The Future of Genetic Testing
Genomic Medicine

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Wayne Heidenreich, MD
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• Types of inheritance patterns
• Types of testing
• What testing is available today
  – Why done
  – What is done with results
• The Genomewide Association study (GWA)
The Basics

- DNA (deoxyribonucleic acid) strands are “blueprint”
- Deoxynucleoside pairs make up DNA strand or chain
  - deoxyadenosine *always* pairs with thymidine
  - deoxyurycytidine *always* pairs with deoxyguanosine
- Double helix made of *paired* strands of DNA
- Chromosome is one long segment of DNA:
  - Total of 46: as 23 pairs, one from each parent
  - 22 numbered: one to twenty-two
  - One sex chromosome pair: XX female, XY male
Cell > Nucleus > Chromosome > DNA > RNA > Protein

(aka, translation of DNA to RNA and transcription of RNA to protein)
• Explosion of genetic science knowledge and technology
  • Human Genome Project began in 1990
  • 3.3 billion base pairs
  • 25,000 genes identified
  • 99% identical across different people
  • The remaining 1% leaves 12 million potential variations between people
    • A variation seen less than 1% of the time, is known as a “mutation”
    • A variation that occurs greater than or equal to 1% of the time is called a “polymorphism”
Types of Inheritance

Mendelian

• Single gene disorders
  – Autosomal dominant or recessive
  – X-linked disorders

• McKusick and the *Mendelian Inheritance in Man; Catalog of Human Genes and Genetic Disorders*

• *Online Mendelian Inheritance of Man*
## Some Autosomal Dominant Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Significant Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan’s</td>
<td>Connective tissue aneurysms</td>
</tr>
<tr>
<td>Huntington’s chorea</td>
<td>Neurodegenerative dementia</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Chronic degenerative myopathy</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Von Hippel Lindau</td>
<td>CNS vascular tumors</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colon cancer and others</td>
</tr>
<tr>
<td>Von Recklinhausen’s disease</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Childhood retinal cancer</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Heart failure and sudden death</td>
</tr>
<tr>
<td>Spinocerebellar ataxia</td>
<td>Movement disorder</td>
</tr>
</tbody>
</table>
### Some Autosomal Recessive Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Significant Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor Leiden Deficiency</td>
<td>Blood clots</td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>Premature COPD</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>RBC abnormality with anemia</td>
</tr>
<tr>
<td>Alport’s Syndrome</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Wilson’s Disease</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Lung disease</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Lysosome storage disorder in soft tissues and bone marrow</td>
</tr>
<tr>
<td>Tay Sachs</td>
<td>Degenerative motor disease</td>
</tr>
<tr>
<td>Familial Dysautonomia</td>
<td>Progressive sensorimotor autonomic neuropathy</td>
</tr>
</tbody>
</table>
### Some X-linked (Sex-linked) Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Significant Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia VIII</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Color blindness</td>
<td>Visual restriction</td>
</tr>
<tr>
<td>Agammaglobulinemia</td>
<td>Immune deficiency due to Ig deficiency</td>
</tr>
<tr>
<td>X-linked spinobulbar atrophy</td>
<td>Progressive limb and bulbar muscle weakness</td>
</tr>
<tr>
<td>Duchenne’s Muscular Dystrophy</td>
<td>Progressive diffuse skeletal muscle atrophy</td>
</tr>
</tbody>
</table>

Session 42: The Future of Genetic Testing
Number of Entries in Mendelian Inheritance in Man
More Types of Inheritance

• Chromosomal disorders:
  – Numerical, deletions, translocations:
    • e.g. trisomy 21 (Down’s)
    • 22q11 deletion syndrome
  – Non-mendelian
    • Mitochondrial inheritance
The Most Common Inheritance

- Multi-factorial:
  - Polymorphisms: multiple variants of a gene
    - Variant vs. mutation
  - Multiple genes interact in biological function
  - Pleiotropy: a single gene is involved in multiple functions

- Post-inheritance
  - Environmental affects
  - Epigenetics
• Task Force on Genetic Testing 1999:

  • *The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites to detect heritable disease related genotypes, mutations, phenotypes, or karyotypes for clinical purposes*
Some Definitions for Genes

