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Personalised Medicine

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Goals of Personalized Medicine

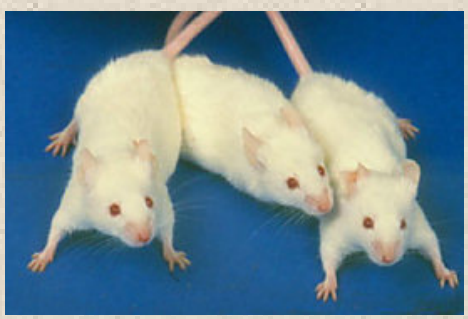
Correct Drug for the disease

Right Dose of drug

At Right time

For the Right Patient

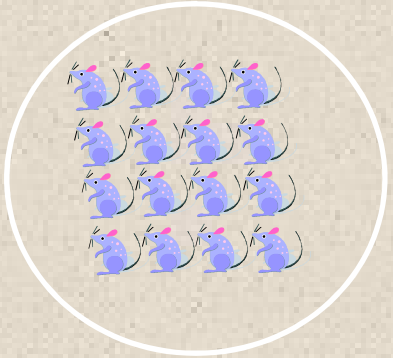
Drug Development – The Testers



But drugs are intended for people not animals

Humans

Lab animals



1. **Large diversity vs. less diversity e.g. in bred**
2. **Many considerations in common**
3. **But also, many considerations unique**
4. **Animals: many factors can be controlled including their genes**
5. ***H*umans: little can be controlled**

Adverse Drug Reactions in the USA

100,000+ therapeutic drug deaths per year

$100+ billion healthcare costs

2 million hospitalisations

4th major cause of mortality

Here in Britain

Typically it takes trial & error trials with at least 4 drugs to find the best one to treat a patient's high blood pressure

20 - 40% of patients are on the wrong drug for their illness

Inter-individual Variability towards some Drugs

Disease	Drug Class	Poor Response Rate
Asthma	Beta-agonists	40-75%
Hypertension	Various	30%
Solid Cancers	Various	70%
Depression	SSRIs, tricyclics	20-40%
Diabetes	Sulfonylureas, others	50%
Arthritis	NSAIDs, COX-2 inhibitors	30-60%
Schizophrenia	Various	25-75%

What are the reasons a person would react differently to drugs?

1. Variations in the receptor to recognize the drug
2. Other physiological traits that enable you to respond to a drug
3. How your body processes the drugs after receiving it

Groups of metabolizers

- **Extensive metabolizers**
  - Two copies of a functioning gene
- **Intermediary metabolizers**
  - One functioning gene
- **Poor metabolizers**
  - No functioning gene
- **Ultrafast metabolizers**
  - Multiple copies of the genes
  - May get no relief from some drugs

Medicine : Science or Art?

If it were not for the great variability among individuals, medicine might well be a science, not an art.

Sir William Osler, Physician 1892
Johns Hopkins School of Medicine

Natural BioDiversity in Man

Although we have 99.5% of our DNA common, there are many well known differences in how we metabolise food stuffs

Alcohol dehydrogenase (ADH)

Mitochondrial enzyme

Dimer - made up of 4 sub-units, encoded by three genes *ADH1*, *ADH2* & *ADH3*.

Many possible combinations of iso-enzymes

Different rates of metabolism amongst

- White
- Black African
- Asian >50 % of Japanese have “inactive” ALDH
- Native American including eskimos

ALCOHOL

Individual Variation

No two people respond exactly the same to an equal amount of alcohol

People develop tolerance with chronic intake of alcohol

Acute tolerance can develop in a short period of time

Asparagus

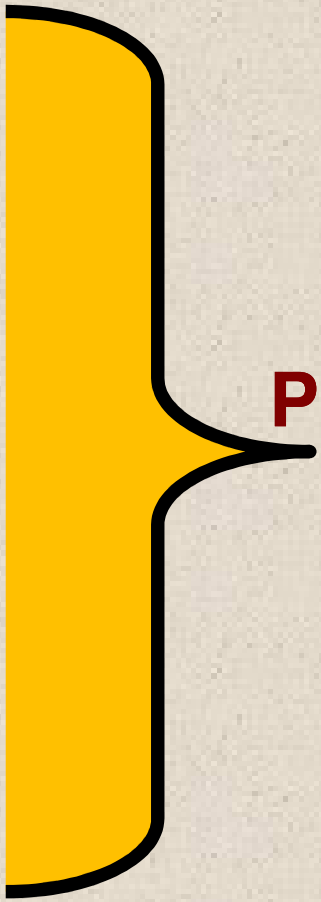
….cause a filthy and disagreeable smell in the urine, as every Body knows."
(Treatise of All Sorts of Foods, Lemery, 1702)

