Human Genome Project Data

• Completion of the Human Genome Project in 2003
• We are all 99.9% similar in our DNA.
• Individuals vary by only 0.1%
• Individual variations may correlate with different responses to medicines and magnitude of disease risk.

Introduction

• “individualized medicine”
  – diagnose and predict disease
  – provide earlier intervention
  – identify new treatment protocols
  – safety & efficacy of drug use
• genetic/genomic information + environmental factors = clinical presentation of patient
(Caldwell, 2013)

Major Outcomes of HGP

• Discovery of:
  – causative genes in Mendelian disorders
  – susceptibility genes in complex disease
• Improved:
  – drug design
  – drug treatment
  – disease management
Introduction

• focus on reduction of cost with quality of care
• difficulties with access to healthcare (Chan & Green, 2013)
  – inadequate supplies
  – inappropriate distribution of resources
• even more significant in patients with chronic diseases (Parikh et al., 2013)
• pharmacogenomics
  – cost-effective solution
  – improved patient outcomes

Healthcare Access & Service Utilization

• challenges to access (Chan & Green, 2013; Wray, 2013)
  – increased patient demands
  • aging population
  • chronically ill
  – longer delays for care
  – rushed treatment
  – adverse patient outcomes

Healthcare Access & Service Utilization

• focus of pharmacogenomic research (Olivier & Williams-Jones, 2014)
  – cancer
  – depression & other psychological disorders
  – cardiovascular & coronary heart disease
• minimal interest in:
  – orphan diseases
  – infectious disease
  – maternal health
Reimbursement

• reimbursement decisions are complicated (Kenkel et al., 2013)
  – lack of data evaluating the economics of genetic testing
  – cost of evaluating new technologies
• limits accessibility & integration into clinical practice
• public insurance plans cover (Cohen & Felix, 2014)
  – chromosomal abnormalities
  – prenatal and neonatal diagnosis
  – pre-implantation genetic diagnosis
• evidence-based coverage
  – look at test accuracy
  – cost-effective treatment
• cover costs if test recommended by provider
• self-pay may be patient's choice (Horn & Terry, 2012)

Adverse Drug Reactions

A major health issue

• annually over 106,000 people in the United States die from adverse reactions to correctly prescribed doses of drugs.
• another 2.2 million suffer serious, but not deadly, side effects.
Adverse Drug Reactions

A major health issue

- 4th leading cause of death in the U.S.
- 15% of U.S. hospital admissions
- $136 billion in medical costs (2010)
- 80-85% of drug response is due to genetics

Minimize/Eliminate the Uncertainties
No 1-on-1 custom tailoring, but towards a much better fit ... 

Remember: All medical decisions/knowledge are based on group-derived (aggregate) data analysis. "Data" on individuals (Harry Finkelstein) are anecdotal and (largely) medically/clinically meaningless.

Genetic Polymorphisms

Pharmacokinetic
- Transporters
- Plasma protein binding
- Metabolism

Pharmacodynamic
- Receptors
- Ion channels
- Enzymes
- Immune molecules

Application

All patients with same diagnosis

1. Remove non-responders and basic responders

2. Treat responders and patients not predisposed to toxicity
Inter-Individual Variability

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

PERSONALIZED MEDICINE

Inter-Individual Variability

<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>

Metabolic enzymes identified in drug labels of FDA-approved drugs

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- TPMT
- UGT1A1

3/20/2015
CYP Nomenclature

- Supergene family
- Family
- Subfamily
- Isoenzyme
- Allelic variant

*1 is usually wild-type

Liver Enzymes

- Break down more than 30 classes of drugs
  - β-blockers
  - tricyclic antidepressants
  - morphine derivatives
  - anti-dysrhythmics
- Poor metabolizers: need lower dose
  - 6% of Caucasians
  - 2% of African Americans
  - 1% of Asians
- Ultra-rapid metabolizers: need higher dose
  - 20% of Ethiopians
  - 7% of Spanish
  - 1.5% of Scandinavians

CYP3A4

- Involved in the metabolism of the largest range of drugs, ~ 50%
- Types
  - Immunosuppressant drugs (cyclosporine, azathioprine)
  - Chemotherapeutic drugs
  - Antifungals
  - Tricyclic antidepressants
CYP3A4 (continued)

- Types (continued)
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Antipsychotics (Haldol)
  - Opiate analgesics (codeine)
  - Benzodiazepines
  - Statins
  - Calcium channel blockers (verapamil)

CYP2C9

- anticoagulant warfarin (Coumadin®)
- non-steroidal anti-inflammatory (NSAID) drugs (Advil®, Aleve®)
- anti-epileptics (phenytoin)
- anti-diabetics (sulfonylurea, tolbutamide).

