Pharmacrogenomics

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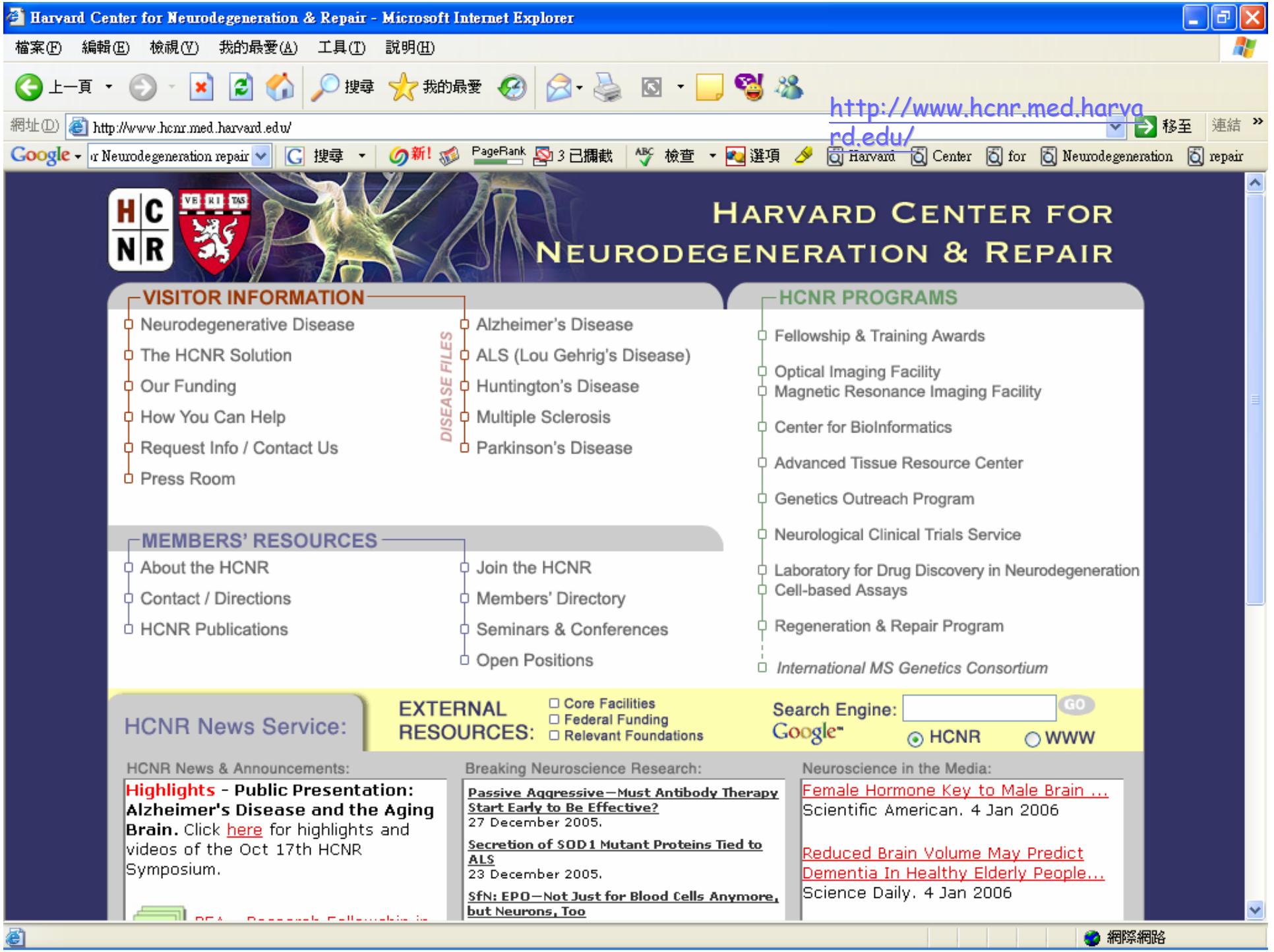
Importance of Genetics/Genomics to Medicine

- >12 million Americans with **genetic disorders (GD)**
- **80%** of **mortality rate (MR)** in America due to genetic component
- **2-3% background** population risk for a major birth defect (BD)
- 15% overall miscarriage risk for any pregnancy
  - 25-50% first trimester miscarriage risk
    - 30-50% first trimester losses due to **chromosome anomalies**
- >30% pediatric hospital admissions due to GD

- GD affect **all major systems**, **any age**, **any race**, **male or female**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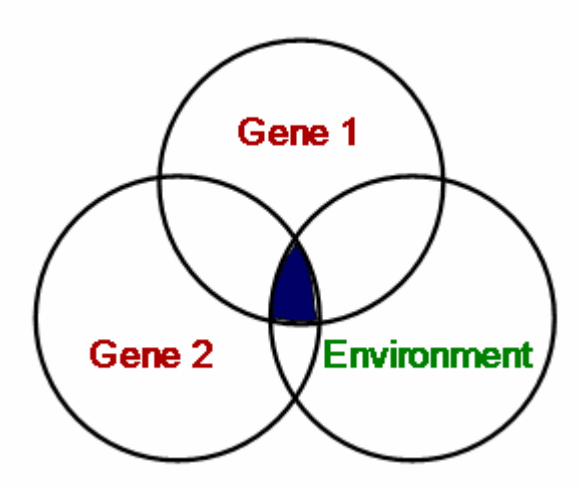
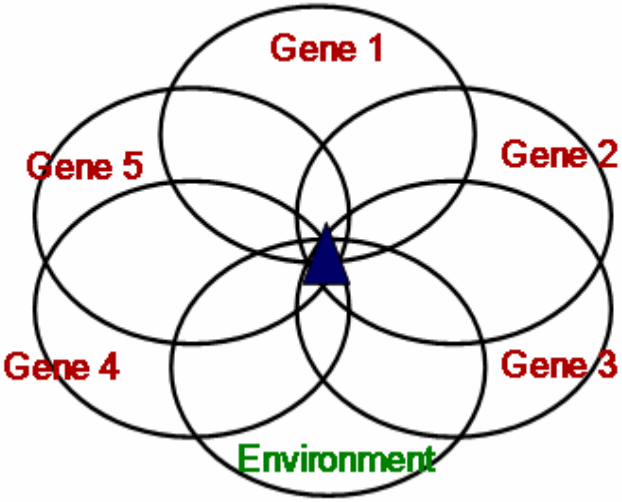
Highlights - Public Presentation: Alzheimer's Disease and the Aging Brain. Click here for highlights and videos of the Oct 17th HCNR Symposium.
Breaking Neuroscience Research:
Passive Aggressive—Must Antibody Therapy Start Early to Be Effective?
27 December 2005.
Secretion of SOD1 Mutant Proteins Tied to ALS
23 December 2005.
SfN: EPO—Not Just for Blood Cells Anymore, but Neurons, Too
Neuroscience in the Media:
Female Hormone Key to Male Brain ...
Scientific American. 4 Jan 2006
Reduced Brain Volume May Predict Dementia In Healthy Elderly People...
Science Daily. 4 Jan 2006

Complex Phenotypes – What can we Expect?