Most people produce the odorous compounds after eating asparagus, but only 22% have the autosomal genes required to smell them

2010, a genome-wide association study on whether subjects "ever noticed a peculiar odour when peeing after eating asparagus?" found a a single-nucleotide polymorphism (SNP) in a cluster of olfactory genes associated with the ability to detect the odour.

Factors contributing to Inter-individual variability in Drug Disposition and Action

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



PERSONALIZED MEDICINE

Drug related factors

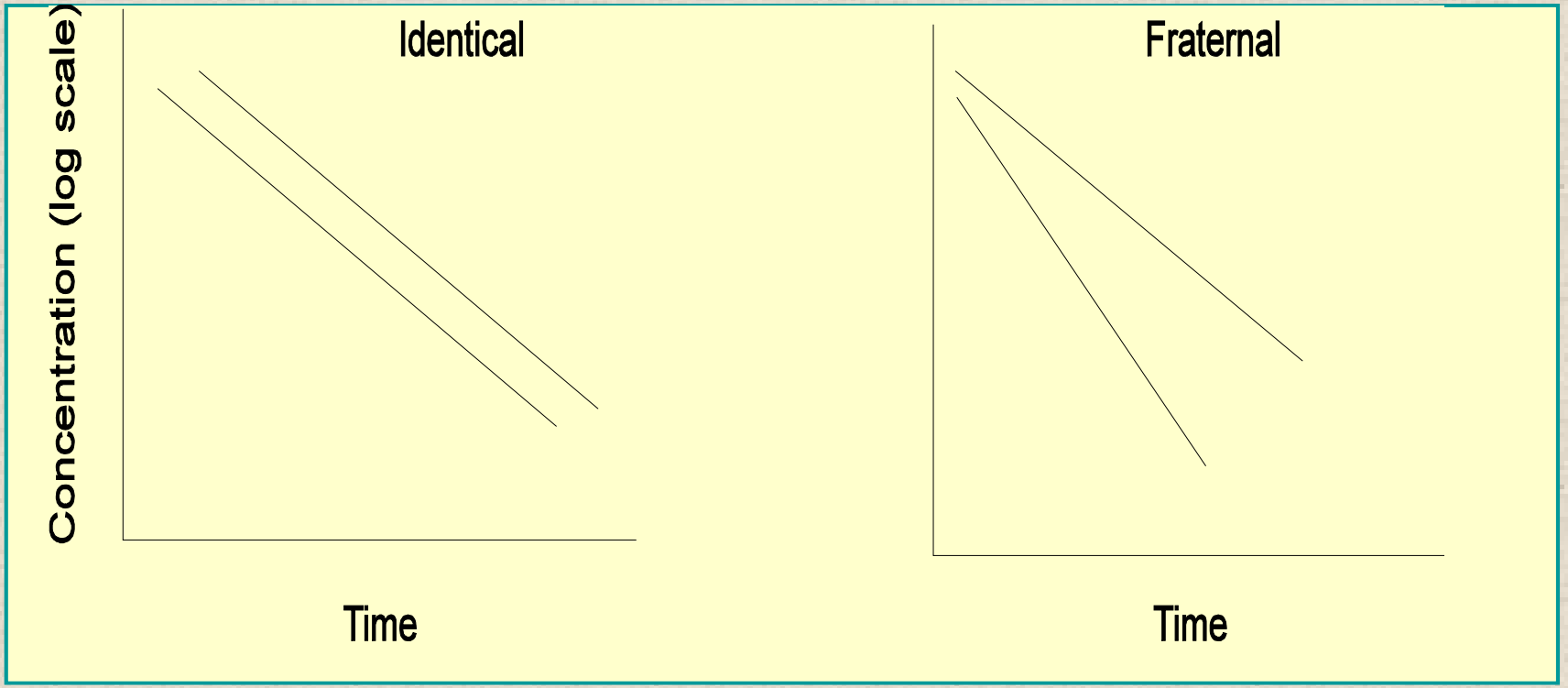
- **Variability due to pharmacodynamics differences**
  - Receptor response, hypersensitivity, tolerance, etc
- **Variability in pharmacokinetics**
  - Assumes relationship between effect and amount of drug in body/plasma concentration
  - Factors include:
    - Drug
      - Formulations – generic
      - Bioavailability
    - Patient
      - **Enzyme induction/inhibition**
      - **Compliance**

