Using Genomics to Individualize Medical Care: Overview and Personal Assessment

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A. Four components of any test assessment
B. Testing for Prevention
C. Testing for Diagnosis and Management
D. Cancer Genomes
E. Path Forward

What I Am NOT Talking About

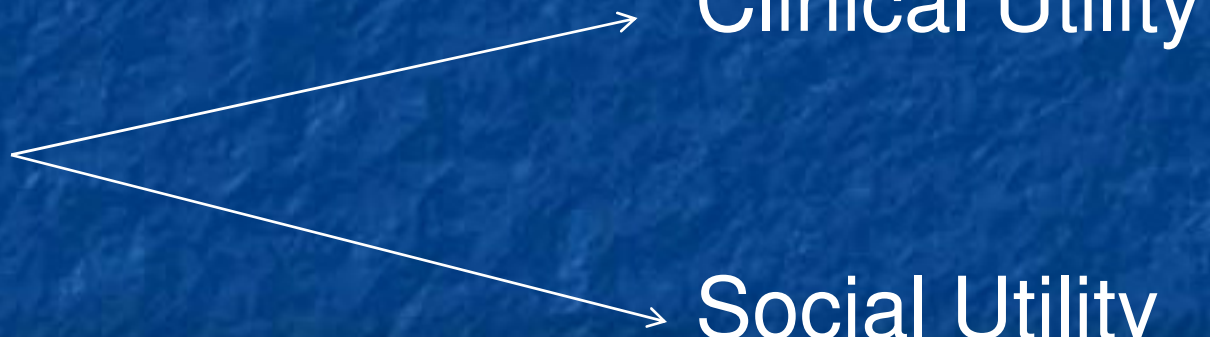
- Use of whole genome sequencing or other genomic technologies for gene discovery or translational research, paid for by grants or private industry - these applications are obvious and already here.

Three Components of Any Genetic Test Assessment

- Analytical Validity
- Clinical Validity
- Utility

A. Split Utility in Two

- Analytical Validity
- Clinical Validity
- Utility



Clinical Utility

- How valuable is the test result to the patient and his/her doctor in making decisions about
  - Whether to do further diagnostic testing or ending the diagnostic odyssey
  - Management and treatment
  - Lifestyle changes

Would the patient pay out-of-pocket for the test if his insurance won't?

Social Utility

- Are private and government insurers so convinced that the test, when compared to current standard of care, would
  - Improve health by reducing the need for less less successful salvage therapy and/or
  - Decrease costs by ending the diagnostic odyssey
  - Decrease costs by preventing more costly outcomes

that they are willing to pay for it?

B. Testing for Prevention

1. Preconception identification of carriers of Mendelian disorders that put offspring at risk
2. Prenatal or preimplanation testing
3. Identifying personal risk for a Mendelian disorder
4. Pharmacogenetic testing to predict efficacy, side-effects, adverse reactions
5. Tissue-typing for transplantation
6. Identification of alleles (rare and common) that increase risk for common disorders

What follows are critical assessments of each of these indications

1. Preconception identification of carriers of Mendelian disorders that put offspring at risk

Cost of testing for the most common autosomal recessive conditions is still far below complete genomic sequencing and, although not complete, is probably cost-effective.

2. Prenatal and Preimplantation

- Prenatal Testing is fraught with problems: A very serious decision must be made under severe time pressure and with unclear genotype-phenotype correlation
- Preimplantation Testing has many advantages but is limited by amount of material (but this is changing with epiblast biopsy)

3. Identifying personal risk for a Mendelian disorder

- Serious Clinical Validity Problem
  - What gene(s) are responsible?
  - What mutations are pathogenic?
  - What is the penetrance of a known pathogenic mutation?