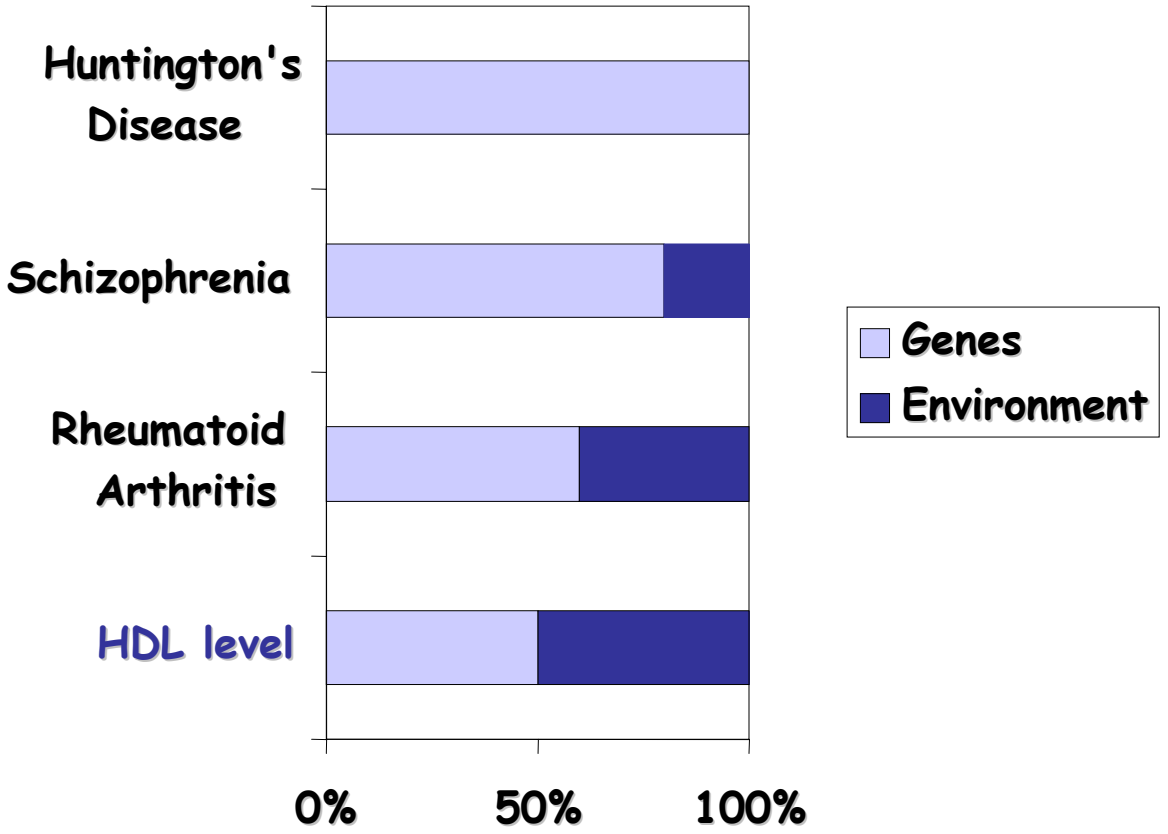
Few genes and **environmental** factors each contributing a **large** risk



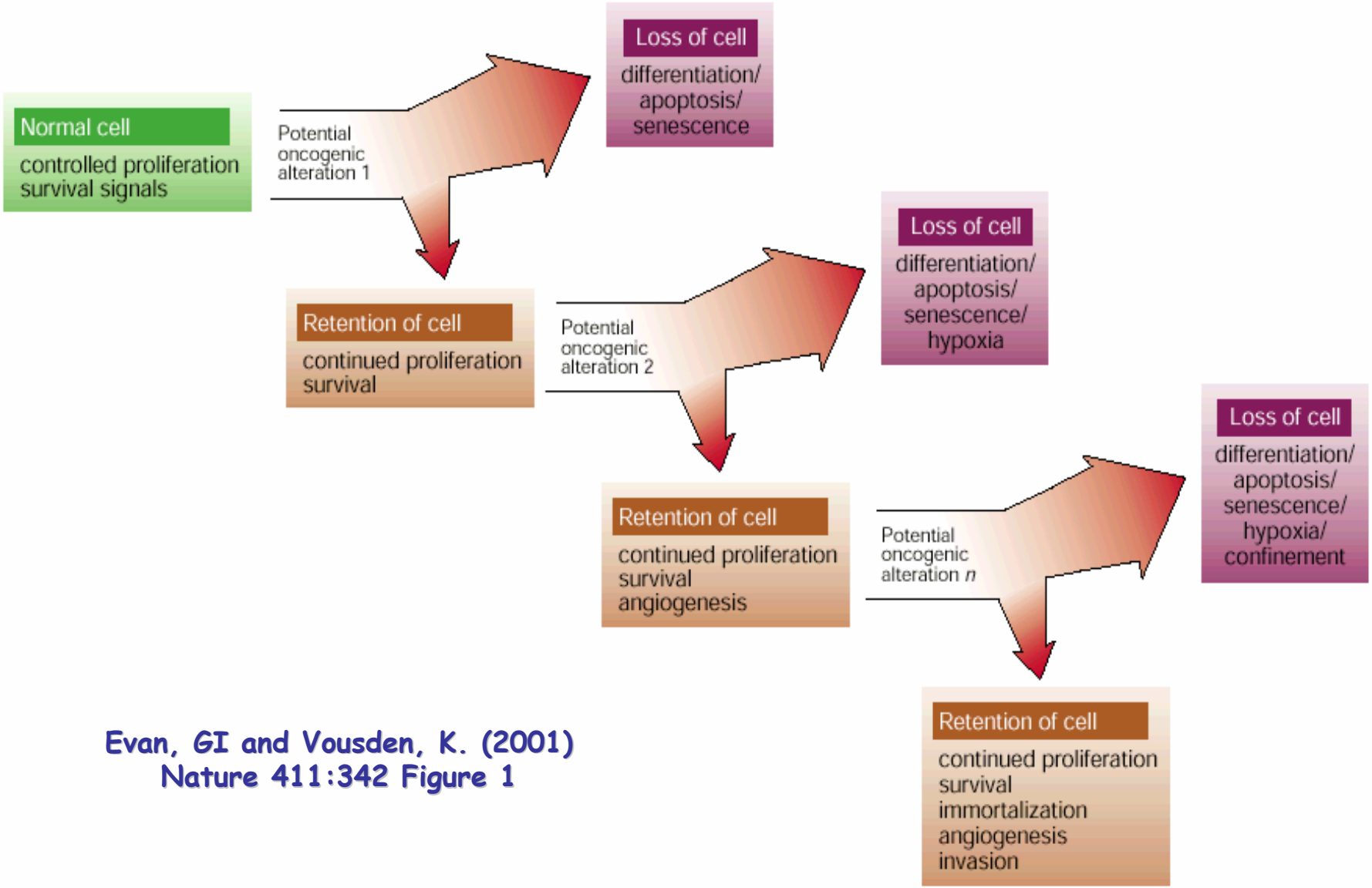
Many genes and **environmental** factors each contributing a **small** risk