Drug Metabolism and Genetics

- **Evidence of an inherited basis for drug response dates back to the 1950s**

  Succinylcholine: 1 in 3000 patients developed prolonged muscle relaxation
- **Monogenic**
- **Phenotype to genotype approach**

Genetic effects on drug PK have been observed for years



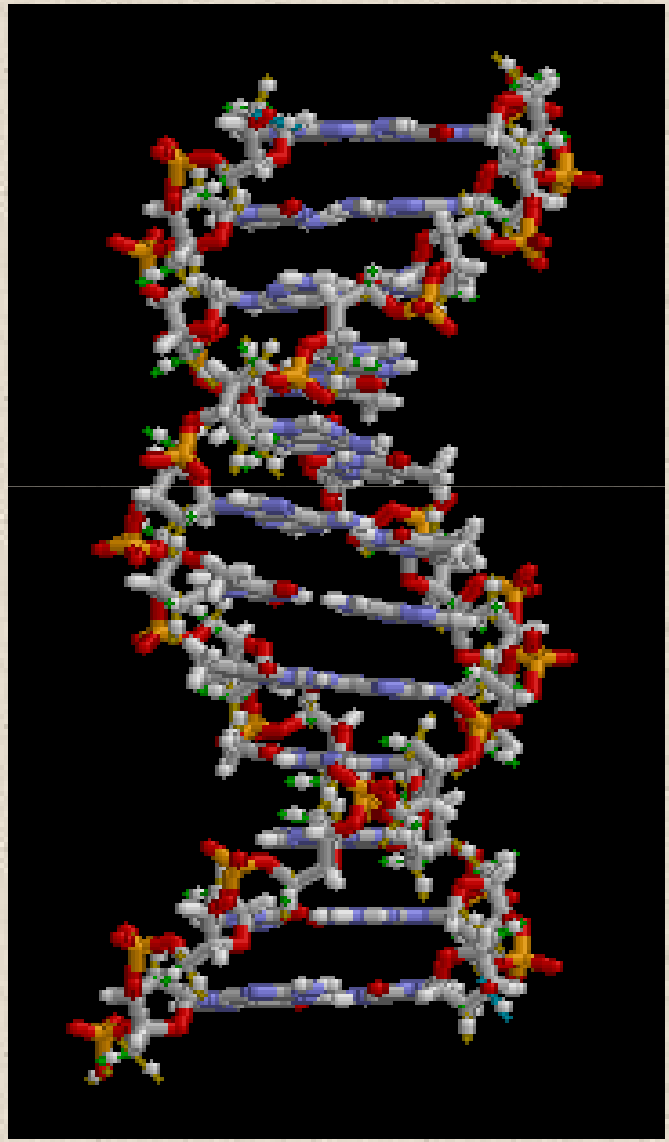
Decline in phenylbutazone concentrations after a single oral dose, in identical (monovular) and fraternal (biovular) twins

For some identical twins the curves were superimposed

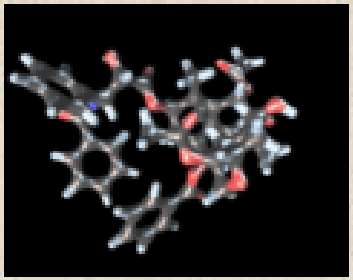
Vessell & Page (1968) Science, **159**, 1479.

Pharmacogenetics attempts to link the large ….

DNA



with the small ….