- Gap in being able to tie genotype to phenotype

4. Pharmacogenetic testing to predict efficacy, side-effects, adverse reactions

- HLA-typing to prevent idiosyncratic adverse reactions (abacavir and carbamazepine) has clinical validity and proven clinical and social utility

- Clinical validity of common variants affecting PK and PD for drugs such as warfarin, clopidogrel, irinotecan, codeine, 6-thiopurine are well established but clinical and social utility remain questionable

4. Pharmacogenetic testing (cont.)

- Drug utilization is a rapidly moving target through replacement by compounds with no genetic variation in PK:
  - Clopidogrel and Prasugrel
  - Warfarin and oral direct thrombin inhibitors (Rivaroxaban and Dabigatran)
- Complete Sequencing when a a drug is about to be prescribed is too late.

5. Tissue-typing

- Number of Organ Transplants in the US, Annualized for 2011: ~27,000

  (United Network for Organ Sharing)

- Is still cheaper than whole genome sequencing

- Although delay in getting tissue-typing results may hold up transplantation for some indications (bone marrow) delays due to limited availability of donor organs are a bigger problem

6. Identification of alleles (rare and common) that increase risk for common disorders

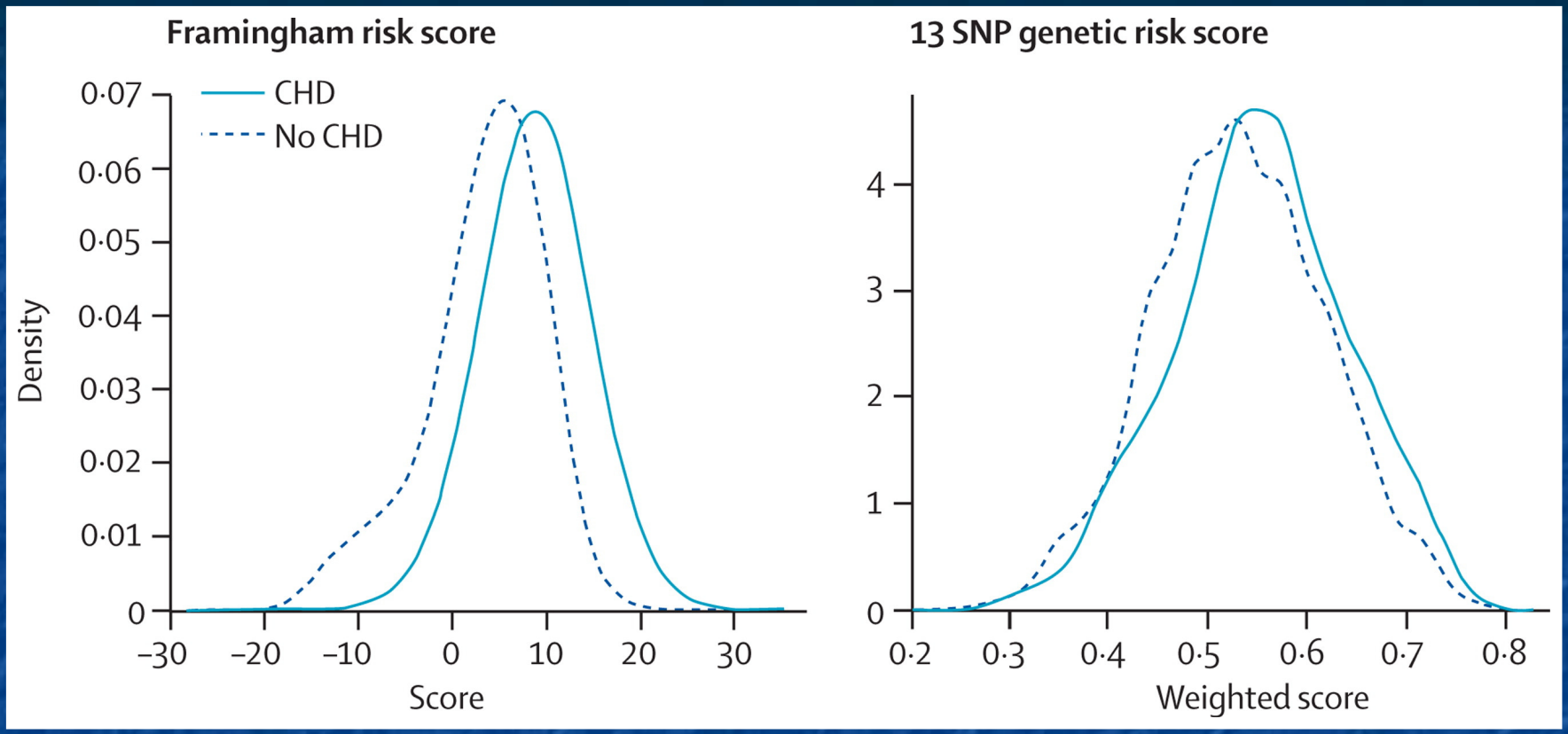
- VERY limited clinical validity and utility
- More in the realm of entertainment than medicine

