Genomic Medicine: Predictive, personalized, pre-emptive

Genomic Medicine
- Study of conditions that are partly caused or prevented by mutation(s) in gene(s)
  “Genomics – study not just of single genes, but of the functions and interactions of all the genes in the genome”
- Mechanism for common/complex diseases – asthma, hypertension, diabetes, psychiatric disorders

Why Do Health Professionals Need to Prepare for Genomic Medicine?
- Need to learn to “think genetically” - to:
  - realize when genetic factors play a role
  - effectively use family hx & genetic tests
  - be able to explain genetics concepts
  - deal with “risk” & genetic predisposition
  - realize personal and societal impact of genetic information
  - protect genetic privacy
  - use genetics to individualize patient care
  - use genetics to preserve health

“If it were not for the great variability among individuals, medicine might as well be a science and not an art”

Sir William Osler, 1892
Genetic Testing
Where will it be used?

• Diagnosis
• Prognosis
• Pharmaceutical Development
• Therapeutic Selection & Monitoring
• Screening & Risk Assessment
• Prevention

Genetic testing will impact nearly every clinical decision health care providers make

Genetic Testing Market
Number of Available Tests*

<table>
<thead>
<tr>
<th>Year</th>
<th>Available Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>303</td>
</tr>
<tr>
<td>1996</td>
<td>420</td>
</tr>
<tr>
<td>1997</td>
<td>485</td>
</tr>
<tr>
<td>1998</td>
<td>625</td>
</tr>
<tr>
<td>1999</td>
<td>667</td>
</tr>
<tr>
<td>2000</td>
<td>811</td>
</tr>
<tr>
<td>2001</td>
<td>862</td>
</tr>
<tr>
<td>2002</td>
<td>945</td>
</tr>
<tr>
<td>2003</td>
<td>est. 1000</td>
</tr>
</tbody>
</table>

* Excludes genetic tests for hereditary cancers and infectious diseases
Source: GeneTests.org

Genetic Testing Market
Growth in Annual Dollars

Largest dollar growth in cancer tests (41% of Total by 2006)

- Cancer (257% growth)
- Prenatal (46% growth)
- Predisposition (254% growth)
- Total (134% growth)

Source: Frost and Sullivan, IVD Technology Nov/Dec 2001

- Genome = all of the DNA in an organism or cell
- Size of human genome: 3.4 billion base pairs
- Number of human genes: ~30,000
- Genes vary in length and can cover thousands of bases
  - average size: ~3,000 bp
- Only about 5% of the human genome contains genes
- Action of much of the genome is unknown

Major sources of variation

• Single Nucleotide Polymorphisms (SNPs)
  - Single base change in DNA
    AAGCCTA
    AAGCTTA
  - Average frequency 1/1000bp
  - SNPs arise as a consequence of mistakes during normal DNA replication
• Genomic rearrangements
  - Duplications, insertions, deletions

Uses of Genetic Information

- Development of gene therapy
- Genetic testing for risk stratification
- Use of genetic information for treatment decisions & drug development
Genetics or Genomics?

- Pharmacogenetics
  Study of how genetic differences in a SINGLE gene influence variability in drug response (i.e., efficacy and toxicity)

- Pharmacogenomics
  Study of how genetic (genome) differences in MULTIPLE genes influence variability in drug response (i.e., efficacy and toxicity)

Interindividual Variability in Drug Response

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug Class</th>
<th>Rate of Poor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Beta-agonists</td>
<td>40-75%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Various</td>
<td>30%</td>
</tr>
<tr>
<td>Solid Cancers</td>
<td>Various</td>
<td>70%</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRIs, tricyclics</td>
<td>20-40%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Sulfonylureas, others</td>
<td>50%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>NSAIDs, COX-2 inhibitors</td>
<td>30-60%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Various</td>
<td>25-75%</td>
</tr>
</tbody>
</table>

Factors Contributing to Interindividual Variability in Drug Disposition and Action

- Age
- Race/ethnicity
- Weight
- Gender
- Concomitant Diseases
- Concomitant Drugs
- Social factors
- GENETICS

Genetics as the basis for variability in drug response

- Pharmacogenetics
  - The effect of genetic variation on drug response.
- Pharmacogenomics
  - The application of genomics to the study of human variability in drug response.
- Pharmacogenetics and pharmacogenomics are expected to play an important role in the development of better medicines for populations and targeted therapies with improved benefit/risk ratios for individuals

Personalized Medicine

The ability to offer
• The Right Drug
• To The Right Patient
• For The Right Disease
• At The Right Time
• With The Right Dosage

Genetic and metabolic data will allow drugs to be tailored to patient subgroups

“We wish to suggest a structure for the salt of [DNA]. This structure has novel features which are of considerable biological interest.”
Human Genome Project

- Determine the sequence of the 3 billion nucleotides that make up human DNA
- Characterize variability in the genome
- Identify all the genes in human DNA
- The Era of Genomic Medicine:
  - Improve prediction of drug efficacy or toxicity
  - Improve the diagnosis of disease
  - Earlier detection of genetic predisposition to disease

Why a Genetic Approach is Warranted

<table>
<thead>
<tr>
<th>Disease</th>
<th># of Deaths*</th>
<th>Genetic Susceptibility?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>696,947</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer</td>
<td>557,271</td>
<td>Yes</td>
</tr>
<tr>
<td>Stroke</td>
<td>162,672</td>
<td>Yes</td>
</tr>
<tr>
<td>Lower Respiratory Disease</td>
<td>124,816</td>
<td>Yes</td>
</tr>
<tr>
<td>Adverse Drug Reactions (est)</td>
<td>106,000</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>73,249</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Newsweek
June 25, 2001

“…pharmacogenetics promises to target treatment to a patient’s genetic profile…”

Will our new knowledge of genomics “revolutionize” health care?