CYP2C19

- anti-platelet drug clopidogrel (Plavix®)
- anti-depressants
- SSRIs
- anti-epileptics
- proton pump inhibitors (Nexium®, Prevacid®)
CYP2D6

- responsible for the metabolism of approximately 20 to 25% of all marketed drugs
- many drug substrates of CYP2D6 have been identified
  - adrenergic receptor blockers, (Metoprolol)
  - antidepressants
  - antiarrhythmics (Tambocor)
  - antipsychotics

Patients with same diagnosis

All patients with same diagnosis

Toxic Responder: Lower dose or alternate drug
Pharmacogenomics

Drug Metabolizer Status

<table>
<thead>
<tr>
<th>Metabolizer Status</th>
<th>Description</th>
</tr>
</thead>
</table>
| Poor Metabolizers (PM)      | • 2 non-functional alleles  
• Little or no enzyme activity |
| Intermediate Metabolizers (IM) | • 1 non-functional allele and 1 functional allele  
• Decreased enzyme activity |
| Extensive Metabolizers (EM) | • 2 normally functioning alleles  
• Normal enzyme activity |
| Ultra-Rapid Metabolizers (UM) | • 1 or more ultra-functioning alleles  
• Increased enzyme activity |

Response depends on the role of the enzyme in metabolism of the specific drug.

Pharmacogenomics

<table>
<thead>
<tr>
<th>Enzyme Activity</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug inactivated by enzyme</td>
<td>UM may need a higher dose of the drug to reach a therapeutic range</td>
</tr>
<tr>
<td>Drug activated by enzyme</td>
<td>UM may be associated with increased exposure to the drug and an increased risk of adverse drug reactions</td>
</tr>
</tbody>
</table>
Pharmacogenomics

Testing

- Tuberculosis
- Cancer
- Heart Failure
- Antibacterials
- Cytostatics
- ACE Inhibitors
- Breast Ca
- Lung Ca

HER-2 negative (2/3)
- Mean survival: 7 yrs
- Cytostatics

HER-2 positive (1/3)
- Mean survival: 3 yrs
- Cytostatics + humMAb

Pharmacogenomics Case Study: trastuzumab

Bimodal response:
- 2/3 of patients: addition of trastuzumab (Herceptin® or Herclon®) to chemoRx → no benefit
- 1/3 of patients: addition of trastuzumab to chemoRx → 50% survival time increased by factor 1.5 (20 → 29 weeks)

Pharmacogenomics Today:

- **Trastuzumab** (Herceptin®, Herclon®)
  - Drug for women whose breast tumors have a specific genetic profile that causes overproduction of the HER2 protein
  - Testing for HER2 levels can determine whether a patient will respond to the treatment with trastuzumab
Goal: Tailoring New Drugs to Target Different Types of Breast Cancer

- Tumor overexpressing HER2
- Sensitive to trastuzumab
- Tumor overexpressing
- Sensitive to ??
- Tumor overexpressing??
- Sensitive to ??

Pharmacogenetics: A Case Study

- Individuals respond differently to the anti-tumor drug 5-fluorouracil.
- The diversity in responses is due to variations in the patient's metabolism of the drug.
- After a simple blood test, medications can be adjusted based on the patient's genetic profile.

Thiopurines

- Cytotoxic drugs with a narrow therapeutic index
- Used for
  - Acute lymphoblastic leukemia (ALL)
  - Inflammatory bowel disease (IBD)
  - Autoimmune diseases
  - Organ transplant recipients
Genetic variants that reduce activity of the thiopurine S-methyltransferase (TPMT) enzyme
- Life-threatening bone marrow suppression
- Identify PM → reduce dose or use alternative drug

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**Depression: Current Practice**

- Three patients, seek treatment for depression. Their doctor prescribed Celexa, a common antidepressant medication.
- After taking the medication for a month, Patient 1 feels much better (fewer episodes of depression and no adverse reactions to the drug)
- Patient 2 depression also had subsided. However, unable to sleep and often felt nauseated and anxious.
- The medication didn’t do much for Patient 3 felt neither better nor worse and had no adverse reactions to the drug.

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**Multiple Sclerosis**
Rheumatoid Arthritis

Tuberculosis

Asthma
Prolonged QT

Benefits of Pharmacogenomics

• New, more accurate diagnostic tests
  - Predict a patient’s response to specific drugs based on the genetic profile
• Personalized drug therapies
  - Match a patient with effective and safe medications based on information from diagnostic tests.
• Personalized disease prevention strategies
  - Developed using genetic tests that estimate a patient’s risk of getting a particular disease, combined with personalized drug therapies.

Issues Related to Pharmacogenomics

• Drug development for less-common SNP profiles
  - Who will pay for development of less profitable drugs?
• Insurance and Medicaid coverage
  - Will potentially expensive diagnostic tests be covered?
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Issues Related to Pharmacogenomics

• Education of health care providers
  - How will providers be trained to understand new diagnostic tests and use them when treating and advising patients?
Issues Related to Pharmacogenomics

• Competency Domains
  - Own attitudes and values regarding genetics
  - Advocating for patient's access
  - Incorporating genomic technologies
  - Risk assessment & interpretation
  - Testing and interpretation of test results
  - Clinical management of patients
  - Ethical, legal & social implications

• Ethical and privacy issues
  - Who will have access to genetic information and databases?
  - How do families handle conflicts when one person wants to be tested and others do not?
  - Should parents decide whether their children should be tested?

In Summary

• The Promise of Individualized Medicine
  – ability to make more informed medical decisions
  – higher probability of desired outcomes due to better-targeted therapies
  – reduced probability of adverse drug effects
  – focus on prevention and prediction of disease (proactive versus reactive)
  – earlier disease intervention
  – reduced healthcare costs
The Future

"Here's my sequence..."

??Questions??
References


