



## Pharmacogenomics principles and concepts

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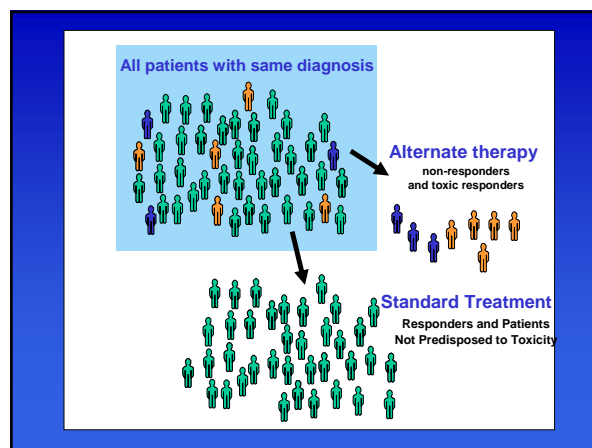
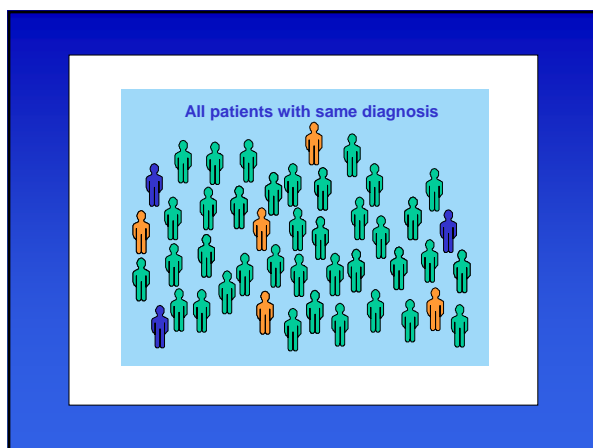
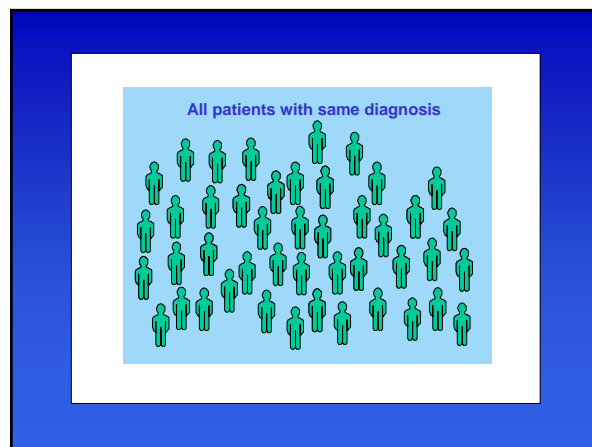
## Objectives:

1. Describe and define pharmacogenomic concepts and taxonomy
2. Identify the key advances that have been made in the Human Genome Project
3. Describe pharmacogenomic principles and the effect on pharmacokinetics and dynamics

**“A surgeon who uses the wrong side of the scalpel cuts her own fingers and not the patient;  
 if the same applied to drugs they would have been investigated very carefully a long time ago”**

*Rudolph Bucheim*  
*Beitrage zur Arzneimittellehre, 1849*

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### The clinical problem

- Multiple active regimens for the treatment of most diseases
- Variation in response to therapy
- Unpredictable toxicity

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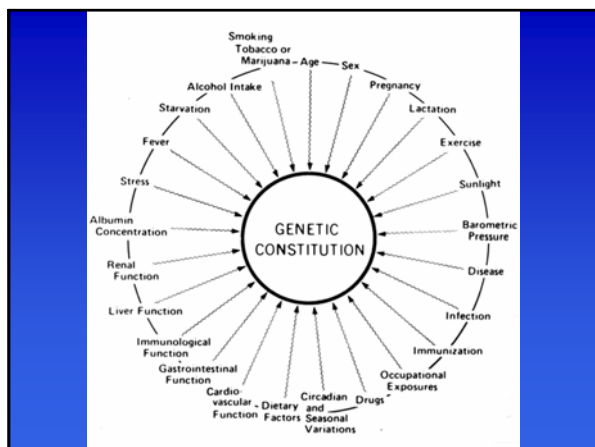
With choice comes decision

Pharmacokinetics

What the body does to the drug

Pharmacodynamics

What the drug does to the body



### What Exactly is Genetics?



Genetics is the study of heredity...

