Genomic Medicine

The Development, Economic and Ethical Challenges of Translating Basic Research into Clinical Practice

Thomas J. White, Ph.D.

Regents’ Lecture 2012-2013

University of California, Berkeley
A Diagnostic Test that Changed AIDS Treatment

- Monotherapy (AZT)
- Combination therapy
- Reference Lab HIV viral load assay
- FDA approval of HIV viral load kit (prognosis) and protease inhibitors
- FDA approval of HIV viral load kit (monitoring)
Impact of Genomics on Medicine

• Identify the underlying causes of disease and reasons for progression
  - Sub-classify complex diseases
• Design therapies to intervene in disease development
  - Treat cause, not symptoms
• Define patient populations most likely to respond
  - Increase efficacy of therapies
  - Minimize adverse reactions
  - Reduce risk in clinical trials
Genetic and Genomic Projects

- Human Genome
- HapMap
- Genome Wide Association Studies
- 1000 Genomes
- Encyclopedia of DNA Elements (ENCODE)
Overview

• Human genetic variation
• Current genetic tests
• Test availability and reliability
• Evidence for clinical utility
• Medical benefit and cost effectiveness
• Reimbursement
• Privacy and ethical issues
Recent Discoveries in the News

• A report is published on a rare genetic mutation that protects people against late-onset Alzheimer’s Disease

• FDA approves a drug that gives a 57% response rate in the 4% of non-small cell lung cancer patients who have a particular gene rearrangement (EML4-ALK)

• Variants accounting for 20% of Autism Spectrum Disorder have been identified; most are “de novo” variants. Another report concludes that older men are more likely to father children with autism
"We think it has something to do with your genome."
Questions About the Alzheimer’s Discovery

• The mother of a 50 year old man had late-onset Alzheimer’s at age 85; should he be tested for the specific protective (and risk) mutations?
• Where is testing available, what will it cost, and will his health insurance cover it?
• Although the Genetic Information Non-Discrimination Act prohibits his test results from being used to deny employment and health insurance, what about disability, life and long-term care insurance?
Questions About the Lung Cancer Discovery

• Since 96% of NSCLC patients’ tumors do not carry the EML4-ALK variant, is it worthwhile to be tested for it?
• Must a patient’s tumor have the variant in order to receive the drug?
• Are there other genetic variants in the tumor that could be used to select other targeted therapies?
• Is there intra-tumor genetic heterogeneity?
• Should the tumor be studied by Whole Exome Sequencing (WES)?
Questions About the Autism Discoveries

• What are “de novo” variants?
• Can they be detected by Non-Invasive Prenatal Testing?
• If most of the known autism variants are not inherited, why are the children of older fathers at greater risk?
• Is it worth having a Whole Genome Sequence (WGS) done on an autistic child to identify variants if there is no targeted therapy?
• How will Variants of Unknown Significance be reported?
• Will the discovery of these variants potentially lead to new drugs for autism?
Some Commonly Used Terms

- Gene
- SNP (Single Nucleotide Polymorphism)
- Phenotype
- “Junk DNA”
- Gene Regulation
- “de novo” Variants
- Genetic Test
- Whole Genome Sequencing
- Whole Exome Sequencing
Human Chromosomes

- Human cells contain 46 chromosomes in 23 pairs – one of each pair is inherited from each parent
- Chromosome pairs 1 – 22 are called autosomes
- The 23rd pair is called sex chromosomes: XX is female, XY is male

Gene for Factor V Leiden (chromosome 1)

Gene for ApoE (chromosome 19)
SNPs

• In humans, there are millions of single-nucleotide polymorphisms (SNPs) or genetic variations between two unrelated individuals.

• Because of the double-stranded nature of DNA, variants cause base pairs of the DNA helix to change.
“Junk DNA” has a Key Role in Gene Regulation

Gene

Junk DNA

Regulation

Disease

>470,000 Genetic Switches

Hierarchy of Genetic Regulators

Malfunctioning Hierarchy
Human Genetic Variation

• The human genome has ~3 billion base pairs
• Humans and chimpanzees are ~98.5% identical
  – 35 million SNPs
  – 5 million insertion/deletions
• Any two people, on average, are ~99.8% identical
  – 3.6 million SNPs
  – 344,000 insertions/deletions
  – 717 large deletions
• Each person has
  – 100 loss-of-function mutations
  – 20 are double mutations that would inactivate the genes
Genome Wide Association Studies
**de novo Mutations**