- **Intergenic**: **epistasis**;
- **Intragenic**: dominant & **polymorphims**

Heritability: the Proportion of the Disease that is Due to the Genetic Factors



The Cancer Problem

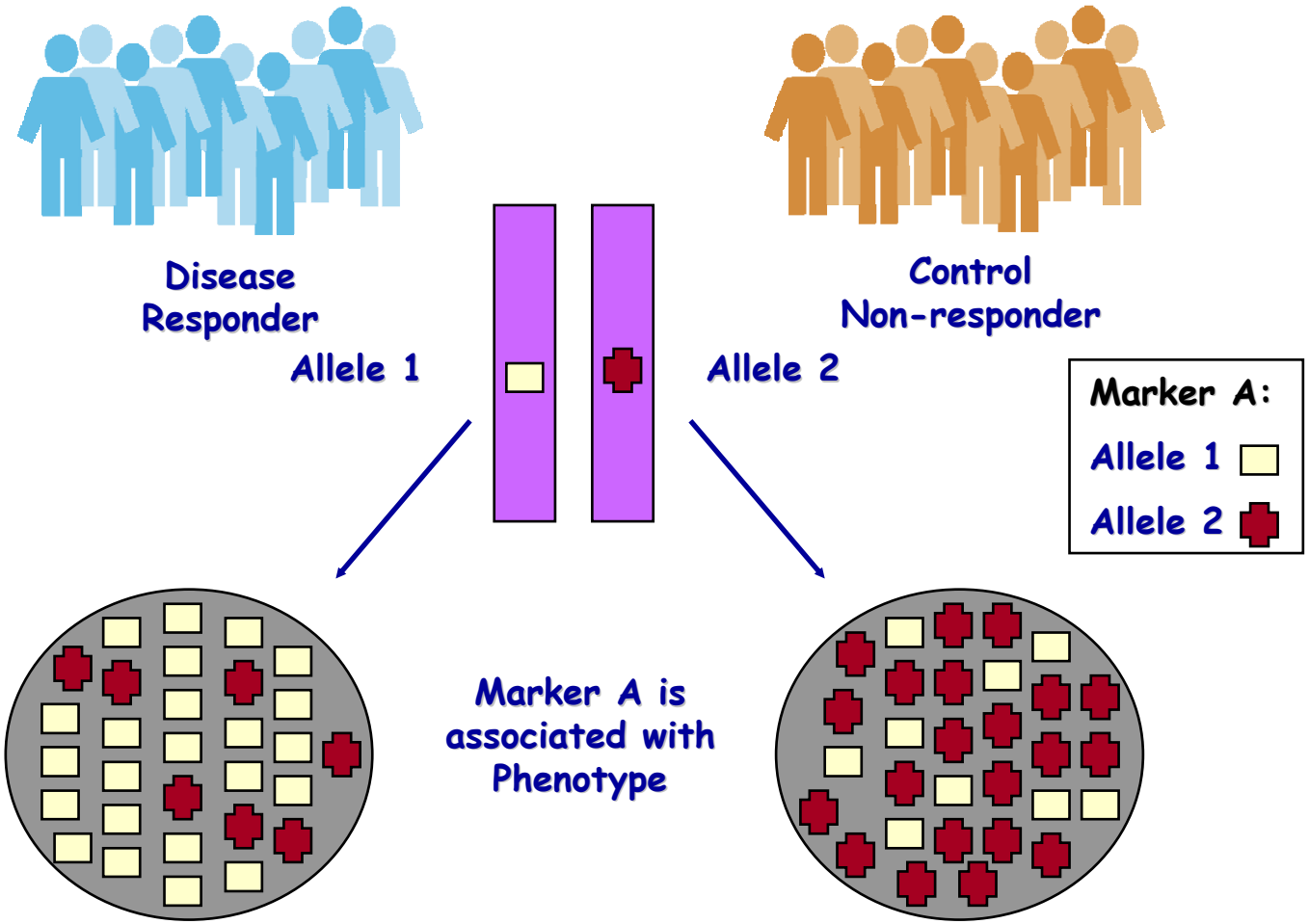


Evan, GI and Vousden, K. (2001)
Nature 411:342 Figure 1

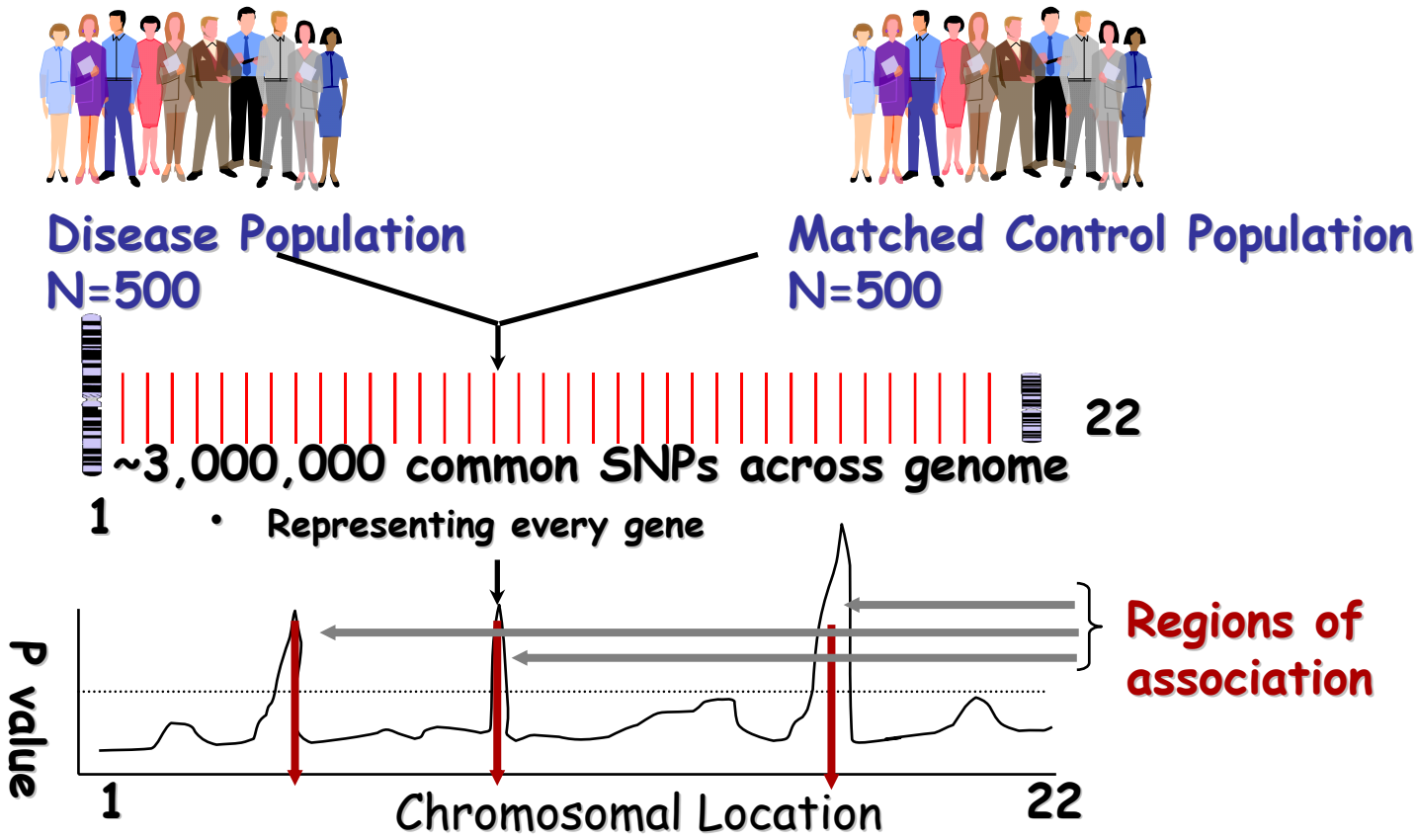
Mapping for Common Complex Diseases

Complexity	Solution
Reduced **penetrance**	Non-parametric study
Genetic heterogeneity	Multipoint linkage analysis; LD mapping; Genome-wide scan
Epistasis	Multipoint linkage analysis; LD mapping; Genome-wide scan
G x E interaction	Case only studies; Case-control study; Family-based design

