Pharmacogenomics
Genomics, Bioinformatics & Medicine
Personalized Medicine

• Medicine is personal:
  o We are all different.
  o Some of our differences translate into how we react to drugs as individuals.
  o This is why personalized medicine is important to everyone.

• Why does someone need twice the standard dose to be effective?
• Why does this drug work for you but not me?
• Why do I have side-effects and you don’t?
• Why do some people get cancer and others don’t?
• Why is anecdotal information irrelevant to your own health and treatment?
## Variability of Disease

### Example: Leukemia and Lymphoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Leukemia Details</th>
<th>Lymphoma Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>“Disease of the Blood”</td>
<td></td>
</tr>
<tr>
<td>1960</td>
<td>Leukemia</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>1970</td>
<td>Chronic Leukemia, Acute Leukemia, Preleukemia</td>
<td>Indolent Lymphoma, Aggressive Lymphoma</td>
</tr>
</tbody>
</table>
| 2007 | ~38 Leukemia types identified:  
- Acute myeloid leukemia (~12 types)  
- Acute lymphoblastic leukemia (2 types)  
- Acute promyelocytic leukemia (2 types)  
- Acute monocytic leukemia (2 types)  
- Acute erythroid leukemia (2 types)  
- Acute megakaryoblastic leukemia  
- Acute myelomonocytic leukemia (2 types)  
- Chronic myeloid leukemia  
- Chronic myeloproliferative disorders (5 types)  
- Myelodysplastic syndromes (6 types)  
- Mixed myeloproliferative/myelodysplastic syndromes (3 types) | ~51 Lymphomas identified:  
- Mature B-cell lymphomas (~14 types)  
- Mature T-cell lymphomas (15 types)  
- Plasma cell neoplasm (3 types)  
- Immature (precursor) lymphomas (2 types)  
- Hodgkin's lymphoma (5 types)  
- Immunodeficiency associated lymphomas (~5 types)  
- Other hematolymphoid neoplasms (~7 types) |

5 Year Survival

- ~0%

- ~70%

*After Mara Aspinall, Genzyme Genetics (modified)*

*Courtesy Felix W. Frueh*
The Goal of Personalized Medicine

• The Right Dose of
• The Right Drug for
• The Right Indication for
• The Right Patient at
• The Right Time.
Pharmacogenetics & Pharmacogenomics

• Pharmacogenetics: The role of genetics in drug responses.
  ○ F. Vogel. 1959

• Pharmacogenomics: The science that allows us to predict a response to drugs based on an individuals genetic makeup.
  ○ Felix Frueh, Associate Director of Genomics, FDA
Pharmacogenetics & Pharmacogenomics

http://www.pharmgkb.org/

- **Pharmacogenetics**: study of individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response (SIMPLE relationship)

- **Pharmacogenomics**: study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, expression, proteomics - COMPLEX interactions)

  - PharmGKB Website: http://www.pharmgkb.org/
Purine Analogs: A Case Study in Pharmacogenetics

- 6-mercaptopurine, 6-thioguanine, azathioprine

- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, after transplant

- Interferes with nucleic acid synthesis

- Therapeutic index limited by myelosuppression (treatment limited by immune suppression side effect)

6-mercaptopurine
6-thioguanine
azathioprine
Metabolism of 6-MP

Pharmacogenetics: A Case Study

Individuals respond differently to the anti-leukemia drug 6-mercaptopurine.

Most people metabolize the drug quickly. Doses need to be high enough to treat leukemia and prevent relapses.

Others metabolize the drug slowly and need lower doses to avoid toxic side effects of the drug.

A small portion of people metabolize the drug so poorly that its effects can be fatal.

Courtesy of Michelle Whirl-Carillo
Pharmacogenetics: A Case Study

Individuals respond differently to the anti-leukemia drug 6-mercaptopurine.

The diversity in responses is due to variations in the gene for an enzyme called TPMT, or thiopurine methyltransferase.

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After a simple blood test, individuals can be given doses of medication that are tailored to their genetic profile.

