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The Human Genome II

M1 Patients and Populations

David Ginsburg, MD

Fall 2012
UMMS faculty often interact with pharmaceutical, device, and biotechnology companies to improve patient care, and develop new therapies. UMMS faculty disclose these relationships in order to promote an ethical & transparent culture in research, clinical care, and teaching.

- I am a member of the Board of Directors for Shire plc.
- I am a member of the Scientific Advisory Boards for Portola Pharmaceuticals and Catalyst Biosciences.
- I benefit from license/patent royalty payments to Boston Children’s Hospital (VWF) and the University of Michigan (ADAMTS13).

Disclosure required by the UMMS Policy on Faculty Disclosure of Industry Relationships to Students and Trainees.
Learning Objectives

UNDERSTAND:

- The basic anatomy of the human genome [e.g., $3 \times 10^9$ bp (haploid genome); 1-2% coding sequence (~20,000 genes); types and extent of DNA sequence variation].
- Recombination and how it allows genes to be mapped
- Genetic data for a pedigree, assigning phase, defining haplotypes
- Linkage: Distinction between a linked marker and the disease causing mutation itself
- Linkage disequilibrium and haplotype blocks
- Genome wide association studies (GWAS) to identify gene variants contributing to complex diseases/traits
- The implications of GWAS findings for clinical care and “Personalized Medicine”
- The implications of “Next-Gen” sequencing for future clinical medicine
genetics/genomics in the clinic

- Better/earlier diagnosis:
  - Mendellian disorders
  - Complex disorders

- Guiding/selecting treatment:
  - Subclassifying cancers
    - Somatic mutations
    - Expression profiles
  - Customized/designer treatment
  - Pharmacogenomics

Exceeding expectations

FAR below expectations /promises
Positional Cloning

- GENETIC MARKERS
- FAMILIES
- MUTATION IDENTIFICATION
- FINE GENETIC MAPPING
- PHYSICAL MAPPING AND CLONING
- TRANSCRIPT IDENTIFICATION
- POSITIONAL CANDIDATE APPROACH
- MUTATION SEARCH

Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E*; Figure 9.15
### OMIM Statistics for December 5, 2010

#### 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>
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<tr>
<td>* Gene with known sequence</td>
<td>12541</td>
<td>617</td>
<td>48</td>
<td>35</td>
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<td>+ Gene with known sequence and phenotype</td>
<td>344</td>
<td>19</td>
<td>0</td>
<td>2</td>
<td>365</td>
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<tr>
<td># Phenotype description, molecular basis known</td>
<td>2646</td>
<td>233</td>
<td>4</td>
<td>28</td>
<td>2911</td>
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<tr>
<td>% Mendelian phenotype or locus, molecular basis unknown</td>
<td>1637</td>
<td>133</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Other, mainly phenotypes with suspected mendelian basis</td>
<td>1845</td>
<td>130</td>
<td>2</td>
<td>0</td>
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<tr>
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<td><strong>59</strong></td>
<td><strong>65</strong></td>
<td><strong>20269</strong></td>
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</tbody>
</table>

Complex Diseases

- Hypertension
- Coronary artery disease
- Diabetes
- Obesity
- Cancer
- ...

Difficult to map in large pedigrees by conventional linkage (multiple genes, variable effects)
• Candidate gene association study
  – Test a SNP (or SNPs) surrounding your favorite gene for association with disease (more common in patients than controls)
    • Publication bias
    • Multiple observations
    • Population substructure
    • “looking under the streetlamp”

vs.

• Genome-wide association study (GWAS)
  – Unbiased
  – No prior assumptions
Human Chromosome 4

- 23,653,737 total human entries in dbSNP

- Chromosome 4
  - 4,311,728 SNPs

- ~1M SNP chip commercially available

Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E*; Figure 10.3
Age-related macular degeneration (AMD)
- > 10 million cases in the US
- Leading cause of blindness among the elderly

Common variant in complement factor H (CFH) gene
- Tyr402His
- His allele = 2-4 X increase risk of AMD
- Accounts for 20-50% of AMD risk
A genome-wide association study identifies novel risk loci for type 2 diabetes

Robert Sladek1,3,4, Ghislain Rocheleau4, Joho Ran6, Christian Dina5, Lishuang Shen1, David Serre1, Philippe Boutin5, David Milan1, Alexandre Belisle1, Sami Hadjadj6, Beverley Balkau7, Barbara Heude7, Guillaume Charpentier8, Thomas J. Hudson5,9, Alexandre Montpetit3, Alexey V. Peshezhtsky10,11, Marc Prentki10,11, Barry I. Posner2,11, David J. Balding13, David Meyre5, Constantin Polychronakos1,13 & Philippe Froguel5,14
The Multiple observations problem

