Assessing the Economics of Genomic Medicine
A Workshop of the Institute of Medicine

Tuesday July 17, 2012
Washington D.C.

Session III (1:05pm)

Unprovoked DVT / Pulmonary Embolism

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My 2003 experience as a real patient in this situation

- Unprovoked pulmonary embolism at age 43 (vs median age 60)
- No prior understanding that I was at risk
- Admitted in ER & told situation was immediately life threatening
- 4 days in the hospital with <u>many</u> tests (e.g. nuclear imaging) $22k
- Started on heparin & coumadin – standard doses
- <u>After</u> release from hospital, a focused genetic test (qPCR) reported heterozygocity for Factor V Leiden genetic variant
- Warfarin dosing unstable for months even with very careful diet, INR tests
- 2nd pulmonary embolism 6 months later
- Months of testing to look for suspected “occult” cancer
- Warfarin dose gradually stabilized, now constant for > 8 years
- No cancer was ever found
- No further genetic tests of any kind ever recommended
- My 18 year old daughter was prescribed estrogen-based contraceptives to treat her acne

Background Research

- Web search of OMIM:
  - Variant identified as causal for embolism in 1994
  - Testing available for 9 years prior to my embolism
    - **IF** you knew you needed it
  - 3-5% of Caucasians
  - Cases include combinations of SNP & Deletion

- Family discussion:
  - Mother hospitalized in 1960's (age 40) for clotting in legs
  - Cause unknown
  - That prior event did not lead to screening of her children

Genome-scale genetic testing

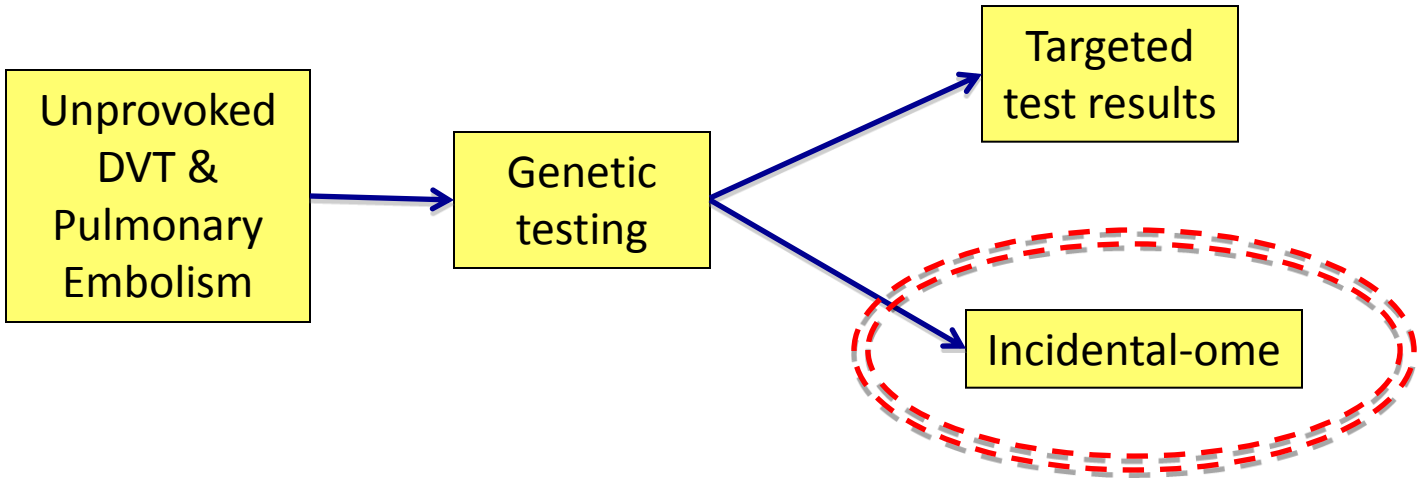
- Extended-family 23andme genotyping in 2007:
  - Factor V heterozygous mutation found in my mother & my daughter
  - The test had no other loci in the Factor V gene
  - No assessment of structural variation

- Core family (2 parents, 2 children) whole genome sequenced in 2009:
  - Vendor-associated physician prescribed test
    - Focus on our understanding of the risks & signing consents
  - No analysis by the sequence provider – used spreadsheets at home
  - 13 other mutations found in Factor V gene
  - 4 non-synonymous variants from my wife combine with my Factor V Leiden variant to form compound het in daughter
  - Non-synonymous mutations have > 20% MAF, PolyPhen “likely benign”
  - No structural variants reported with sequence, but subsequent search found none in Factor V gene

Action-ability

- Daughter refused her dermatologist's estrogen-based prescription, citing genome data
- Choice of medication: Tylenol, not aspirin
- > 40 subsequent round trip flights to Europe from San Francisco:
  - No coffee or alcohol
  - Major effort to stay hydrated
  - Periodic exercise of feet & legs
- Avoid foods high in Vitamin K : e.g. Spinach & miso
- Avoid injuries which could provoke internal bleeding
- Very careful compliance to warfarin dosing
- Monthly INR blood test confirms coagulation levels

Question as posed for this panel



How much ?