- The variant is found in a newborn, but not in either parent’s genome
- Result of spontaneous mutations during spermatogenesis and oogenesis
- ~60 new variants per generation, depending on age of father at conception (+2 per year of paternal age)
  - 25 mutations from a 20 year old father
  - 65 mutations from a 40 year old father
  - 15 mutations from a mother regardless of her age
- ~10% of the mutations will be deleterious
  - A newborn will have ~6 new deleterious mutations
Growth of Laboratory Directory

Genetic Tests for Inherited Diseases

- 12 tests approved by US Food & Drug Agency (FDA)
- 2,667 tests offered by clinical laboratories (CLIA)
- 254 tests available from research labs (not for Dx or Rx)
- Association for Molecular Pathology
  - [www.amptestdirectory.org](http://www.amptestdirectory.org)
  - FDA-approved/cleared molecular diagnostic tests (pdf)
- National Center for Biotechnology Information
- Lab Tests Online
  - [labtestsonline.org](http://labtestsonline.org)
FDA-Approved/Cleared Diagnostic Tests

• Cystic Fibrosis
• HLA Typing for Transplantation
• Factor V Leiden and Prothrombin
• Four Drug Metabolizing Enzymes
• Prenatal (chromosome 13, 18, 21, X and Y)
• Chromosome 8 (AML, CML, MPD, MDS)
• MTHFR
• Heart Transplant Rejection
Laboratory Developed Tests (LDTs)

Clinical Laboratory Improvement Amendments (CLIA)

• 2,667 tests for rare inherited diseases & cancer
• LDTs are called “home-brew” tests
• Overseen by Center for Medicare and Medicaid Services
• Requires analytical validation (internal)
• Does not require or establish clinical utility
• Lab can offer test as a service; cannot sell reagents
Genetic Tests Offered by Research Laboratories

- 254 tests
- For basic research
- For identifying potential clinical utility
- Reagents must be labeled: “For Research Use Only (RUO). Not for use in diagnostic procedures”
- May not be represented as an effective diagnostic product
Quality System Components

- Personnel skills and training
- Audit preparedness
- Document controls
- Record keeping
- Design controls
- Purchasing controls
- Component and test acceptance criteria
- Component and test ID and traceability
- Production and process controls
- Non-conforming test criteria
- Corrective and preventative actions
- Complaint file procedures
- Device labeling procedures
- Device packaging criteria
- Handling & storage methods
- Distribution control
- Installation and servicing
FDA Medical Device Process

Concept & Design
Pre-Clinical Development
Clinical Trials
FDA Review
Reimbursement

2-3 years  1-3 years  1-2 years
Hierarchy of Evidence

Meta-analysis of large randomized trials
Evidence for Clinical Utility

• Gold standard: a prospective, randomized clinical trial to prove that a test improves clinical outcomes
  – Impractical, lengthy, too costly, or even impossible to enroll patients in a treatment-by-genotype trial, when giving a placebo would now be unethical
• Post hoc analysis of previously conducted randomized clinical trials - if informed consent was given for genetic studies and samples are available
• Professional organization’s recommendation
  – American College of Obstetrics and Gynecology
  – American Society of Clinical Oncology
• Multiple peer-reviewed publications
Evidence for Clinical Utility

• Need for a national, dynamically updated, interpretative database of evidence for clinical utility of genetic variants
• A means to convey updates to patient and/or physicians
• Government, academic and commercial databases
  – EuroGentest Clinical Utility Gene Cards  [www.eurogentest.org](http://www.eurogentest.org)
  – GET-Evidence  [evidence.personalgenomes.org](http://evidence.personalgenomes.org)
  – 23andMe  [www.23andme.com](http://www.23andme.com)
Volunteers from the general public working together with researchers to advance personal genomics.

We believe individuals from the general public have a vital role to play in making personal genomes useful. We are recruiting volunteers who are willing to share their genome sequence and many types of personal information with the research community and the general public, so that together we will be better able to advance our understanding of genetic and environmental contributions to human traits. Learn more about how to participate in the Personal Genome Project.

Project Overview. The PGP hopes to make personal genome sequencing more affordable, accessible, and useful for humankind. Learn more about our mission.

Want to participate? We aim to enroll 100,000 informed participants from the general public. Learn more about participation in the PGP and how you can get involved.

Meet our volunteers. Participants may volunteer to publicly share their DNA sequence and other personal information for research and education. Meet the "PGP-1K".
23andMe can help you manage risk and make informed decisions...

Get personalized health reports based on your DNA.