13 SNP Combined To Generate Genetic Risk Score for CAD

rs17465637	1q41	*MIA3*	1·14
rs11206510	1p32	*PCSK9*	1·15
rs646776	1p13	*CELSR2–PSRC1–SORT1*	1·19
rs6725887	2q33	*WDR12*	1·17
rs9818870	3q22	*MRAS*	1·15
rs3798220	6q26	*LPA*	1·68
rs9349379	6p24	*PHACTR1*	1·12
rs4977574	9p21	*CDKN2A–CDKN2B*	1·29
rs1746048	10q11	*CXCL12*	1·17
rs2259816	12q24	*HNF1A*	1·08
rs3184504	12q24	*SH2B3*	1·13
rs1122608	19p13	*LDLR*	1·15
rs9982601	21q22	*SLC5A3–MRPS6–KCNE2*	1·20

Sipatti et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses, The Lancet Volume 376, Issue 9750, Pages 1393-1400 (October 2010)

Figure



Risk for CAD is 1.7-fold higher in the top quintile of risk score versus lowest quintile

Source: The Lancet 2011; 377:379-380 (DOI:10.1016/S0140-6736(11)60125-6)
Terms and Conditions

C. Testing to Make a Diagnosis

- Cost effective replacement for candidate gene panels

(e.g. cardiomyopathy, pheochromocytoma, long QT, X-linked mental retardation, immunodeficiency detected by newborn screening)

- UnDiagnosed Diseases likely to be hereditary in nature

Testing for Diagnosis

- Replacing Disease-Specific Panels: It's all about Analytic Validity and Cost

Testing for Diagnosis

UnDiagnosed Diseases likely to be hereditary in nature:

- Miller Syndrome gene discovery
- X-linked inhibitor of apoptosis gene (XIAP) finding in IBD
- Etc.

Are these the exceptions or the rules? And what volume of such cases are there? What happens when you apply the technique to children with lower and lower prior probability of there being something to find?

D. Sequencing Cancer Genomes

- Wonderful research tool to find variants of value for classification, prognosis or therapeutic management. But…
- Once these variants are identified for different tumors, will clinical application rely on whole tumor genome sequencing or on assaying for a few key variants that can be done cheaply and quickly?

I’m not just trying to throw cold water

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It’s not all doom and gloom:

- The Analytical Validity of Whole Genome Sequencing is Improving and costs are coming down
- The poor state of genotype-phenotype correlation is a recognized problem and steps are being taken to address it

Testing for Diagnosis

- Replacing Disease-Specific Panels: It's all about Analytic Validity and Cost

Testing for UnDiagnosed Diseases

Unknown conditions likely to be hereditary in nature:

- Miller Syndrome
- X-linked inhibitor of apoptosis gene (XIAP) in IBD
- Etc. – there are others…

Are these the exceptions or the rules? And what volume of such cases are there? What happens when you apply the technique to children with lower and lower prior probability of there being something to find?

Path Forward (2)

- Prevention: there is not any one indication right now - so
  1. Stress “Completeness”. Divorce it from any one indication.
  2. We need a few demonstration projects with a large health plan/provider in using complete genome sequencing as part of an overall health assessment throughout all stages of life.

Path Forward (3)

3. Stress ongoing interpretation rather than a one-shot test. Genome sequencing is a subscription.
4. Aggressively pursue the software for variant interpretation and decision support
5. Establish partnerships with EMRs