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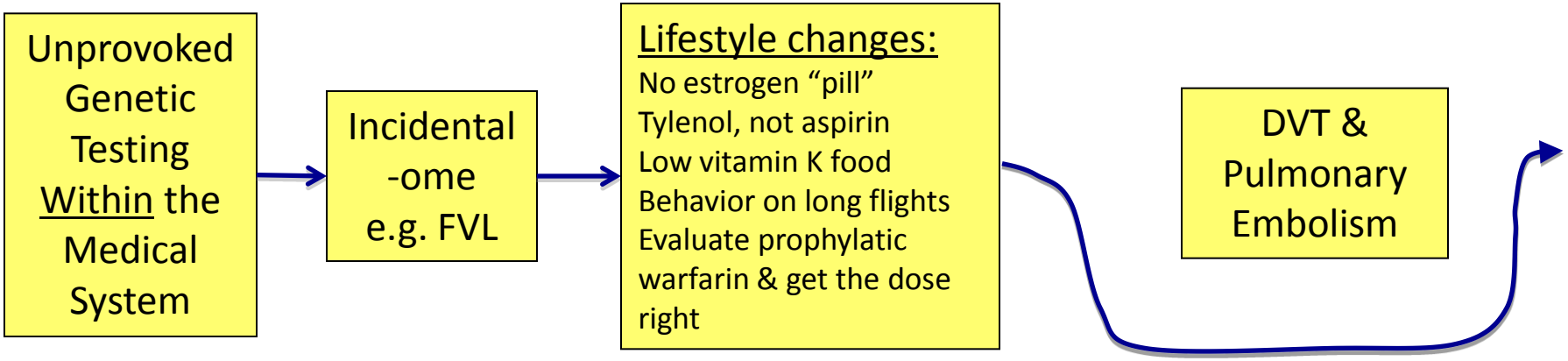
Question as re-posed by this panelist



Both the assay (genotyping, exome, WGS) and the interpretation can be delivered at a wide range of price points

Support consumer choice of cost / benefit within the medical system

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Cautionary note about accuracy of whole genome sequencing variant detection

- False positive & negative rates are high and apparently not declining:
  - 2009 : Eric Topol, et al : False positives 8%; False negatives 2%
  - 2010 : 1,000 Genomes data : 8-9% SNP error rate
  - 2011 : Stanford team : 11% SNP discordance
- Errors are strongly systematic, so higher sequencing coverage does not solve the problem
- Same person sequenced twice:
  - 400,000 different SNP's called
  - 40,00 of these "high confidence"
  - 70% of structural variants were not reproduced

Cautionary note about public databases for interpretation

- Thousands of disease-related alleles are in the Human Reference Sequence, so homozygotes at risk don't report as "variant"
- Many public databases have no mechanism to remove old data
  - Example: Many disease variants were originally mapped to protein coordinates, and then incorrectly, or multiply (!) mapped to chromosomal coordinates
- No medical terminology standards
- No system to combine risks associated with multiple variants associated with the same disease

Patient Perspectives

- Patient expectations: the amount of genomic information and mode of delivery ?
  - Start with the accurate, confident info, deliver it through the medical system
  - Thousands of low probability in-actionable “findings” were not useful
- What are the arguments for and against providing more information in your scenario?
  - The key point is to provide it before the medical event, to avoid it
- Would having different amounts of genomic information alter your behavior?
  - Yes, if actionable, I would act on it
- Would the additional info cause you to demand more from the health care provider?
  - If that was an add-on insurance option, like dental insurance, I would opt for it
  - If actionable, check my family & take preventative action
- What is the threshold of evidence for information to cause this demand?
  - Reasonably confident & actionable (medically, financially or politically)
- What are the non-health economic issues associated with genomic info ?
  - Political action for health research, as happened with AIDS

Discussion