Increased understanding of genomics raises hopes that health care can become more “personalized”

Hope that personalized medicine can improve quality & decrease costs

Drug Development Life Cycle

Adverse Drug Reactions

- ADR is one of the leading causes of hospitalization and death
- 6.7% of hospitalized patients have serious ADRs
- 0.3% of hospitalized patients have fatal ADRs
What is “Personalized Medicine”?

Multiple names for similar concepts:
- Predictive Medicine
- Individualized Medicine
- Information-based Medicine

Common Goals:
- Increase the efficacy of treatment
- Minimize side effects
- Improve cost-efficiency

The Need for Improved Therapeutics

- Estimated that in the United States alone each year adverse events account for
  - Over 100,000 deaths
  - More than 2 million hospitalizations
- The effectiveness of prescribed medications ranges from 20-60%

Better diagnosis (e.g. with biomarkers) makes existing therapies safer

Everyone who receives a therapy is subject to an adverse event, but only a minority benefit

If you can predict the responders, you achieve all of the benefit with fewer adverse events

Predicting Responsiveness Improves the Overall Outcome of Treatment

Predicting Adverse Events Improves the Outcome Even More

Components of Personalized Medicine
Predicted economic benefit of CYP2C9 testing for warfarin dosing

• Predict 1 major bleed prevented for every 44 patients screened ($135/assay)
• $6,000 testing costs ~ cost of 1 major bleed
• Neutral economic result, but significant improvement in patient outcome
• Prospective trial needed

Higashi and Veenstra, Am J Manag Care 2003; 9: 493-500

Benefits of Personalized Medicine

• Better matching patients to drugs instead of “trial and error”

• Customized pharmaceuticals may eliminate life-threatening adverse reactions

• Reduce costs of clinical trials by
  – Quickly identifying total failures
  – Favourable responses for particular backgrounds

• Improved efficacy of drugs

Using Genetic Information to Predict Drug Metabolism: The AmpliChip CYP450

A range of drug metabolism phenotypes is observed for individuals based upon the particular cytochrome P-450 genes they possess.


Personalized Medicine : BiDil

• Combination pill containing two medications for heart failure, cardiovascular disease, and/or diabetes.

• Clinical trials did not show overall benefit across entire population.

• Subgroup of African-descent patients showed benefit
  – BiDil approved for use in African-descent patients.

Pharmacokinetics and pharmacodynamics are essential to assess the drug efficacy.

• Pharmacokinetics
  – What the body does to the drug
    – dose, dosage regimen, delivery form
    – Drug fate: Absorption, distribution, metabolism, and elimination of drugs (ADME)

• Pharmacodynamics
  – What the drug does to the body
    – Biochemical and physiological effects of drugs
    – mechanism of drug action
    – relationship between drug concentration and effect

Pharmacokinetics
conc. vs. time

Pharmacodynamics
conc. vs. effect

PK/PD
effect vs. time
Pharmacogenomics

- Drug Targets
- Drug Transporters
- Drug Metabolizing Enzymes
- Pharmacodynamics
- Pharmacokinetics

Variability in Efficacy/Toxicity

Things to Consider
- Does my doctor know enough about genomic medicine to be advising me?
  - Are there genetic counselors available?
- Will the test only be for this condition?
  - What if I am susceptible to another disease?
- Who will know about this?
  - Doctors... insurance companies?
- How exactly will the results be kept secure and in confidence?

Moving Pharmacogenomics to Clinical Practice
- Document Pgx superiority: Pgx-guided versus usual care
- Documenting sufficient variability to predict clinical utility
- Studies that mimic clinical practice
- Proof-of-concept clinical studies
- In vitro functional studies
- Identify sequence variability in candidate genes

The Future of Pharmacogenomics
- Genome wide approach versus candidate gene approach
- Thousands of SNPs
- Thousands of patients
- Replication studies
- Sophisticated databases housing pharmacogenomic information
- Drug selection and dosing algorithms incorporating non-genetic and genetic information
- Point of care genetic testing
Preparing for the Age of Genetic Medicine

Genetics is becoming a driving force in medical decision making

“Here’s my sequence...”

The New Yorker

“Personalized medicine: elusive dream or imminent reality? In summary: it is both.”

Larry Lesko
Director of the FDA Office of Clinical Pharmacology and Biopharmaceutics

Clin Pharmacol Ther; 2007: 807-816