Taxol

Consequences of Polymorphisms

- May result in a different amino acid or stop codon
- May result in a change in protein function or quantity
- May alter stability of mRNA
- No consequence

Examples drug polymorphism

- ***N*-acetyltransferase**
  - Isoniazid
  - Sulfonamides
  - Others
- **Pseudocholinesterase**
  - **Suxamethonium**
- **Cytochrome P-450**
  - CYP2D6
    - Debrisoquine
    - Codeine?
    - SSRIs
  - CYP2C9
    - Phenytoin, tolbutamide, valproate, and warfarin
  - CYP2C19
    - Omeprazole

Phenytoin & warfarin have narrow therapeutic windows

Single Nucleotide Polymorphisms (SNP)

- Pronounced “snip”
- Single base pair difference in the DNA sequence
  - Over 2 million SNPs in the human genome
- Other polymorphisms:
  - Insertion/deletion polymorphisms
  - Gene duplications
  - Gene deletions

Consequences of Polymorphisms

- May result in a different amino acid or stop codon
- May result in a change in protein function or quantity
- May alter stability of mRNA
- No consequence

Pharmacogenetics & Pharmacogenomics

Pharmacogenetics: The role of genetics in drug responses

F. Vogel. 1959

Pharmacogenomics: Prediction a patient's response to a drug based on that their genome

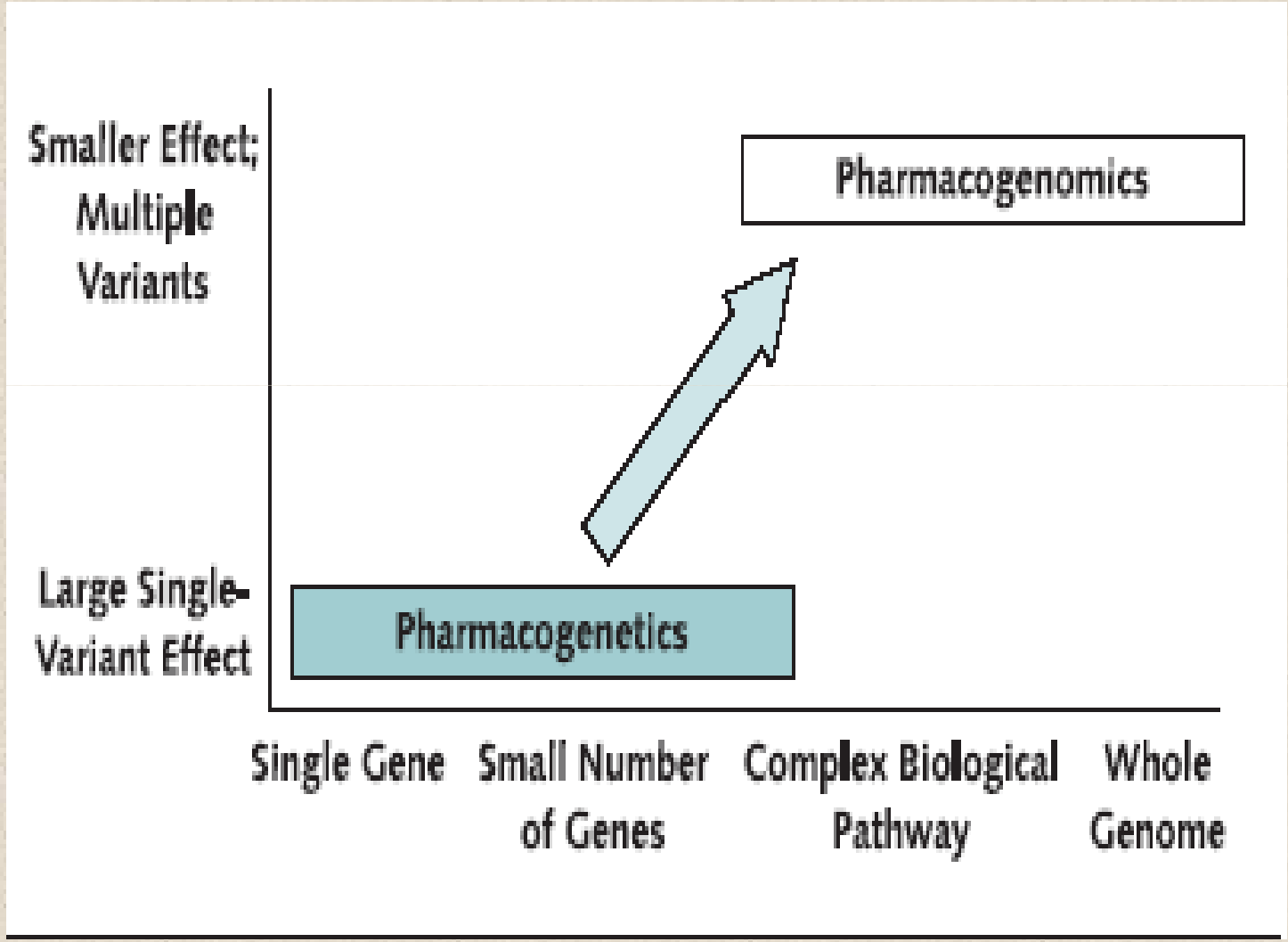
Pharmacogenetics & Pharmacogenomics

Molecular Biology Definitions

Pharmacogenetics the study of how genetic differences in a single gene influence variability in drug response

