**Adverse Drug Reaction**

- Severe negative reaction to a prescribed drug
- 1994: more than 2.2 million serious cases and over 100,000 deaths by ADR
  - Made ADRs one of the leading causes of hospitalization and death in the U.S.
- Can’t determine how each individual will respond to a medication
  - Drugs use the “one size fits all” system
  - Suits only the “average” patient
Adverse Drug Reaction

Problem:
one size does NOT fit all

Probable solution:
pharmacogenomics
Responses to drugs (positive and negative) are complex traits influenced by many different genes.

- Hard to develop genetic tests to predict drug response without knowing all the genes.
- People’s gene shows small variations in their nucleotide content → made genetic testing for predicting drug response possible.

Most of human genome are identical, varies in single nucleotide polymorphisms (SNPs or “snips”): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered.

- Occurs once every 1,000 base pairs along the 3-billion-base human genome.
Definitions

- **Pharmacogenomics**: general study of all the genes that determine drug behavior
- **Pharmacogenetics**: study of inherited differences in drug metabolism & response
What is Pharmacogenomics?

- Combination of human genome knowledge (genes, proteins, SNPs) and pharmaceutical sciences (biochemistry, medicines)
- Examines inherited variations in genes that dictate drug response
- Explores ways these variations can be used to predict whether a patient will have a good/bad/no response to a drug
- Ultimately, researchers hope to be able to customize drug therapies for specific patient populations or even individuals
Current Uses

- **Cytochrome P450 (CYP) family of liver enzymes**
  - Responsible for breaking down more than 30 different classes of drugs
  - DNA variations in genes → ability to metabolize drugs
  - Inactive forms of CYP enzymes → cause drug overdose
  - Clinical trials researchers: use genetic tests for variations in cytochrome P450 genes to screen and monitor patients
  - Pharmaceutical companies: screen chemical compounds for how well they are broken down by variant forms of CYP enzymes

![Image of Cytochrome P450](http://quanta.synchem.kyoto-u.ac.jp/bioquant/images/p450.jpg)
Current Uses

- TPMT (thiopurine methyltransferase)
  - Important in chemotherapy treatment of a common childhood leukemia → breaks down a class of therapeutic compounds called thiopurines
  - Some Caucasians have genetic variances that prevent them from producing an active form of thiopurines
    - Since the inactive form of TMPT cannot break down the drug, thiopurines elevate to toxic levels in the patient
  - Doctors use this genetic test to screen for this deficiency → TMPT activity is monitored to determine appropriate thiopurine dosage levels
**Current Uses**

- **Cardiovascular pharmacogenetics**
  - **Goals:**
    - to guide cardiovascular drug development and selection
    - to optimize therapeutic benefit
    - to minimize the potential for toxicity
  - Researchers are exploring differences in the efficacy and efficiency of these cardiovascular drugs (regardless of drug concentration) based on common genetic variations (polymorphisms) → will become prominent in the future
    - e.g. antiarrhythmic, reninangiotensin, beta-blocker, lipid-lowering, and antithrombotic classes
Benefits

- More effective medicines
  - Can create drugs based on proteins, enzymes, and RNA molecules
  - Facilitated drug discovery
  - Therapy targeted to specific diseases
    - Decrease damage to healthy cells

- “Right” drugs the first time:
  - No more trial-and-error; process:
    - analyze patient’s genetic profile
    - prescribe best available drug therapy
  - Speedy recovery; increase in safety
Benefits

More appropriate drug dosages
- Current bases for appropriating dosage:
  - Weight and age
- With pharmacogenetics:
  - Based on genetics
- Maximizes therapy value; decreases over dosage

Advanced screening for diseases
- Decide on lifestyle and adapt to environmental changes early on → to avoid and/or lessen the seriousness of genetic diseases
- Allows for careful monitoring; treatments at right age ("optimal" age)
Benefits

- Better vaccines
  - Vaccines made of DNA/RNA → existing vaccines in our bodies without risks
  - Activation of the immune system without causing infections
  - Inexpensive, stable, easy to store and engineer

- Improvements in drug discovery
  - Using genome targets → more easily discover potential therapies
  - Previously failed drug candidates can be revived
Benefits

- Improves approval process
  - Drug approval process will be facilitated
    - Trials are targeted for specific genetic population groups
    - Greater degrees of success
  - Cost/risk of clinical trials will be reduced because of the individual-target basis

- Decreases overall cost of health care
  - Decreases in ADR, failed drug trials, time to get drug approval, medication times, number of trial medications, effects of disease on body
  - Increase in range of possible drug targets
Issues

- Still a complicated method of finding the SNPs that affect a specific drug response
- Limited drug alternatives
- Disincentives for drug companies for make multiple pharmacogenomic products
- Educating healthcare providers
- Economic issues
- Ethical issues
Current:
- Researchers are now trying to catalog as many genetic variances (SNPs) in the human genome as possible.
- DNA must be sequenced for presence of SNPs.
- Problem: traditional gene sequencing technology = slow and expensive.

Future:
- DNA microarrays (DNA chips) can make it possible for doctors to examine patients for specific SNPs quickly and affordably.
  - Takes only a couple of hours to screen 100,000 SNPs.
- SNP screening in the doctor’s office to determine drug response prior to drug prescription.