• Roll the dice once
  – Probability of rolling two 6’s = 2.8% (1:36=1/6 X 1/6)

• Roll the dice twice
  – Probability of rolling two 6’s at least once = 5.5%

• Roll the dice 100 times
  – Probability of rolling two 6’s at least once = 94%

Test 1 million SNPs, 100 phenotypes . . .
Type 2 Diabetes GWAS: Manhattan Plot


Conclusions:
“As compared with clinical risk factors alone, common genetic variants associated with the risk of diabetes had a small effect on the ability to predict the future development of type 2 diabetes.”
Diabetes Risk

- Obesity $\text{OR} => 3$
- Family history $\text{OR} => 3$
- GWAS SNPs $\text{OR} <= << 1.4$

Ricardipus (wikipedia)
Other Genome Wide Association Studies (GWAS)

- Heart disease
  - MI, AF, QT prolongation, CAD, lipids
- Inflammatory bowel disease
- Asthma
- Neuropsychiatric disorders
  - ALS, MS, Alzheimer, schizophrenia, bipolar disorder
- Rheumatologic disorders
  - RA, SLE
- Cancer risk
  - breast, prostate, colon
- Common traits
  - BMA, height, hair/eye/skin color
<table>
<thead>
<tr>
<th>Health Condition</th>
<th>Health Condition</th>
<th>Health Condition</th>
<th>Health Condition</th>
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<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Cognitive function</td>
<td>Homocysteine levels</td>
<td>Osteoporosis</td>
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<tr>
<td>Adhesion molecules</td>
<td>Conduct disorder</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Otosclerosis</td>
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<td>Adiponectin levels</td>
<td>Colorectal cancer</td>
<td>IgE levels</td>
<td>Other metabolic traits</td>
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<td>Age-related macular degeneration</td>
<td>Corneal thickness</td>
<td>Inflammatory bowel disease</td>
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<td>AIDS progression</td>
<td>Coronary disease</td>
<td>Intracranial aneurysm</td>
<td>Pancreatic cancer</td>
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<td>Alcohol dependence</td>
<td>Creutzfeldt-Jakob disease</td>
<td>Iris color</td>
<td>Pain</td>
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<td>Alzheimer disease</td>
<td>Crohn’s disease</td>
<td>Iron status markers</td>
<td>Paget’s disease</td>
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<td>Amyotrophic lateral sclerosis</td>
<td>Cutaneous nevi</td>
<td>Ischemic stroke</td>
<td>Panic disorder</td>
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<td>Angiotensin-converting enzyme activity</td>
<td>Dematitis</td>
<td>Juvenile idiopathic arthritis</td>
<td>Parkinson’s disease</td>
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<td>Drug-induced liver injury</td>
<td>Kidney stones</td>
<td>Periodontitis</td>
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<td>Arterial stiffness</td>
<td>Eosinophil count</td>
<td>Leprosy</td>
<td>Peripheral arterial disease</td>
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<td>Asthma</td>
<td>Eosinophilic esophagitis</td>
<td>Leptin receptor levels</td>
<td>Phosphatidylcholine levels</td>
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<td>Atherosclerosis in HIV</td>
<td>Erythrocyte parameters</td>
<td>Liver enzymes</td>
<td>Phytoester levels</td>
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<td>Atrial fibrillation</td>
<td>Esophageal cancer</td>
<td>LP (a) levels</td>
<td>Platelet count</td>
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<td>Attention deficit hyperactivity disorder</td>
<td>Essential tremor</td>
<td>LpPLA(2) activity and mass</td>
<td>Primary biliary cirrhosis</td>
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<td>Autism</td>
<td>Exfoliation glaucoma</td>
<td>Lung cancer</td>
<td>PR interval</td>
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<td>Eye color traits</td>
<td>Major mood disorders</td>
<td>Prostate cancer</td>
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<td>F cell distribution</td>
<td>Malaria</td>
<td>Protein levels</td>
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<td>Biliary atresia</td>
<td>Fibrinogen levels</td>
<td>Male pattern baldness</td>
<td>Psoriasis</td>
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<td>Bilirubin</td>
<td>Folate pathway vitamins</td>
<td>Matrix metalloprotease levels</td>
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<td>Birth weight</td>
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<td>MCP-1</td>
<td>QRS interval</td>
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<td>QT interval</td>
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<td>Menarche &amp; menopause</td>
<td>Quantitative traits</td>
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<td>Glycemic traits</td>
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<td>Response to antipsychotic therapy</td>
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<td>C-reactive protein</td>
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<td>Nicotine dependence</td>
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<td>Cardiac structure/function</td>
<td>Height</td>
<td>Obesity</td>
<td>Restless legs syndrome</td>
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<td>Hemostasis parameters</td>
<td>Open angle glaucoma</td>
<td>Rheumatoid arthritis</td>
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<td>Carotenoid/tocopherol levels</td>
<td>Hepatitis</td>
<td>Open personality</td>
<td>Schizophrenia</td>
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<td>Hirschsprung’s disease</td>
<td>Optic disc parameters</td>
<td>Skin pigmentation</td>
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<td>Chronic lymphocytic leukemia</td>
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<td>Smoking behavior</td>
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<td>Speech perception</td>
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<td>Sphingolipid levels</td>
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<td>Statin-induced myopathy</td>
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<td>Stroke</td>
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<td>Triglycerides</td>
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<td>Type 2 diabetes</td>
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<td>Ulicerative colitis</td>
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<td>Urate</td>
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<td>Venous thromboembolism</td>
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<td>Vertical cup-disc ratio</td>
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<td></td>
<td>Vitamin B12 levels</td>
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<td>Vitamin D insufficiency</td>
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<td>Vitiligo</td>
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<td>Warfarin dose</td>
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<td></td>
<td>Weight</td>
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<td></td>
<td></td>
<td></td>
<td>White cell count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>YKL-40 levels</td>
</tr>
</tbody>
</table>
Published Genome-Wide Associations through 6/2010