- The “genome”: the entire sequence of base pairs of inherited DNA
- Gene: a segment of DNA that typically codes for one protein
- Genotype: an individual’s total DNA sequence or single gene sequence
- Allele: one of several variants of a gene, usually referring to one location
  - Insertion or deletion of extra DNA
  - Repeating pattern of fragment
  - Single-nucleotide pair change:
    - Single-nucleotide polymorphism or SNP
    - Millions of SNP’s catalogued
    - 12 million in 2009
Type of Tests

• Cytogenetics:
  • Chromosome staining and analysis of structure
  • In situ fluorescent DNA sequence probes
    • Detect smaller changes than more general stains
• End products of genes: proteins
  • Hemoglobin S
  • Single SNP accounts for this variant hemoglobin
• Sometimes we do not have the genetic regions identified and analyzed.
  – Known mutations or identified SNP’s may only account for a fraction of the inheritable risk.
  – Familial Early-Onset Alzheimer’s Disease
  – This changes constantly as knowledge increases

• Linkage is the tendency of genes or DNA sequences to be inherited together
  – When there is a gap in our knowledge a family can be studied to identified shared segments of DNA that differ from controls
• Microarray technology improvements
  • Basis of why whole genome sequencing has gone from a cost of $3 billion to a cost approaching $1000
  • Can sequence the entire genome
  • Testing can look for one or more gene sites
    • Sometimes site is known or postulated site and chosen as a “candidate” causative gene site
    • Can look at the entire genome and find associations in population with studied attribute
Microarray Technology

• Library of identified SNP’s
  – Continually being added to
  – Millions already catalogued

• Assay for specific ones can be put into a panel
  – The microchip technology
  – Disease specific panels
    • Note, these polymorphism may not be causative
  – Preconception carrier screen
    • 448 severe recessive genes for childhood diseases
    • Identifies carrier status for parent
    • Challenge if risk documented in child’s records
Tests in Use Today

• Reasons tests are done today:
  • Carrier testing for family planning
  • Prenatal diagnosis
  • Neonatal screening
  • Screening for carrier status in a family member of someone with an inherited disease
  • Identification of risk for disease
  • For diagnosis of manifest signs and symptoms of a disorder
  • For screening for response to a treatment
**OMIM Entry Statistics:**

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Autosomal</th>
<th>X Linked</th>
<th>Y Linked</th>
<th>Mitochondrial</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Gene description</td>
<td>12,961</td>
<td>635</td>
<td>48</td>
<td>35</td>
<td>13,679</td>
</tr>
<tr>
<td>+ Gene and phenotype, combined</td>
<td>191</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td># Phenotype description, molecular basis known</td>
<td>3,012</td>
<td>257</td>
<td>4</td>
<td>28</td>
<td>3,301</td>
</tr>
<tr>
<td>% Phenotype description or locus, molecular basis unknown</td>
<td>1,637</td>
<td>134</td>
<td>5</td>
<td>0</td>
<td>1,776</td>
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<tr>
<td>Other, mainly phenotypes with suspected mendelian basis</td>
<td>1,804</td>
<td>128</td>
<td>2</td>
<td>0</td>
<td>1,934</td>
</tr>
<tr>
<td>Totals</td>
<td>19,605</td>
<td>1,161</td>
<td>59</td>
<td>65</td>
<td>20,890</td>
</tr>
</tbody>
</table>

NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.

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Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD.: October 14, 2011:

Session 42: The Future of Genetic Testing
## Number of Entries

<table>
<thead>
<tr>
<th>Category</th>
<th>Autosomal</th>
<th>X-Linked</th>
<th>Y-Linked</th>
<th>Mitochondrial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Gene with known sequence</td>
<td>13073</td>
<td>640</td>
<td>48</td>
<td>35</td>
<td>13796</td>
</tr>
<tr>
<td>+ Gene with known sequence and phenotype</td>
<td>157</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>165</td>
</tr>
<tr>
<td># Phenotype description, molecular basis known</td>
<td>3099</td>
<td>259</td>
<td>4</td>
<td>28</td>
<td>3390</td>
</tr>
<tr>
<td>* Mendelian phenotype or locus, molecular basis unknown</td>
<td>1651</td>
<td>137</td>
<td>5</td>
<td>0</td>
<td>1793</td>
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<tr>
<td>Other, mainly phenotypes with suspected mendelian basis</td>
<td>1795</td>
<td>128</td>
<td>2</td>
<td>0</td>
<td>1925</td>
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<tr>
<td><strong>Total</strong></td>
<td>19775</td>
<td>1170</td>
<td>59</td>
<td>65</td>
<td>21069</td>
</tr>
</tbody>
</table>

Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD.: October 14, 2011:
Carrier Screening

Counseling regarding planning pregnancy. Test found in medical chart.