...and of variation between individuals



### Pharmacogenetics vs Pharmacogenomics

#### Pharmacogenetics

- The effect of genetic variation on drug response (disposition, safety, tolerability, and efficacy)

#### Pharmacogenomics

- The application of genome science (genomics) to the study of human variability in drug response

<http://www.fda.gov/downloads/Drugs/ScienceResearch/Research/Pharmacogenetics/ucm116702.pdf>

### The History of Pharmacogenetics

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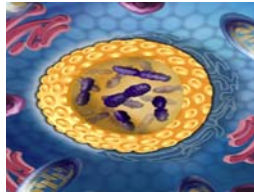
1866 – Gregor Mendel establishes rules of heredity

2003 – FDA issues draft guidelines for submission of pharmacogenetic data with NDAs

Source: U.S. Nature Reviews Genetics 5, 659-676 (September 2004)

## Chromosomes

- Every human cell with the exception of the gametes contains 23 pairs of chromosomes
- code for all the proteins in every cell
  - Resides in the cell nucleus
- Each chromosome contains one DNA molecule

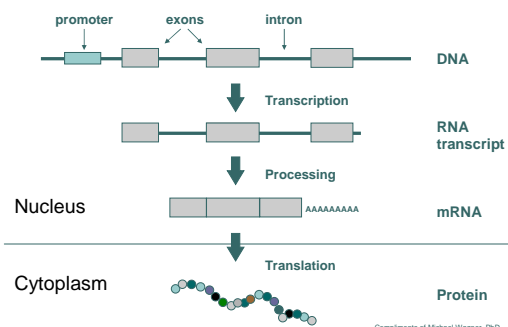


http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm116702.pdf

## DNA

- DNA building blocks = 4 nucleotide bases
  - A (adenine)
  - G (guanine)
  - T (thymine)
  - C (cytosine)
- Single strand
  - sugar-phosphate backbone
- Double strand
  - Double helix
  - Bound by hydrogen bonds
  - Always A-T; C-G

## Anatomy and Expression of a Gene



Compliments of Michael Wagner, PhD

## SNP (pronounced snip) single nucleotide polymorphism

- Variation in DNA sequence
- >1% population = genetic polymorphism
- Variations
  - Cause of human differences
- Alter protein synthesis and mRNA function

PharmGenEd Module 1: University of California at San Diego

## SNP's and Human Variation

- |                                 |                                  |
|---------------------------------|----------------------------------|
| ○ ...CCATTGACT                  | ○ ...GAAAGCCCC                   |
| ○ CCGTTGACT                     | ○ GAAGGCCCC                      |
| ● CCA = proline                 | ● AGC = serine                   |
| ● CCG = proline                 | ● GGC = glycine                  |
| ○ No AA change = synonymous SNP | ○ AA change = non-synonymous SNP |

## Other Polymorphisms -- Insertions

- Insertion
  - UGT1A1
  - Nucleotide change = Insert T and A repeat
  - (TA)<sub>6</sub>>(TA)<sub>7</sub>
  - ↓ function; ↓ glucuronidation
  - Gilbert's syndrome, drug toxicity

Oncogene (2003) 22, 6621-6628

## Other Polymorphisms – Deletion and Duplication

- Deletion (see diagram a)
  - CYP2D6
  - Delete several nucleotide base pairs
  - Loss of function; decreased metabolism
  - Phenotype = Poor metabolizer
- Copy Number Variation (see diagram b)
  - CYP2D6
  - Increased copies of CYP2D6 gene
  - Phenotype = Ultra-extensive metabolizer

Nature Reviews Drug Discovery 3, 749-761 (September 2004)

## Allele

- Alternative forms at a genetic locus on one chromosome
- Most loci – humans have 2 chromosomes which carry the same or 2 different alleles
- One of several variants of a gene
  - Usually specific site within a gene