904 published GWA at \( p \leq 5 \times 10^{-8} \) for 165 traits

www.genome.gov/GWAStudies
Lessons from GWAS

• Most (nearly all) previous “candidate” gene association studies are wrong
• Most common variants have only modest effects on risk (<< 2 fold OR)
• For most common diseases/traits: identified SNPs only account for <5-10% of overall risk— NOT USEFUL clinically
• But useful new biology (maybe) ??
  – New biologic pathways
  – New drug targets

• Other diseases may be different
  – AMD
  – Thrombosis
  – BCL11A and fetal hemoglobin
Lots of tests: when should we use them?

- Class I: test result will significantly alter medical management
  - Newborn screening (eg. sickle cell, PKU)
  - Some cancer predisposition syndromes (eg. VHL, MEN2, FAP, ?BRCA)

- Class III: test result will have no impact on medical management
  - Huntington Disease, Alzheimer predisposition

- Class II: the grey zone
Venous Thrombosis

**GENES**
- Factor V Leiden
- Elevated FVIII
- Prothrombin 20210
- Protein C/S deficiency
- AT III deficiency

**ENVIRONMENT**
- Smoking
- Flying
- Pregnancy

? Others

(stochastic/chance)
Genetic testing for thrombophilia

- **Established risk factors for thrombosis**
  - Factor V Leiden – 5% population frequency (European)
  - Prothrombin 20210 mutation – 1%
  - Protein C, Protein S deficiency – each ~1:500
  - Antithrombin III deficiency – ~1:2500
  - ? Elevated plasma FVIII (or ?FIX, FXI) – 5-10%
  - Dysfibrinogenemia, others – rare

- **Commonly tested factors that DO NOT increase thrombosis risk**
  - “Thermolabile” MTHFR (C677T, Ala222Val) – 40% het, 10% homoz
  - PAI-1 4G-5G polymorphism – 25% 4G/4G, 50% 4G/5G
## Treatment of Venous Thrombosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rx with FVL</th>
<th>Rx without FVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Thrombosis</td>
<td>Heparin/wararin</td>
<td>Heparin/warfarin</td>
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<tr>
<td>Prophylaxis after 1st event</td>
<td>Warfarin X 3-12 months</td>
<td>Warfarin X 3-12 months</td>
</tr>
<tr>
<td>Prophylaxis after recurrent thrombosis</td>
<td>extended warfarin (? lifelong)</td>
<td>extended warfarin (? lifelong)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>???</td>
<td>???</td>
</tr>
<tr>
<td>Oral contraceptives/estrogens</td>
<td>?? Relatively contra-indicated (?) or not</td>
<td>?? Relatively contra-indicated (?) or not</td>
</tr>
<tr>
<td>Other special cases</td>
<td>???</td>
<td>???</td>
</tr>
</tbody>
</table>
Testing for Factor V Leiden
*(and other thrombophilia mutations)*

- **Current Indications for testing**
  - ????