Pharmacogenomics the study of how genetic differences in multiple genes influence variability in drug response

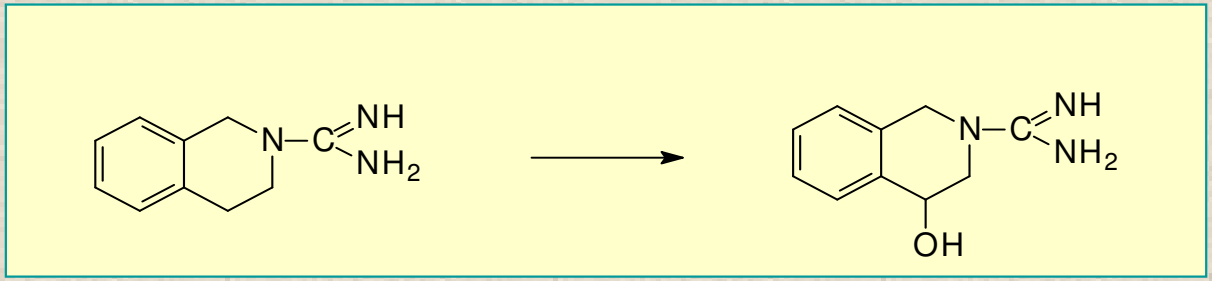
Current Concept of Pharmacogenomics



Roden DM et al. Ann Int Med 2006; 145:749

Polymorphic cytochromes

- First observed with debrisoquine:



- Debrisoquine – obsolete anti-hypertensive
- Number of patients collapsed from hypotension
- Distribution 5-10% population
- Isoform of CYP2D6

Some examples of Drug Metabolism Pharmacogenomics

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China[17]	Debrisoquin[15] Sparteine[16] Nortriptyline[23] Codeine[27,28]	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 14.6% in China[17] 18% in Japan[33]	Omeprazole[34,35]	Enhanced drug effect[36,37]
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous[38]	Fluorouracil[39,40]	Enhanced drug effect[39,40]
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans[41]	Succinylcholine[9,41]	Enhanced drug effect[9,41]

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

NEJM 2003; 348: 529-537

Following publication of the Human genome

"…pharmacogenetics promises to target treatment to a patient's genetic profile…"

NextFrontiers

The Next New Thing

A revolution in genetic research is targeting treatments to patients' unique characteristics. It can mean the difference between life and death. By Sharon Begley

Made-to-Order Medicine

JILL WAS ONLY 2 WHEN the diagnosis came: acute lymphoblastic leukemia (ALL). This rare childhood cancer, the doctors assured her parents, is highly curable with a cocktail of four chemotherapy drugs. But from the very beginning the chemo made Jill acutely ill: her white-cell, red-cell and platelet counts plummeted, and even with biweekly transfusions "her counts kept going lower and lower," says Dr. Mary Relling of St. Jude Children's Research Hospital in Memphis, where Jill was treated. Doctors didn't know whether the leukemia was knocking out her blood production—or whether the chemo itself was. But they had a way to find out. Researchers at St. Jude and at the Mayo Clinic in Rochester, Minn., had recently discovered that patients with a single mistake in a gene called TPMT fail to produce the enzyme that metabolizes the chemo drug, 6-mercaptopurine. As a result, the drug builds up in the body to toxic levels. Jill belonged to the 0.3 percent of the population—one person in 300—that carries two copies of the misspelled TPMT

SPECIAL TREATMENT: Herceptin, a drug developed by Dr. Dennis Slamon, targets a receptor found in only 30 percent of breast cancers

Newsweek June 25, 2001

Pharmacogenetics – the future

Personalised medicine

using gene chip technologies

is coming "soon"