Normal dose

Dose for an extra slow metabolizer (TPMT deficient)

Courtesy of Michelle Whirl-Carillo
Thiopurine S-methyl Transferase Activity and Personalized Dosage

Second Example: Codeine and Cytochrome P450 CYP2D6

• Codeine is a commonly used opioid
  o Codeine is a prodrug
  o It must be metabolized into morphine for activity
• Cytochrome P450 allele CYP2D6 is the metabolizing enzyme in the liver
• 7% of Caucasians are missing one copy of the Cytochrome P450 CYP2D6 gene
  o codeine does not work effectively in these individuals

Courtesy of Michelle Whirl-Carillo
Codeine and Morphine Metabolism

[Diagram showing the metabolism of Codeine and Morphine]
Cytochrome Oxidase P450 Enzymes

• 57 Different active genes
• 17 Different families
• CYP1, CYP2 and CYP3 are primarily involved in drug metabolism.
• CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 are responsible for metabolizing most clinically important drugs
### Polymorphic Cytochrome P-450s

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Location</th>
<th>Poor Metabolizer Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupropion, cyclophosphamide, efavirenz, methadone, ifosfamide</td>
<td>Chromosome 19</td>
<td>3-4% of Caucasians</td>
</tr>
</tbody>
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<tr>
<th>Substrates</th>
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</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs, celecoxib, diclofenac, ibuprofen, naproxen, piroxicam, Oral Hypoglycemic Agents, tolbutamide, glipizide, ARBs, irbesartan, losartan, fluvastatin, warfarin, phenytoin</td>
<td>Chromosome 10</td>
<td>1-3% Caucasians</td>
</tr>
</tbody>
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<th>Substrates</th>
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<tbody>
<tr>
<td>Proton pump (-), amitriptyline, cyclophosphamide, diazepam, indomethacin, phenytoin, phenobarbital, progesterone, voriconazole</td>
<td>Chromosome 10</td>
<td>2-4% African-Americans, 3-5% Caucasians, 15-20% Asians</td>
</tr>
</tbody>
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<tr>
<td>antidepressants, beta-blockers, antipsychotics, chlorpheniramine, codeine, dextromethorphan, ondansetron, lidocaine, promethazine, tamoxifen, tramadol</td>
<td>Chromosome 22</td>
<td>5-10% Caucasians</td>
</tr>
</tbody>
</table>

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# Effect of Metabolic Rate on Drug Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>Poor Metabolizer Phenotype</th>
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<tbody>
<tr>
<td><strong>Prodrug, needs metabolism to work</strong></td>
<td><strong>Poor efficacy</strong></td>
</tr>
<tr>
<td>(e.g. codeine is metabolized by CYP 2D6 to</td>
<td><strong>Possible accumulation of prodrug</strong></td>
</tr>
<tr>
<td>morphine)</td>
<td></td>
</tr>
<tr>
<td><strong>Active drug, inactivated by</strong></td>
<td><strong>Good efficacy</strong></td>
</tr>
<tr>
<td><strong>metabolism</strong> (example is omeprazole)</td>
<td><strong>Accumulation of active drug can produce adverse reactions</strong></td>
</tr>
<tr>
<td></td>
<td><strong>May need lower dose</strong></td>
</tr>
</tbody>
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<table>
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<tr>
<th>Drug</th>
<th>Ultra-rapid Metabolizer Phenotype</th>
</tr>
</thead>
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<tr>
<td><strong>Prodrug, needs metabolism to work</strong></td>
<td><strong>Good efficacy, rapid effect</strong></td>
</tr>
<tr>
<td>(e.g. codeine is metabolized by CYP 2D6 to</td>
<td></td>
</tr>
<tr>
<td>morphine)</td>
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</tr>
<tr>
<td><strong>Active drug, inactivated by</strong></td>
<td><strong>Poor efficacy</strong></td>
</tr>
<tr>
<td><strong>metabolism</strong> (example is omeprazole)</td>
<td><strong>Need greater dose or slow release formulation</strong></td>
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