- **Potential future indications:**
  - Choice and duration of primary therapy for thrombosis
  - Choice and duration of thrombosis prophylaxis:
    - During pregnancy
    - Postoperatively
    - following 1st or subsequent thrombotic event
  - Screening before OCP prescription
Lots of tests: when should we use them?

• Class I: test result will significantly alter medical management
  – Newborn screening (eg. sickle cell, PKU)
  – Some cancer predisposition syndromes (eg. VHL, MEN2, FAP, ?BRCA)

• Class III: test result will have no impact on medical management
  – Huntington Disease, Alzheimer predisposition

• Class II: the grey zone
What do we mean by “personalized medicine”?

- Personalized = tailored, individualized, customized
- *Medicine has always been personalized:*  
  - The physician’s charge – the individual patient  
    - Personalized history, physical exam, laboratory tests  
    - Personalized diagnosis  
    - Personalized treatment  
  - Non “personalized” medicine for the whole community = public health  
    - Vaccination  
    - Safe water and food supply  
    - Waste management  
    - Much larger global impact than “personalized” medicine
What DO we mean by “personalized medicine”?

- Harness the power of genetic information to:
  - Improve diagnosis
  - Tailor treatment to diagnosis
  - Identify disease susceptibility before illness
  - Facilitate preventive treatment
  - Facilitate treatment prescription with minimum toxicity and maximum efficacy (parmacogenomics)
Gleevec™ – Specifically Targets An Abnormal Protein, Blocking Its Ability To Cause Chronic Myeloid Leukemia

Chromosome 9;22 translocation

Bcr-Abl fusion protein

Normal

Gleevec™
Pharmacogenomics today

• Pharmacogenomic Biomarkers for 71 drugs (FDA)

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

• Oncology applications
  – Her2/Neu, EGFR, BCR/ABL (efficacy)
  – Thiopurine methyltransferase (TPMT)
    • 6-MP, azathioprine
    – UGT1A1 (irinotecan)
    – Dihydropyrimidine dehydrogenase (5-FU)

• Cytochrome P450
  – warfarin
  – Multiple other drugs:
    • antidepressants, tamoxifen, PPIs

• VKORC1
  – warfarin
Genetic determinants of Warfarin dose

A. Association with CYP2C9 and VKORC1

B. Warfarin and the Vitamin K Cycle

The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose.

In all patients, subsequent dosage adjustments must be made based on the results of PT/INR determinations.\textsuperscript{17,18}

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes\textsuperscript{†}

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

\textsuperscript{†}Ranges are derived from multiple published clinical studies. Other clinical factors (eg, age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.
Pharmacogenomics for warfarin dosing

- Clinical value unproven
- Practical limitations:
  - VKORC1/CYP2C9 genotype only accounts for ~30% of variance in warfarin requirement
  - Turnaround time
  - Pill size

Sconce et al., *Blood* **106**:2329, 2005
Rieder et al., *NEJM* **352**:2285, 2005
Pharmacogenomics today

• Pharmacogenomic Biomarkers for 71 drugs (FDA)
  http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

• Oncology applications
  – Her2/Neu, EGFR, BCR/ABL (efficacy)
  – Thiopurine methyltransferase (TPMT)
    • 6-MP, azathioprine
    – UGT1A1 (irinotecan)
    – Dihydropyrimidine dehydrogenase (5-FU)

• Cytochrome P450
  – warfarin
  – Multiple other drugs:
    • antidepressants, tamoxifen, PPIs

• VKORC1
  – warfarin
TMPT variant and chemotherapy toxicity

- TMPT variant alleles (decreased activity)
  - 11% heterozygotes
  - 0.3% homozygotes

**Conclusion:** Insufficient evidence addresses the effectiveness of TMPT pretesting in patients with chronic inflammatory diseases.
DTC Genetic Testing

- Mendellian Genetic disorders
- pharmacogenomics
- Complex (multigenic) disorders
- Ancestry
<table>
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<th>Disease</th>
<th>Female A</th>
<th>Female B</th>
<th>Female C</th>
<th>Male D</th>
<th>Male E</th>
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<tr>
<td>Breast cancer</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td></td>
<td></td>
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<tr>
<td>Coeliac disease</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>=</td>
<td>=</td>
<td>=↓</td>
<td>↑↑</td>
<td>=↓</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>↓↑</td>
<td>↓↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓=</td>
</tr>
<tr>
<td>Heart attack</td>
<td>↓↓</td>
<td>=↓</td>
<td>=↓</td>
<td>=↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Lupus</td>
<td>↑↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑=</td>
<td>↑=</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑=</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>↓↑</td>
<td>↓↑</td>
<td>↑↓</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>=↓</td>
<td>↑↑</td>
<td>=↓</td>
<td>↓↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>↓↓</td>
<td>=↓</td>
<td>↓↓</td>
<td>↑↓</td>
<td>=↓</td>
</tr>
</tbody>
</table>

↑ increased risk (RR > 1.05), ↓ decreased risk (relative risk (RR) < 0.95), = average risk (0.95 ≤ RR ≤ 1.05). First prediction is from 23andMe; second prediction is from Navigenics. Different predictions are highlighted in beige.