Human Genetic Association Study Design



Whole Genome Association



Informatics to identify gene(s) mapped to associated SNP

Mutations & Polymorphisms

- Mutations become **polymorphisms** or "common alleles" when frequency > 1% **in a population** (arbitrary)
- *All* Single Nucleotide Polymorphisms (SNPs) (probably) exist in the human population
  - 3 billion x 4 (ACGT) at frequencies near 10^{-5}
- SNPs linked (associated) to a phenotype or causative

Haplotypes

- Representation of the DNA sequence of **one chromosome** (or **smaller segments in *cis***)
- Indirect inference from pooled diploid data
- **Direct observation** from **meiotic** or **mitotic** segregation
  - Cloned or physically separated
  - Chromosomes or segments

Linkage & Association

- Family Triad
  - Parents & child (vs. case-control)
- **Case-control studies** of association in structured or admixed populations (Pritchard & Donnelly 2001)
  - *Theor. Pop. Biol.* Program STRAT
- **Null hypothesis**: allele frequencies in a candidate locus **do not** depend on phenotype (within subpopulations)

Searching for Disease Genes Almost Always Start with the DNA of Affected individuals

- Process at Decode Genetics Inc. **(Example)**
  1. Identify people with **a particular disease**
  2. Find affected people who are related in such a way that they are likely to share genes **(pedigree)**
  3. Extract the DNA of these individuals
  4. PCR amplify (robotically) SNPs along each person's chromosomes
  5. Look for **clusters of** SNPs among the DNA of patients from a single family
  6. Such clusters suggest ➔ ?

Such Clusters Suggest a Gene Involved in the Disease is Located Nearby

- Big deal?
  - If this data is correct, the gene has now been linked to a particular chromosomal region
  - Presumably the gene will soon be found

- Where do you go **next**??
  - Gene annotation
    - Gene ontology, function, cellular localization, structure *etc.*
  - Identification of candidate drug targets

Defining Disease Phenotypes

- Some mechanisms underlying **variation** in clinical expression of disease traits
  - To choose a consistent phenotype for studies

- Phenotype definition & delineation
  - "Gene mapping" ⇨ "phenotype mapping"
  - Gaps between "phenotypes" & "genotypes"
    - **Alleles cause phenotypes**

Pharmacogenomics vs. Pharmacogenetics (definitions)

- Pharmacogenetics or Pharmacogenomics
  - Study of **the genetic basis** for differences in drug response *or* response to illness

- **Pharmacogenetics**
  - Effect of **variation** **in specific genes** and their protein products on **therapeutic response** - **monogenic variation**

- **Pharmacogenomics**
  - **Multigenic variation**, may also include environmental factors (Kalow 2001)

Reasons for Differences in Drug Response (1)

- **Genetic differences** in
  - Drug **metabolism** enzymes
  - Ability of drug to **bind** to target (**drug target**)
  - **Amount** of **drug target** produced
- **Different pathways** causing same disease
  - Genetic heterogeneity

Reasons for Differences in Drug Response (2)

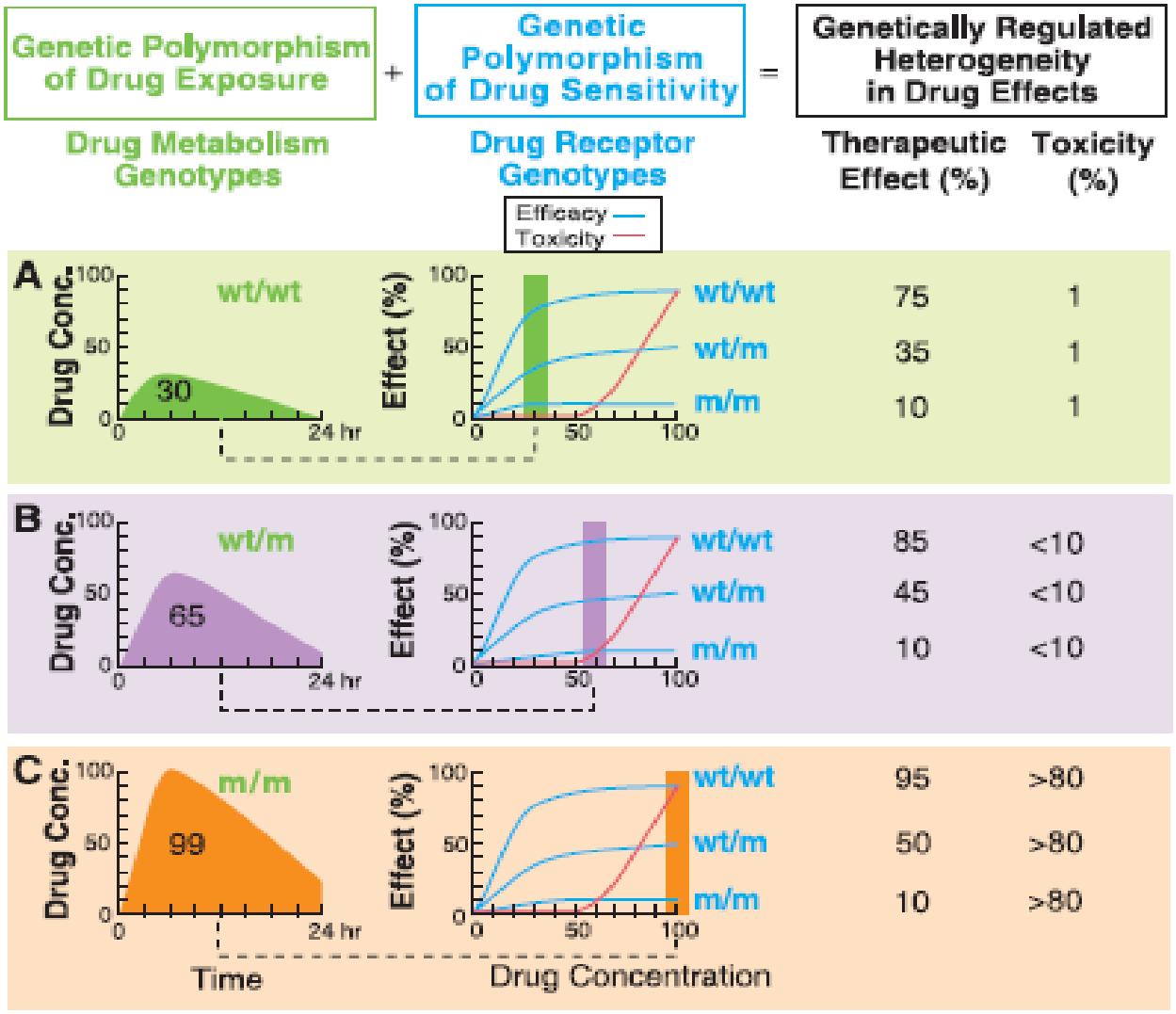
- **Genetic mutations**
  - Genome is **master program** for **all cells**
  - **Proteome** is **functional** program for a specific cell
  - Genetic mutations cause **defects** **in working proteins**
    - Responsible for **much** of human disease

Reasons for Differences in Drug Response (3)

- **Single nucleotide polymorphisms (SNPs)**
  - One-unit changes in DNA sequence in **at least 1%** of the population
    - Major source of **genetic variation**
  - On average, any two people may vary by one nucleotide base in every thousand (2/1,000)
    - Millions of SNPs have been identified
  - **"SNP chips"** being developed to identify **an individual's SNP profile**
    - SNP research may lead to hundreds of new drugs