Affymetrix

1992 Co-founded by Dr. Stephen Fodor.

Company had begun as part of Affymax N.V. in 1991

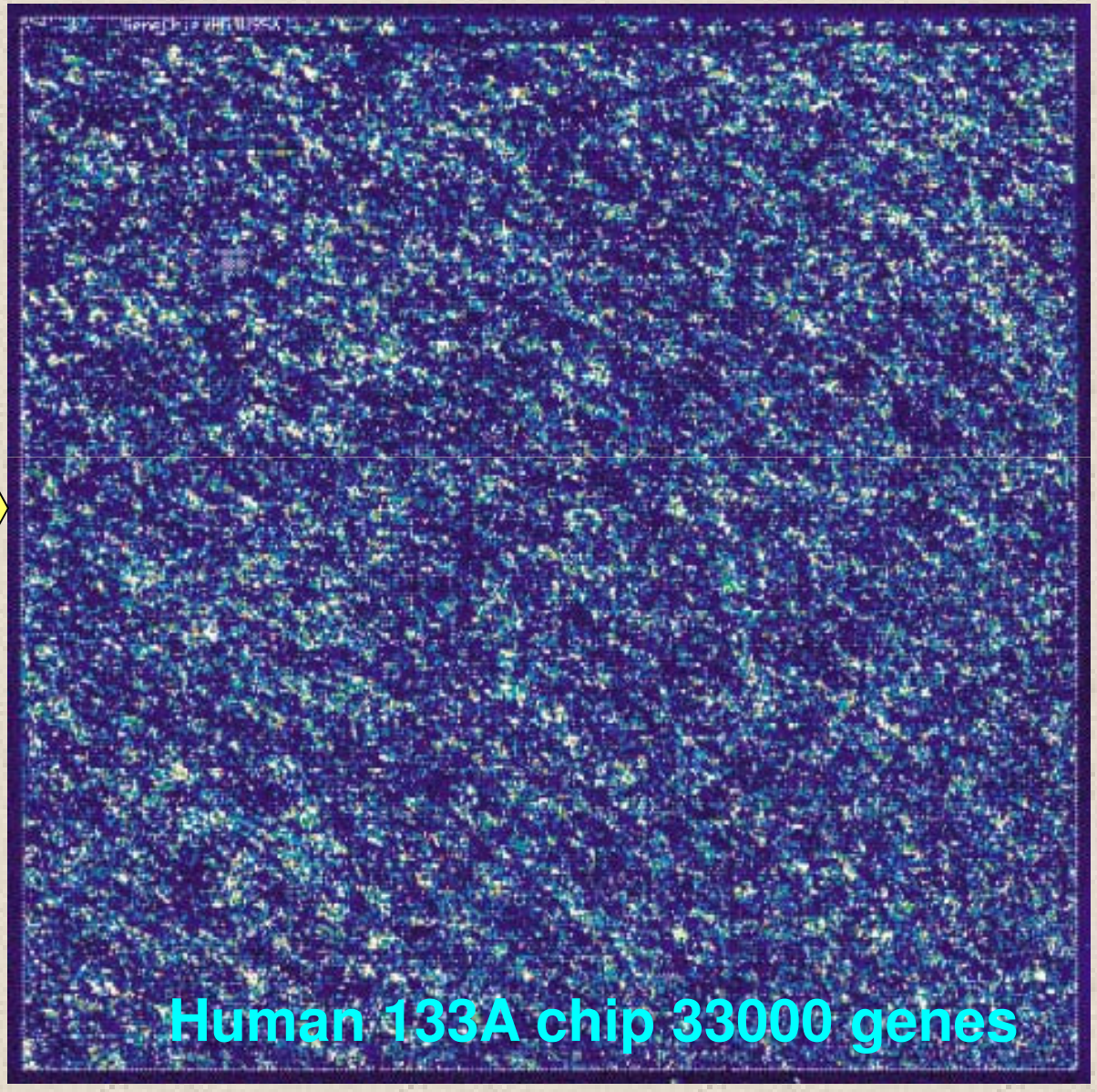
In the late 1980's Affymax had developed methods for fabricating DNA microarrays, called "GeneChips" using derived semiconductor industry technologies

Affymetrix Human Genome U133 Plus 2.0 Array

Complete coverage of the Human Genome U133 set plus 6,500 additional genes for analysis of over 47,000 transcripts

Bioformatics

Microchip analysis



Roche Chip for Cytochrome P450 Genes: CYPC19 and CYP2D6

Claims for Genetic Analysis for Warfarin

- More rapid determination of stable therapeutic dose.
- Better prediction of dose than clinical methods alone.
- Applicable to the 70-75% of patients not in controlled anticoagulation centers.
- Reduces between 4,500 and 22,000 serious bleeding events annually in US.
- Genetic testing now required by FDA

One size definitely does not fit all

There are proven correlations between genotypes
&
Therapeutic efficacy for some drugs
&
Adverse drug reactions

Does one test do all?