Specimen Type: Peripheral Blood

Clinical Data: Carrier Test/No family history

Specimen ID #: Specimen(s) Received: 2 - Yellow (ACD) 10 ml round bottom tube(s)

Ethnicity: Caucasian

RESULTS: SMN1 copy number: 2 (Reduced Carrier Risk)

INTERPRETATION:
This individual has an SMN1 copy number of two. This result reduces but does not eliminate the risk to be a carrier of SMA. Ethnic specific risk reductions based on a negative family history and an SMN1 copy number of two are provided in the Comments section of this report.

COMMENT:
Spinal muscular atrophy (SMA) is an autosomal recessive disease of variable age of onset and severity caused by mutations (most often deletions or gene conversions) in the survival motor neuron (SMN1) gene. Molecular testing assesses the number of copies of the SMN1 gene. Individuals with one copy of the SMN1 gene are predicted to be carriers of SMA. Individuals with two or more copies have a reduced risk to be carriers. (Affected individuals have 0 copies of the SMN1 gene.)
FDA is requiring pharmacogenomic test to demonstrate efficacy in approval process

- Driven partly by cost concerns
- Who will respond
- Safety issues
  - E.g. Warfarin Safety Warning
    - Identified SNP's at CYP2C9 can be tested for
    - Certain ones are associated with decreased efficiency to metabolize warfarin
    - Clinicians might question the benefit
    - Could play a part in standard of care if there is a hemorrhagic complication from initial dosing
### 116 Medications Listed as of February 7th, 2012

#### Pharmacogenomic Biomarkers in Drug Labels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Label Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tretinoin</td>
<td>Dermatology and</td>
<td>PML/RARα</td>
<td>Boxed Warning, Dosage and Administration, Precautions</td>
</tr>
<tr>
<td></td>
<td>Dental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Psychiatry</td>
<td>UCD (NAGS; CPS; ASS; OTC; ASL; ARG)</td>
<td>Contraindications, Precautions, Adverse Reactions</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Indications and Usage, Warning and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Psychiatry</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Antifungals</td>
<td>CYP2C19</td>
<td>Clinical Pharmacology, Drug Interactions</td>
</tr>
<tr>
<td>Warfarin (1)</td>
<td>Hematology</td>
<td>CYP2C9</td>
<td>Dosage and Administration, Precautions, Clinical Pharmacology</td>
</tr>
<tr>
<td>Warfarin (2)</td>
<td>Hematology</td>
<td>VKORC1</td>
<td>Dosage and Administration, Precautions, Clinical Pharmacology</td>
</tr>
</tbody>
</table>
### Positive for a Deleterious Mutation

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>G834X (2619G&gt;T) BRCA1</td>
<td>G834X (2619G&gt;T)</td>
<td>Deleterious</td>
</tr>
</tbody>
</table>

This test is designed to detect the specific mutation(s) or variant(s) indicated above. The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available.

The results of this analysis are consistent with the germline BRCA1 mutation G834X, resulting in premature truncation of the BRCA1 protein at amino acid position 834. Although the exact risk of breast and ovarian cancer conferred by this specific mutation has not been determined, studies in high-risk families indicate that deleterious mutations in BRCA1 may confer as much as an 87% risk of breast cancer and a 44% risk of ovarian cancer by age 70 in women (Lancet 343:692-695, 1994). Mutations in BRCA1 have been reported to confer a 20% risk of a second breast cancer within five years of the first (Lancet 351:316-321, 1998), as well as a ten-fold increase in the risk of subsequent ovarian cancer (J Clin Oncol 16:2417-2425, 1998). This mutation may also confer an increased (albeit low) risk of male breast cancer (Am J Hum Genet 62:676-689, 1998), as well as some other cancers. Each first degree relative of this individual has a one-in-two chance of having this mutation. Family members can be tested for this specific mutation with a single site analysis.
### ApoE