Polygenic Determinants of Drug Effects

(Evans & Relling, 1999; Science 286, 487)

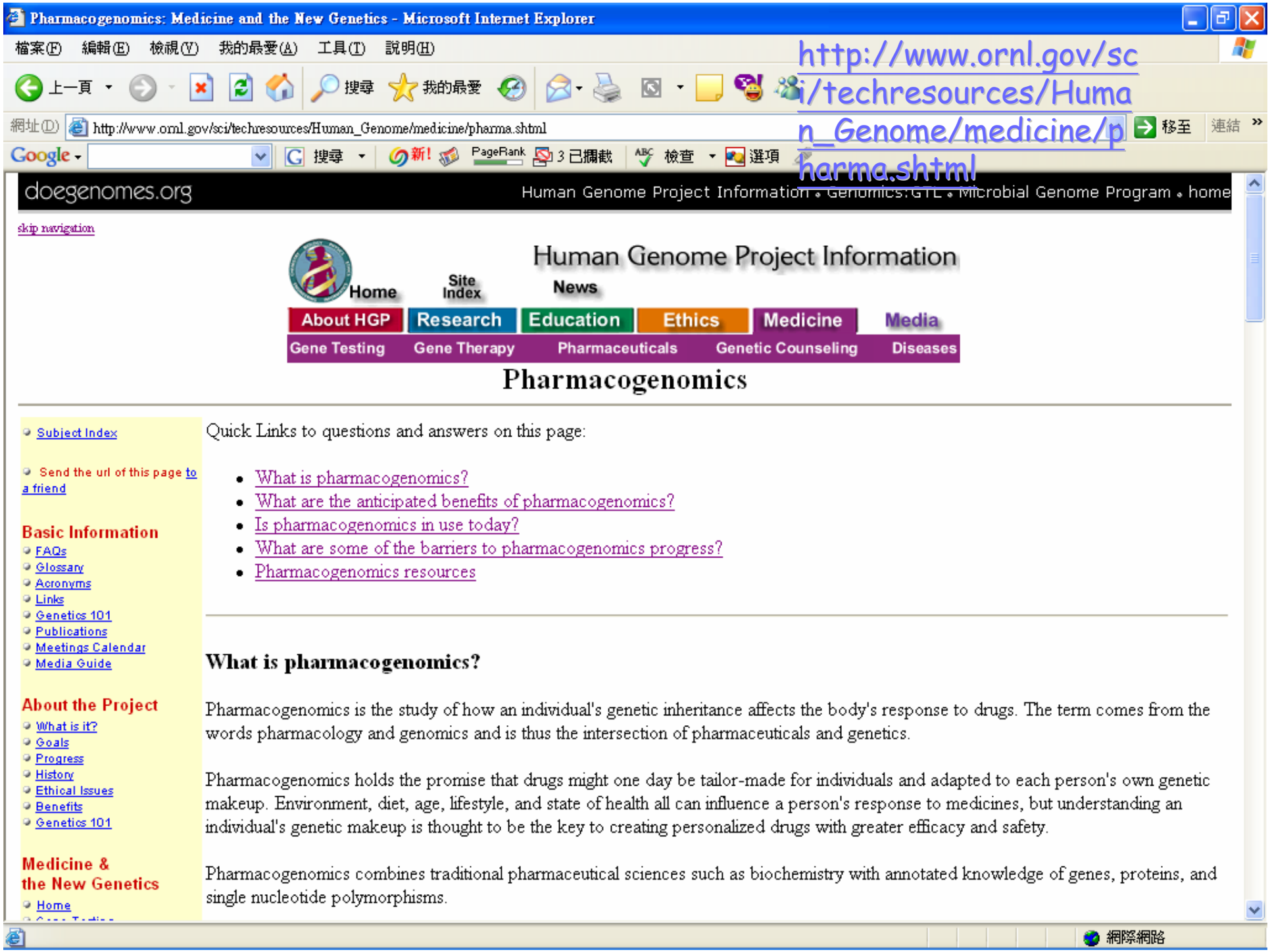


Consequences of Differences of Drug Metabolism (Wolf CR, Smith G, Smith RL, 2000)

- **Extended effect** from drug
- Adverse drug reaction/toxicity
- Inability **to activate prodrug**
- **Increased dose** needed for effect
- Alternative metabolic pathway
- Drug-drug interactions

Potential Benefits of Pharmacogenomics (1)

- **More powerful drugs**
  - Based on the proteins, enzymes, RNA molecules associated with genes and diseases
- More **effective, safer** drugs from the beginning
  - To reduce 100,000 deaths and 2 million hospitalizations in USA as the result of **adverse** drug response
- More accurate **doses**
  - Current method: **weight & age** ⇨ dosages based on **a person's genetics**
    - How well the body processes the medicine & the time it takes to metabolize it
  - www.ornl.gov/hgmis/medicine/pharma.html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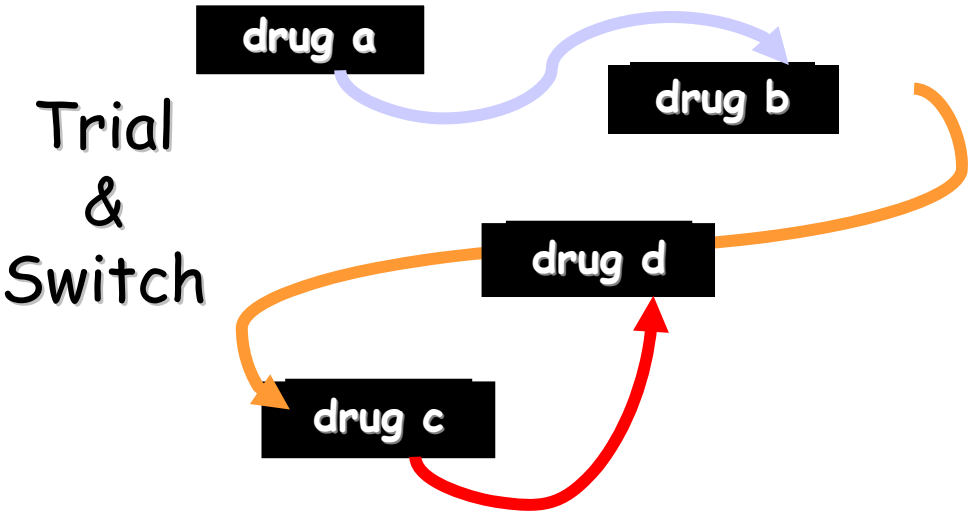
What are the anticipated benefits of pharmacogenomics?
Is pharmacogenomics in use today?
What are some of the barriers to pharmacogenomics progress?
Pharmacogenomics resources
What is pharmacogenomics?
Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. The term comes from the words pharmacology and genomics and is thus the intersection of pharmaceuticals and genetics.
Pharmacogenomics holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety.
Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms.