Post-translational to enzymes and receptors very difficulty to predict

Are functional tests better than genetic ones?

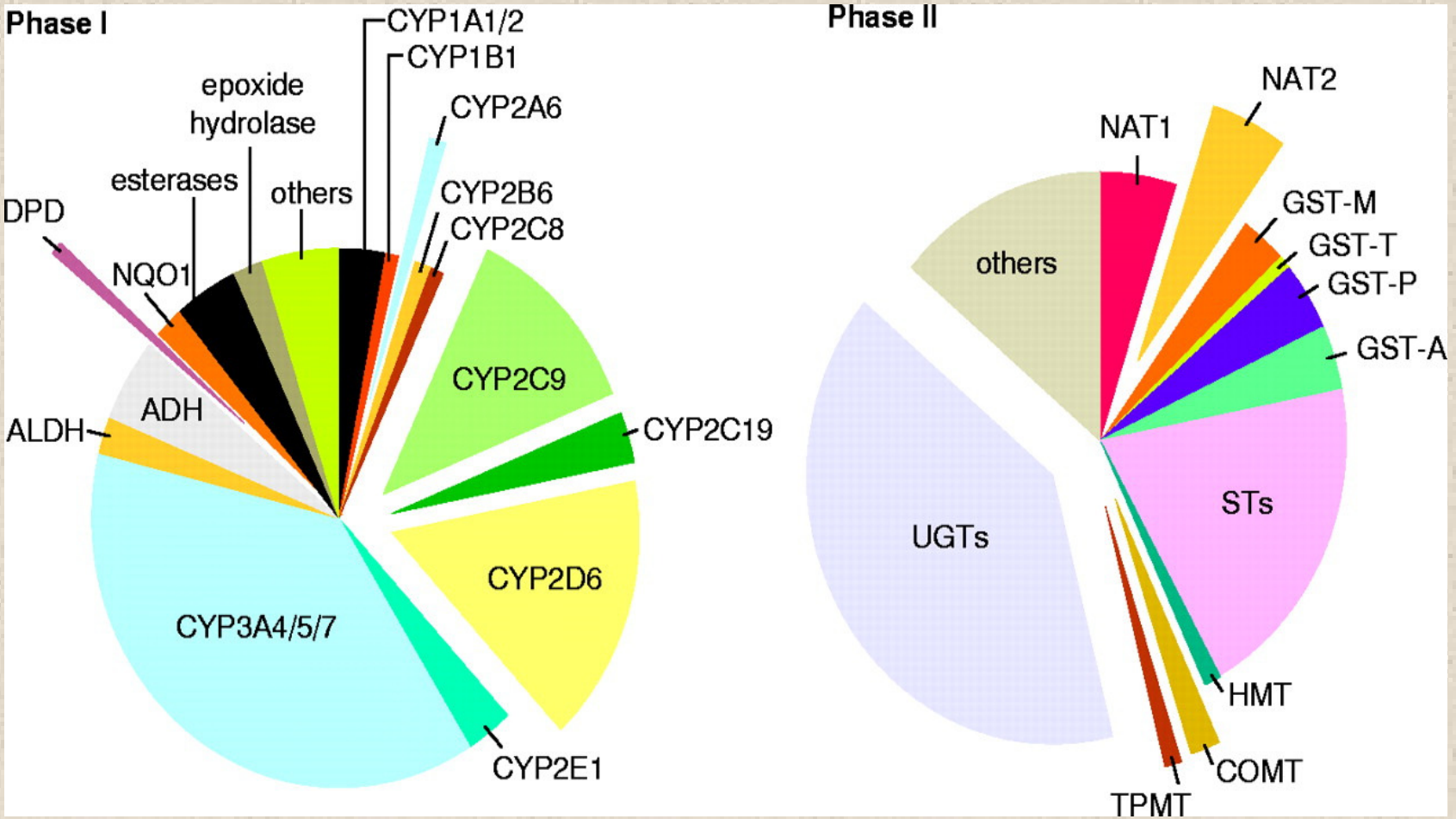
Can we predict by pharmacogenomics the responses to bio-therapeutic drugs?