#### NCEP ATP III Lipid Tests

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Intermediate</th>
<th>At Risk</th>
<th>Last Visit</th>
<th>Alert Value</th>
<th>ATP III Goal</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td></td>
<td>243</td>
<td></td>
<td>&gt;=200</td>
<td>&lt;200</td>
<td>&lt;200</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td></td>
<td>152</td>
<td></td>
<td>&gt;=100</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>77</td>
<td></td>
<td></td>
<td>&lt;40</td>
<td>&gt;=40</td>
<td>&gt;=40</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td></td>
<td>72</td>
<td></td>
<td>&gt;=150</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td></td>
</tr>
</tbody>
</table>

#### Advanced Cardiovascular Risk Markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Normal</th>
<th>Intermediate</th>
<th>At Risk</th>
<th>Last Visit</th>
<th>Alert Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Lp(a), Extended Range (mg/dL)</td>
<td>11</td>
<td></td>
<td></td>
<td>&gt;30</td>
<td>&lt;=30</td>
<td>0 - 30</td>
</tr>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>12.9</td>
<td></td>
<td></td>
<td>&gt;15</td>
<td>&lt;=15</td>
<td>3.0 - 15.0</td>
</tr>
<tr>
<td>Lp-PLA2 (ng/mL)</td>
<td>163</td>
<td></td>
<td></td>
<td>&gt;223</td>
<td>&lt;200</td>
<td>131 - 376</td>
</tr>
<tr>
<td>Ferritin (mg/dL)</td>
<td>391</td>
<td></td>
<td></td>
<td>&gt;496</td>
<td>&lt;496</td>
<td>227 - 496</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>4</td>
<td></td>
<td></td>
<td>&gt;25</td>
<td>&lt;25</td>
<td>3 - 25</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>18</td>
<td></td>
<td></td>
<td>&gt;450</td>
<td>&lt;=125</td>
<td>5 - 125</td>
</tr>
</tbody>
</table>

† BHL Goals are intended for patients with established CAD.

#### Result

ApoE Genotype: 2/3

Please refer to additional information for genetic testing results on the Cardiovascular Genetics Detail Report on subsequent pages.
Remember “Pleiotropy”?

Cardiovascular Genetics Detail Report

<table>
<thead>
<tr>
<th>TEST PERFORMED</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE Genotype</td>
<td>2/3</td>
</tr>
</tbody>
</table>

**Test Summary**
- ApoE Genotype: 2/3
  * See Guidance Statements

**GUIDANCE STATEMENT: ApoE (Apolipoprotein E) Genotype**
This patient has the ApoE genotype E2/E3. Over 95% percent of individuals with type III hyperlipoproteinemia are homozygous for the E2 allele. Only rarely does this disorder occur with the heterozygous genotype E2/E3; results must be interpreted within the context of the appropriate clinical setting and with other laboratory data. E2 carriers have a slightly lower risk of coronary heart disease (CHD) compared to individuals with the E3/E3 genotype.

**GUIDANCE STATEMENTS: General (Cardiovascular Genetics)**
1. Non genetic factors contribute to coronary heart disease (CHD), cardiovascular disease (CVD), or myocardial infarction (MI) risk. Examples of such factors include smoking, hypertension, age, diabetes, elevated blood lipid levels, obesity and sedentary lifestyle.

2. Other genetic factors (e.g. family history of heart disease) may contribute to CHD, CVD, or MI risk.

3. These genetic test results should be considered in context of other clinical criteria by a qualified physician. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

4. Genetic consultation for this individual may be helpful in understanding the genetic implications of these test results and management options.
Sample of a Direct to consumer test

Your estimated lifetime risk

Click anywhere on the colored boxes below to access in-depth information about each health condition, your genetic predispositions, what you can do, your specific genetic markers, and much more.

You can also click on the Medications tab above to see how certain medicines affect you. This new Navigenics feature provides personalized genetic information to help you understand which drugs work best for you, starting with your responses to 12 medications.

0 - 1%
- Crohn's disease
  - You: 0.93%
  - Avg: 0.58%

>1 - 10%
- Colon cancer
  - You: 8%
  - Avg: 6%

>10 - 25%
- Atrial fibrillation
  - You: 22%
  - Avg: 26%

>25 - 50%
- Obesity
  - You: 27%
  - Avg: 34%

>50 - 100%
- Ostearthritis
  - You: 56%
  - Avg: 40%

Brain aneurysm
  - You: 0.80%
  - Avg: 0.64%

Lung cancer
  - You: 8%
  - Avg: 8%

Prostate cancer
  - You: 20%
  - Avg: 17%

Heart attack
  - You: 54%
  - Avg: 42%
Genome-wide association (GWA) studies identify “SNP’s” or Single Nucleotide Polymorphisms.

