<td>None</td>
</tr>
<tr>
<td>General population, positive family history</td>
<td>0.06(^b)</td>
<td>0.04</td>
<td>2500</td>
<td>None</td>
</tr>
</tbody>
</table>

\(^a\) Based on family studies as outlined in Table 1
\(^b\) Based on a population baseline risk of VTE in young women of 0.01% per year [64], a relative risk of VTE by use oral contraceptives of three [65], and a relative risk of two of VTE by having a positive family history [21]
Management

• Routine IT screening prior to starting is NOT recommended.
  • 92,000 carriers would have to be identified to prevent 1 death
  • Cost of screening to identify that many carriers >$300 million

• Screen if **FHx** suggestive of IT or tendency to clot esp with OCP/pregnancy
  • multiple relatives, or 1 under age 50 affected
  • Or a mutation is known
  • It is ALWAYS appropriate to take a full FHx into account when making any therapeutic decision

• Decisions may change re: contraception and pregnancy (esp post-partum)

• Estrogen relatively contraindicated with personal or family hx of VTE, of any cause
  • Provoked or unprovoked
  • Unless on anticoagulation (warfarin itself warrants reliable contraception)
  • For HRT, transdermal patches may be safer as they reduce upward excursions in circulating hormone level