Targeted Prescription of Medicines: Applied Pharmacogenomics

Today

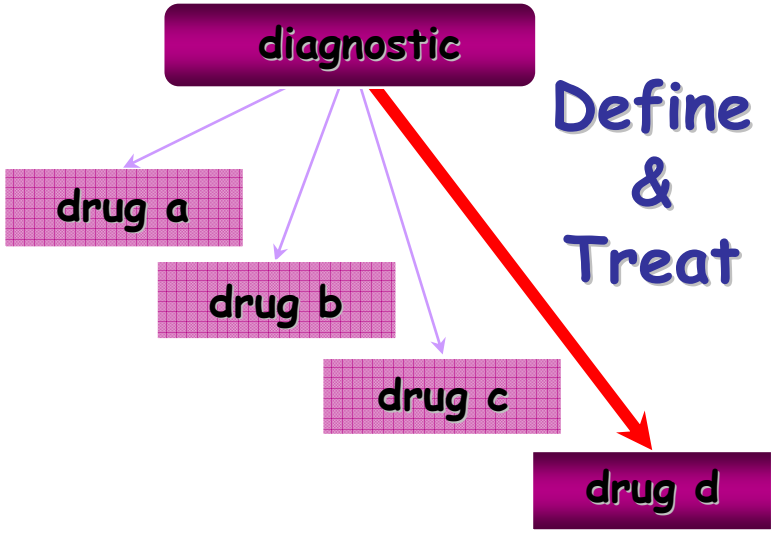
Empirical prescription
"**mass market**"



Individual physician experience
Cost: time, money & well-being

Future

Rational prescription
"**individualized**"



Informed physician diagnosis
Savings: time, money & illness

Potential Benefits of Pharmacogenomics (2)

- Screening for disease **in advance** & **prevention**
  - Knowing one's **genetic code** will allow a person to make adequate **lifestyle & environmental changes** at an early age ⇨ to avoid or lessen the severity of a genetic disease
  - Advance knowledge of a particular **disease susceptibility** will allow **careful monitoring**, & treatments can be introduced at the most appropriate stage to **maximize** their **therapy**

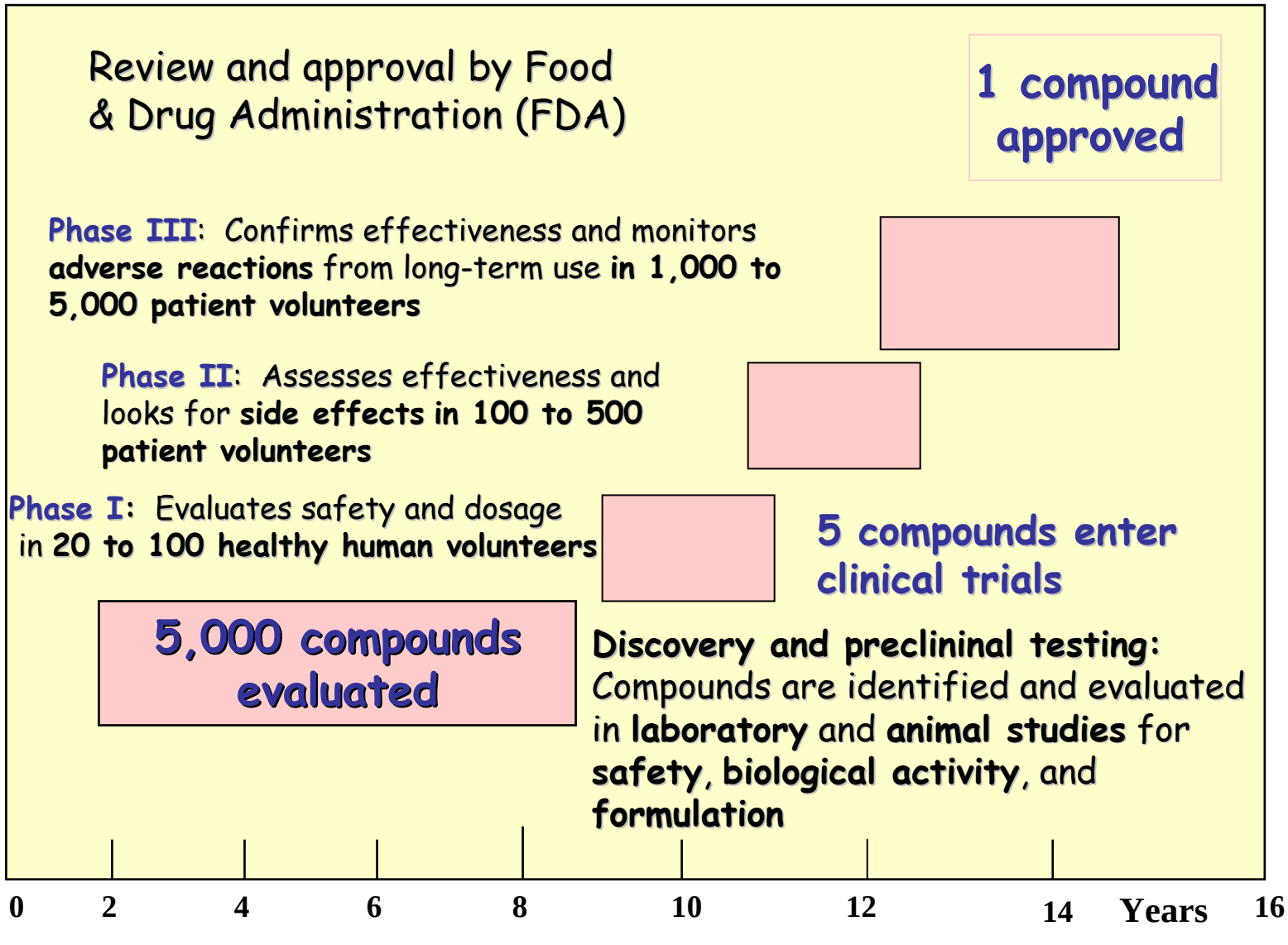
Potential Benefits of Pharmacogenomics (3)

- **Better vaccines**
  - Vaccines made of genetic materials, DNA or RNA
  - Promise all the benefits of existing vaccines **without all the risks**
    - Activate the immune system, unable to cause infections
  - **Inexpensive**, **stable**, easy to **store** & capable of being engineered to carry **several strains of a pathogen at once**

Potential Benefits of Pharmacogenomics (4)

- Improved **drug discovery** and **approval process**
  - More easy to discover potential therapies using **genome targets**
  - Previously failed drug candidates may be **revived** as they are matched with **the niche population** they serve
  - The **drug approval process** should be facilitated as trials are targeted for **specific genetic population** groups ⇨ providing greater degrees of success

Bringing a New Drug to Market



Source: Tufts Center for the Study of Drug Development

Potential Benefits of Pharmacogenomics (5)

- **Lower overall health care costs**
  - Decreases in the number of **adverse drug reactions**, the number of **failed drug trials**, the **time** it takes to get a drug **approved**, the length of time patients are on medication, the number of medications patients must take to find an **effective therapy**, the effects of a disease on the body (through early detection) & an increase in the range of **possible drug targets** will promote a net decrease in the cost of health care

Current Research Directions

- Identify **new targets** for new drugs
  - *i.e.*, **genes** or their **protein products** that are **associated with diseases**
- Identify **metabolic enzymes** with **genetic variations** that **alter response** to current drugs
  - **Wolf CR, Smith G, Smith RL, 2000**

Pharmacist's Role in Pharmacogenomics

- Expanded role/additional responsibilities in
  - Drug selection and dose
  - Counseling on side effects and drug-drug interactions
  - **Compounding** - customized drugs, doses and dosage forms
- Strengthening of **team approach** to health care