## Heterozygous vs Homozygous

- Homozygous = two of the exact same alleles
  - Example CYP2C19\*1/\*1 (2 \*1 alleles)
- Heterozygous = two different alleles
  - Example CYP2C19\*2/\*3 (one \*2 and one \*3 allele)

## Human Genome Project

- Genomics: study of genes and their function
- Human Genome Project (HGP)
  - Began in 1990
  - Coordinated by Dept of Energy & NIH
  - Working draft published (90% complete) Science & Nature Feb 2001

## Human Genome Project

- HGP Goals:
  1. Determine the sequence of the 3 billion DNA nucleotides
  2. Chart variations among the sequences
  3. Label functions of the ~ 30,000 human genes
  4. Address ethical, legal, and social issues

## Genetic polymorphisms of drug disposition and drug targets

Growing list of published examples

- > 35 Drug metabolizing enzymes
- > 12 Drug transporters
- > 40 Drug targets

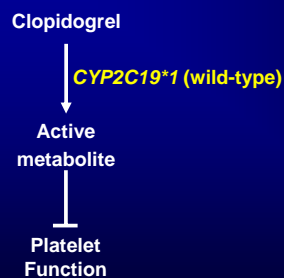
McLeod & Evans, *Annu Rev Pharmacol Tox*, 2001  
Evans & McLeod, *N Engl J Med*, 2003  
Weinshilboum, *N Engl J Med*, 2003

### Clonidogrel Clinical Pharmacology

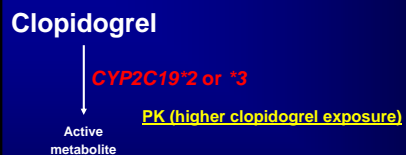
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Ellis KJ et al. Pharmacogenomics. 2009; (in press).

### Clonidogrel PGx – PK/PD

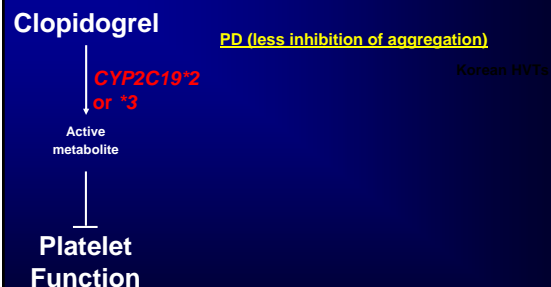


### Clonidogrel PGx - PK



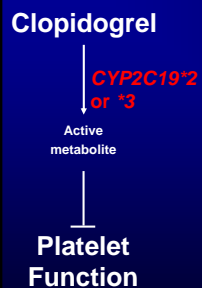
Kim et al. CP&T. 2008;84:236-42.

### Clonidogrel PGx - PD



Kim et al. CP&T. 2008;84:236-42.

### Clonidogrel PGx – PK/PD



Mega et al. NEJM. 2009;360:354-62.

### Clonidogrel PGx – Clinical Outcome TRITON-TIMI 38, PGx Sub-Analysis (N=1459)

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Mega et al. NEJM. 2009;360:354-62.

### Pharmacogenomic examples-2009

- *bcr/abl* or 9:22 translocation—imatinib mesylate
- HER2-*neu*—trastuzumab
- C-kit mutations—imatinib mesylate
- Epidermal growth factor receptor mutations—gefitinib
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine
- UGT1A1-irinotecan
- CYP2C9/VKORC1-warfarin
- CYP2C19-clopidogrel
- HLA-B\*5701-abacavir
- HLA-B\*1502-carbamazepine
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives, tamoxifen

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## PharmGKB ( [www.pharmgkb.org](http://www.pharmgkb.org) )

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## Resources for Pharmacogenomic Information

- PharmGKB ( [www.pharmgkb.org](http://www.pharmgkb.org) )
- NLM ( <http://ghr.nlm.nih.gov/> )
- JAMA 3 article series 2009
  - How to use an article about genetic association
  - Author John Attia
  - Great appendix of terms
- FDA
  - <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm116702.pdf>
  - <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>

## Goal of Pharmacogenomics

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