$99

Order Now

Welcome to you®

23andMe DNA Spit Kit
### Locked Reports

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Your Risk</th>
<th>Avg. Risk</th>
<th>Compared to Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Elevated Risk

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Your Risk</th>
<th>Avg. Risk</th>
<th>Compared to Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>★★★★</td>
<td>16.8%</td>
<td>11.4%</td>
<td>1.48x</td>
</tr>
<tr>
<td>Esophageal Squamous Cell Carcinoma (ESCC)</td>
<td>★★★★</td>
<td>0.43%</td>
<td>0.36%</td>
<td>1.21x</td>
</tr>
<tr>
<td>Stomach Cancer (Gastric Cardia Adenocarcinoma)</td>
<td>★★★★</td>
<td>0.28%</td>
<td>0.23%</td>
<td>1.22x</td>
</tr>
<tr>
<td>Alcohol Dependence</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia Areata</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hay Fever (Allergic Rhinitis)</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension)</td>
<td>★★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[31]
Contradictory Risk Predictions

A 48 year old man has a 1 million SNP test yielding the following results

<table>
<thead>
<tr>
<th>Lab</th>
<th>Prostate Cancer</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Average</td>
<td>Average</td>
</tr>
<tr>
<td>2</td>
<td>Average</td>
<td>Below Average</td>
</tr>
<tr>
<td>3</td>
<td>Below Average</td>
<td>Above Average</td>
</tr>
<tr>
<td>4</td>
<td>Above Average</td>
<td>Not Tested</td>
</tr>
</tbody>
</table>
Test Report Issues for WGS Results

• Interpretation
  – Need protocols for censoring results that are meaningless, misleading, or harmful
  – Need a process for updating the patient/physician when new clinically meaningful information becomes available
  – Duty to report (ethical issues)
  – Patent infringement

• Sample/results storage
  – Is it more cost effective to store the data securely or to store the DNA and run the sample again when needed?

• Informed consent
  – What does it mean to the patient, physician and researcher?
  – How will it apply to updated genetic and clinical information on previously unknown disease risks and new therapies?
  – Is the lab responsible for informing the patient or physician?
Cost per Megabase of DNA Sequence

Moore's Law

National Human Genome Research Institute
genome.gov/sequencingcosts
Is Whole Genome Sequencing Cost-Effective?

• It’s not about the costs of the sequencing reagents and data interpretation, as much as ...
  what is the **outcome** being measured?
    number of true variants identified
    multiple diagnoses and relevance to current condition
    clinical actions over a lifetime
    patient outcomes — morbidity and mortality
• ... and what is the comparator?
• The answers may be different for the patient, healthcare provider, insurer(s) and public health
Cost Effectiveness Analysis

• Evaluation of costs and benefits of a healthcare intervention to assist in decision making

• Does an intervention, when used to prevent, diagnose or treat an illness:
  – improve clinical outcomes...enough to
  – justify the additional dollars spent compared with alternative uses of the same money?
Incremental Cost Effectiveness of B vs A

\[
\frac{\text{Cost (B) - Cost (A)}}{\text{Effectiveness (B) - Effectiveness (A)}}
\]
Interpretation of CEA Results

### CEA Results Interpretation

- **Costs and Effects**:
  - Higher
  - Lower

- **Effects**:
  - Δ

- **Costs**:
  - Δ

#### Quadrant Analysis

- **Bad**: Costs and Effects Higher
- **Good**: Costs and Effects Lower

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<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost (per life-year gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow transplant for relapsed Hodgkins</td>
<td>$421,000</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>$237,000</td>
</tr>
<tr>
<td>Mammography (&lt;50 years)</td>
<td>$232,000</td>
</tr>
<tr>
<td>2-vessel coronary artery bypass graft</td>
<td>$106,000</td>
</tr>
<tr>
<td>ACE inhibitor for moderate hypertension</td>
<td>$82,600</td>
</tr>
<tr>
<td>Mammography (&gt;50 years)</td>
<td>$20-50,000</td>
</tr>
<tr>
<td>Diuretic for moderate hypertension</td>
<td>$23,500</td>
</tr>
<tr>
<td>Left main coronary artery bypass graft</td>
<td>$17,400</td>
</tr>
<tr>
<td><strong>Genome Test</strong></td>
<td><strong>$10,000-100,000?</strong></td>
</tr>
<tr>
<td>Smoking cessation (men)</td>
<td>$1,300</td>
</tr>
</tbody>
</table>