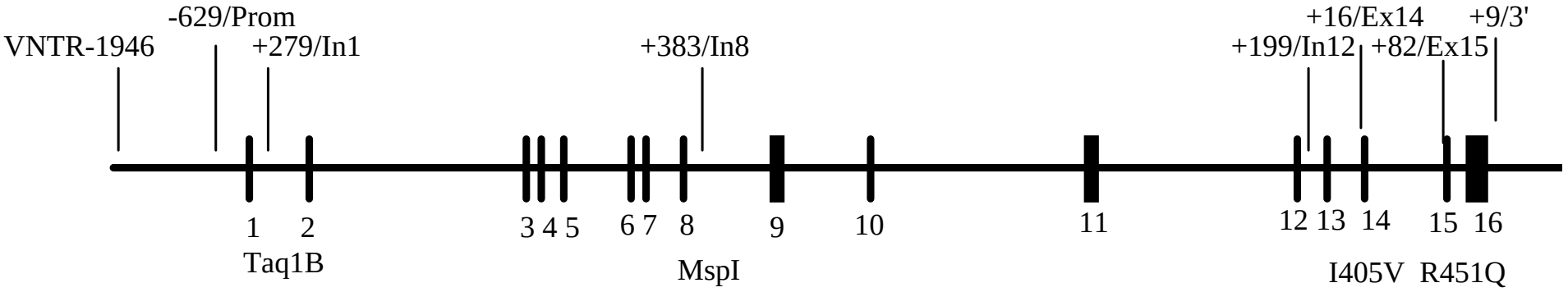
Example: Pharmacogenomics at Pfizer

- The study of genome-derived data, including **human genetic variation, RNA and protein expression differences,** to predict drug response in individual patients or groups of patients
  - Kitasato – Harvard Symposium (Oct. 2003)

Target Prioritization – Coronary Artery Disease

- **High density lipoprotein (HDL)** modulation
  - A significant market
- So many targets, but which is the best?
- **Locus specific genetic association study**
  - Candidate genes screened for **polymorphism**
  - Correlate genotypes with **HDL levels**
  - Increase CIR in the target
    - Consumption & injection room

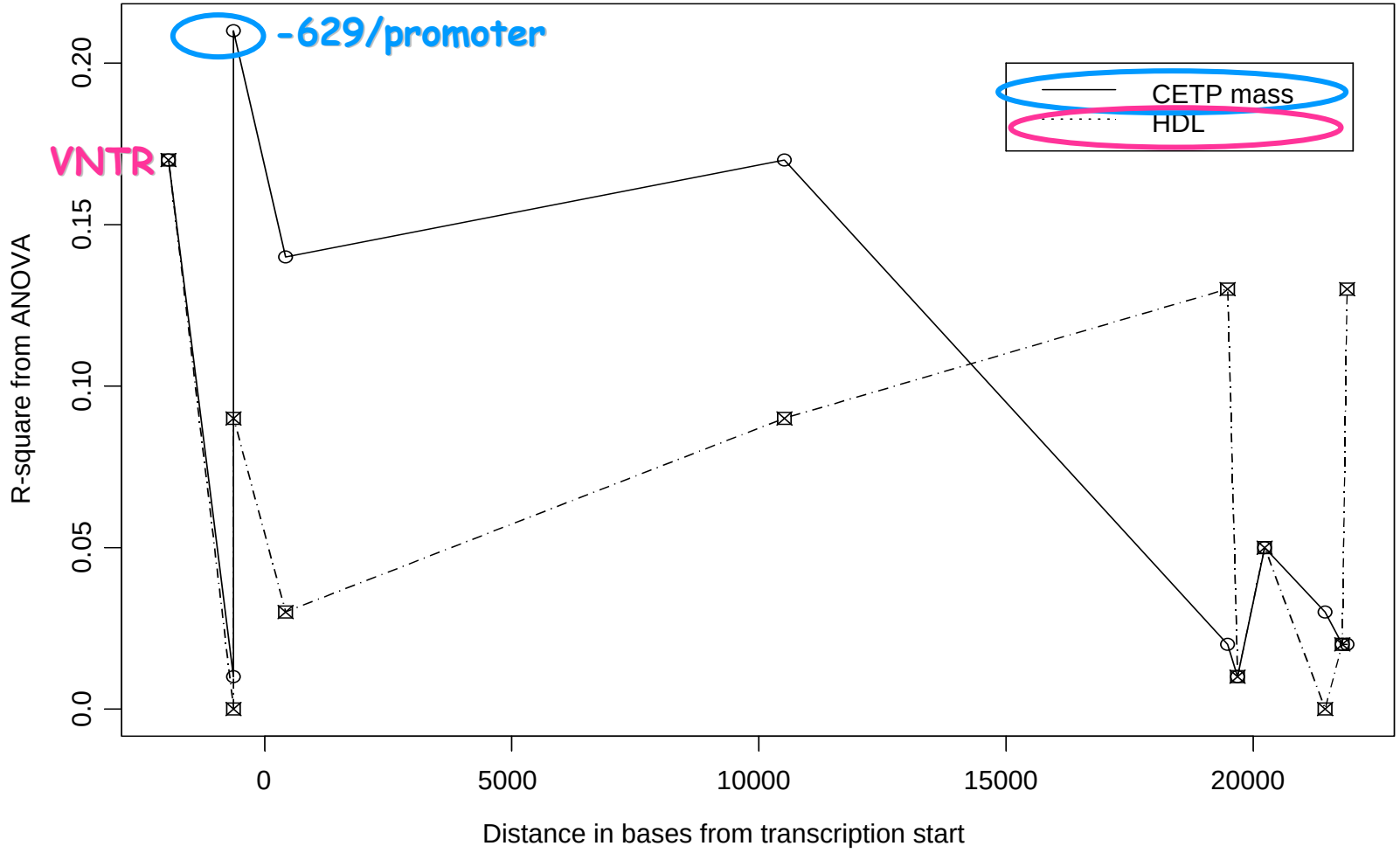
Cholesteryl Ester Transfer Protein (*CETP*)



- Spans **22 Kb** on human **chromosome 16**
- Several **polymorphisms** identified
- Implicated in modulation of **HDL levels**
- SNPs genotyped in 110 healthy subjects

CEPT Association Study (1)

Association of CETP markers and baseline phenotype



Clinical Study Population

- 54-week **Phase IIIb** open label assessment of the **safety** and efficacy of Atorvastatin (a-TOR-va-stat-in)
  - 3,916 patients randomised into **5 treatment groups**
- Subjects with **coronary heart disease (CHD)** and/or CHD risk factors
- 4 pretreatment visits, data on **blood pressure**, **lipids** *etc.* including **HDL level**

CETP Study (2)