The pharmaco-'omics

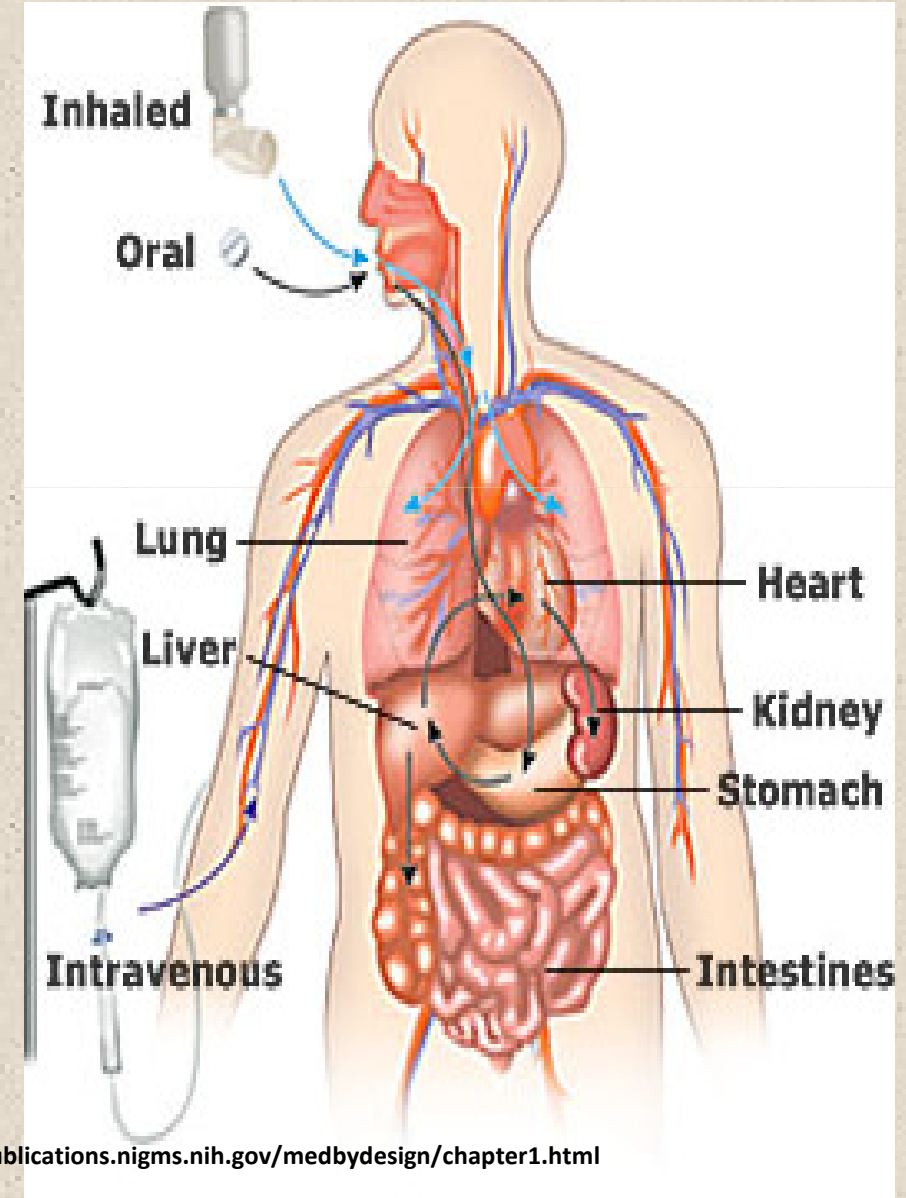
Genome	DNA
Expressome	mRNA
Proteome	Proteins
Metabolome	Metabolites/catabolites

Thank you
and
now for the detailed lectures

Drug Metabolizing Enzymes



A Drug's Life



http://publications.nigms.nih.gov/medbydesign/chapter1.html

ADME

- Absorption
- Distribution
- Metabolism
- Excretion