- Your speaker

- Selected from the audience

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
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- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
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- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
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- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
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- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
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- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- AGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

- ATAGTATCGTAGCTAGCTAGATAATGATCGTAGTATCGTTTCTGATATAGCTGATATC
  GATTGATGATCTAGGTATAAAATGATCGTAGTATCGTAGATCGATATCGATTGATGATCTAG

Session 42: The Future of Genetic Testing
GWA Studies

- Compare groups with and without a disorder
- Can have “target genes” or be genome wide
- Studies are done in groups with shared phenotype
- The “Wellderly” study
  - Reached age without chronic illness and no medication
  - 1200 enrolled individual who are over 80 years old
    - Entire genome defined
    - No difference in common variants of late-onset disease
    - Question is what modifier genes might be identified
GWA studies have identified relative risks

- But clinical utility still being studied
- Associations are not necessarily causative
- Predictive value is not always powerful
- Example of study on diabetes type 2
  - GWA study on 3501 controls and 2809 diabetics
  - 13 polymorphisms identified in 10 different loci
  - Traditional risk factors: family hx of diabetes, smoking, alcohol, physical activity, BMI, fat and fiber intake
  - 7 of 13 loci statistically associated with diabetes type 2
    - Independent sensitivity for identifying diabetics type 2
  - When used with traditional risk factors, no improvement in the sensitivity and specificity of identifying diabetics

Privacy: GINA and the States
Security: HITECH and HIPAA
Informed Consent: Clinical responsibilities include offering counseling
Property rights: Genetic Bill of Rights in States
Clinical Responsibility: Who is responsible for updating patients on new interpretations is debated
Direct-to-consumer Testing: DTC
Every time you spend a few minutes with your Navigenics results, you can open new doors to better health. Personalized wellness lies in prevention and awareness — which is why understanding your genetic risks is so important. We’re here to help.

Your genetic counselor

At no additional charge, speak with a qualified genetics expert who can help you understand your results. Click the button below to start.

You have unviewed results for deep vein thrombosis, hemochromatosis (HFE-related) and 27 other conditions.

Your Navigenics subscription is currently active. Learn more.

Latest headlines

- “Scripps Study: When it Comes to Genomics, Consumers Can Handle the Truth”
- Video: Dr. Vanler joined by Dr. Eric Topol to discuss NEJM study data
- Working with regulators -- the road ahead
- New! Updated results for warfarin, an important medication
- Working closely with state and federal regulators -- a core Navigenics principle
What is being offered?

Genetics for simple inheritable metabolic disorders.
  Pre or post conception
  Newborn
Genetics of response to drugs, pharmacogenetics.
  Response to Serotonin reuptake receptor blockers
  Warfarin
Genetics for predictive risk of future disease.
  Alzheimer's
  Cardiovascular disease
  Diabetes
Who are some of the players.

- **DTC Genetic Testing:**
  - https://www.23andme.com/
  - http://www.dnadirect.com/
  - http://www.healthanddna.com/
  - http://www.navigenics.com
  - http://www.decodeme.com/warfarin-metabolism
  - Others, at least 19 others.
Current conundrums

- Test today is benign
- Test today is positive
- Test is positive for a specific condition/indication
- Test of your infant indicates you may have a problem.

- New data says test is positive.
- Test is no longer positive.
- Test has a larger footprint
- Metabolic disorder in the young may be manifest in the parent/sibling/relative
Potential impact for insurance companies of Genetic Testing

• Genetic Testing and Human Impact
  – Pre-selection
• Genetic Diagnosis and Disease Risks
  – Better classification of disease
• Genetically-Tailored Treatment
  – Target to regulators or pathways
• Genetics and the Law
  – Regulation by FDA/CLIA/States
• Ethical Considerations
Future of Genetic Testing.

Currently huge amounts of gene sequence data are being collected. That data needs to be analyzed in the context of the families genetic makeup. During the next five years data will be converted into information. For complex diseases, involving multiple pathways, it may be ten or more years before accurate models of future risk may be developed. And last but not least, “The current models are extremely simplistic, every day new levels of complexity are discovered”. Also Genetic predisposition must be placed in the context of environment.