DIRECT-TO-CONSUMER GENETIC TESTS

Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices

What GAO Found

GAO’s fictitious consumers received test results that are misleading and of little or no practical use. For example, GAO’s donors often received disease risk predictions that varied across the four companies, indicating that identical DNA samples yield contradictory results. As shown below, one donor was told that he was at below-average, average, and above-average risk for prostate cancer and hypertension.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Condition</th>
<th>Company 1</th>
<th>Company 2</th>
<th>Company 3</th>
<th>Company 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>48</td>
<td>Prostate cancer</td>
<td>Average</td>
<td>Average</td>
<td>Below average</td>
<td>Above average</td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>Hypertension</td>
<td>Average</td>
<td>Below average</td>
<td>Above average</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

Source: GAO.

GAO’s donors also received DNA-based disease predictions that conflicted with their actual medical conditions—one donor who had a pacemaker implanted 13
Is there any evidence that DTC Genetic Testing will improve your health?

Testimonials:

- “It convinced me to go to my doctor who found my prostate cancer. _____’s DTC genetic testing saved my life!!”
- “When I found out about my increased risk of diabetes, I went out and lost 30 pounds!!”
- “When I found out about my increased risk of lung cancer, I stopped smoking!!”
- …
Is there any evidence that DTC Genetic Testing will improve your health?

Actual scientific evidence:

• “It convinced me to go to my doctor who found my prostate cancer. ___’s DTC genetic testing saved my life!!”

• “When I found out about my increased risk of diabetes, I went out and lost 30 pounds!!”

• “When I found out about my increased risk of lung cancer, I stopped smoking!!”

• …
Minimally regulated tools available to the public for predicting/modifying health

• **Traditional:**
  – Astrology
  – Tarot cards
  – Palm reading

• **Modern “scientific”**
  – “Alternative” medicine ($38 billion/yr)
    • Nutraceuticals, homeopathic remedies ($22 billion)
  – SNP genotyping
Recreational Genetics

• Ancestry
• Paternity, long lost relatives
### New Sequencing Technologies

#### Searching for Cheaper Genome Sequencers

<table>
<thead>
<tr>
<th>Company</th>
<th>Format</th>
<th>Read Length (bases)</th>
<th>Expected Throughput MB (million bases)/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>454 Life Sciences</td>
<td>Parallel bead array</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Agencourt Bioscience</td>
<td>Sequencing by ligation</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>Applied Biosystems</td>
<td>Capillary electrophoresis</td>
<td>1000</td>
<td>3–4</td>
</tr>
<tr>
<td>Microchip Biotechnologies</td>
<td>Parallel bead array</td>
<td>850-1000</td>
<td>7</td>
</tr>
<tr>
<td>NimbleGen Systems</td>
<td>Map and survey microarray</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Solexa</td>
<td>Parallel microchip</td>
<td>35</td>
<td>500</td>
</tr>
<tr>
<td>LI-COR</td>
<td>Electronic microchip</td>
<td>20,000</td>
<td>14,000</td>
</tr>
<tr>
<td>Network Biosystems</td>
<td>Biochip</td>
<td>800+</td>
<td>5</td>
</tr>
<tr>
<td>VisiGen Biotechnologies</td>
<td>Single molecule array</td>
<td>NA</td>
<td>1000</td>
</tr>
</tbody>
</table>

*Generation next.* Companies racing for the $1000 genome sequence strive simultaneously for low cost, high accuracy, the ability to read long stretches of DNA, and high throughput.
How many human genomes can you sequence for $10M?

2000: <1 Human Genome

2010: 250-500 Human Genomes
The Future...

- Will be different
  - Newborn screening by full genome sequencing
  - New/improved therapies
  - Complex computational analysis - combinatorial risk factors
  - Much larger data sets – health system wide
  - Data to support genotype-specific therapy / prophylaxis
Additional Source Information
for more information see: http://open.umich.edu/wiki/AttributionPolicy

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