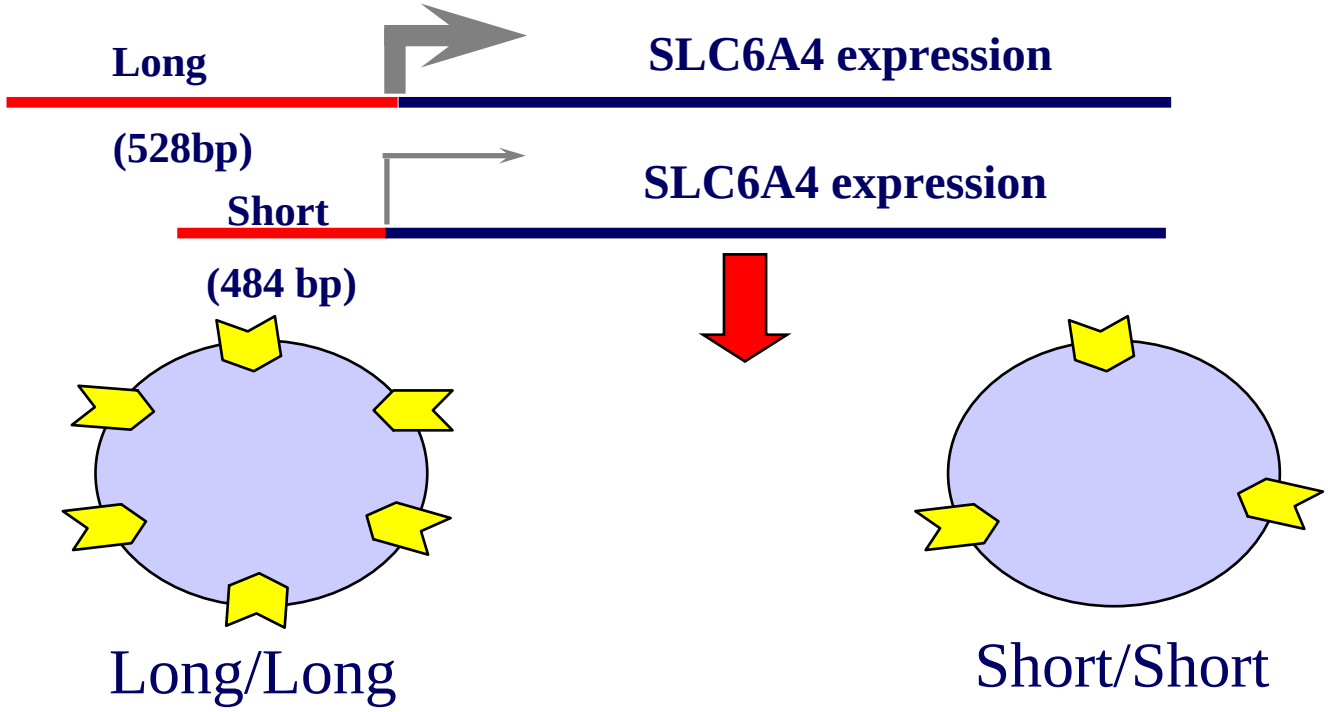
- Genetic variation in *CETP*
- Associated with **protective HDL levels**
- Increasing CIR for target
- Additional information obtained
  - Linkage disequilibrium
  - Ethnic diversity
- Studies in **larger populations** required

Selective Serotonin Reuptake Inhibitors

- Selective Serotonin Reuptake Inhibitors **(SSRIs)**
- Impacted on treatment of **depression**
- Improved tolerability and efficacy
  - **BUT not all patients benefit**
- The challenge for new compounds
  - Increased **efficacy**
  - Reduction in **adverse events**
  - Differentiation

Target Variation – *SLC6A4*

- Variation in **promoter sequence**
- 44-bp insertion/deletion (L and S alleles)



Molecular Psychiatry (1998) 3, 508-511

ORIGINAL RESEARCH ARTICLE

Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine

E Smeraldi[1,2], R Zanardi[1], F Benedetti[1], D Di Bella[1,2], J Perez[1] and M Catalano[1,2]

- **Solute carrier family 6** (neurotransmitter transporter, serotonin), member 4 (***SLC6A4***): 5HT transporter (*5HTT*)

Sertraline Targeting *SLC6A4*

- **Sertraline**
  - Zoloft (Pfizer), sertraline (HCI)

- **Antidepressant effect**
  - To inhibit the neuronal reuptake of **serotonin**
  - Very weak effects on **norepinephrine** & **dopamine** neuronal reuptake

  - At **clinical** doses, sertraline blocks the uptake of **serotonin into human platelets**
  - In **receptor binding studies**, sertraline has no significant affinity for **adrenergic** [alpha(1), alpha(2) and beta], **cholinergic**, GABA, **dopaminergic**, **histaminergic**, **serotonergic** (5-HT1A, 5-HT1B, 5-HT2) or **benzodiazepine binding sites**

SLC6A4 & Sertraline Response

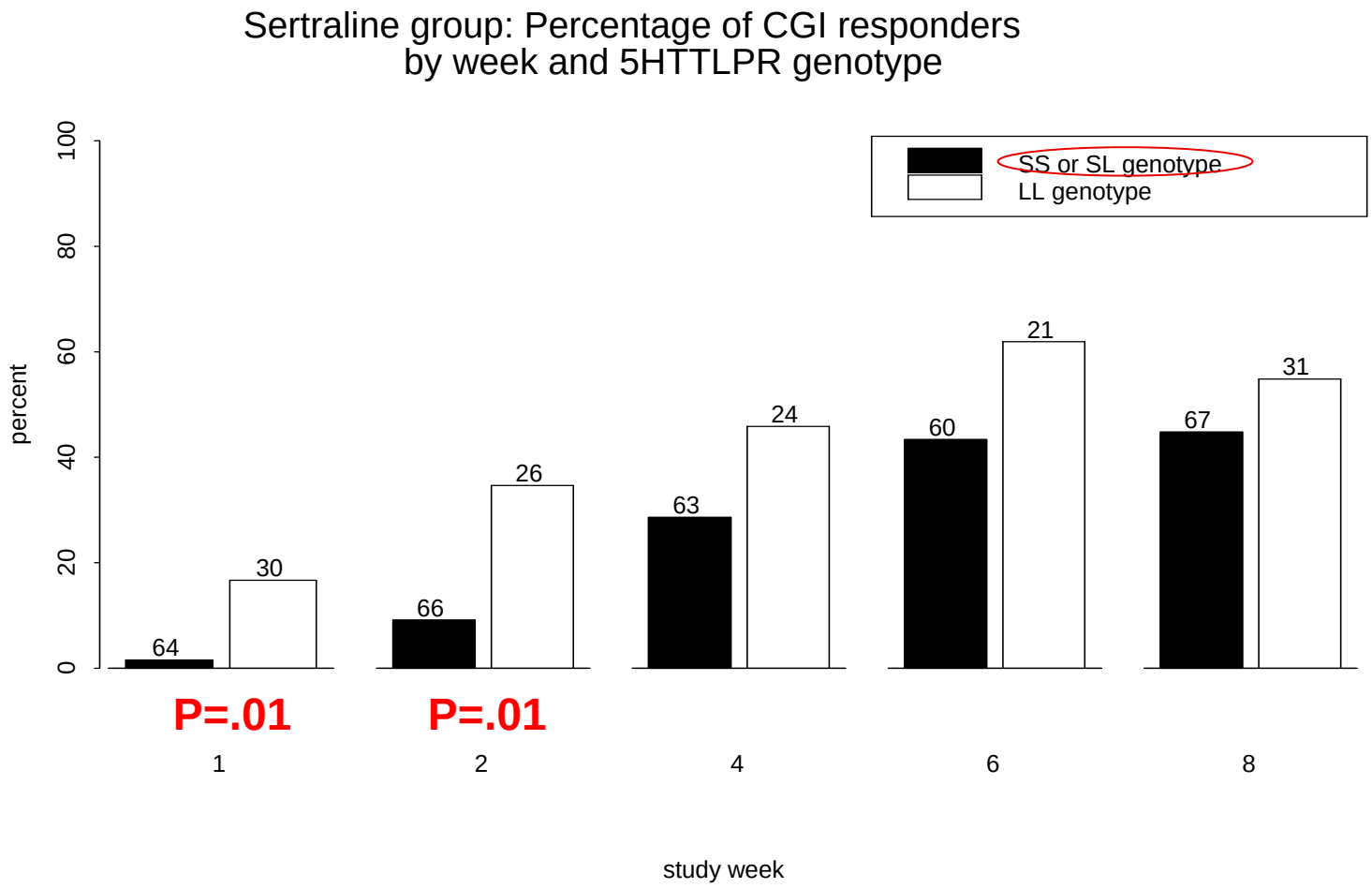
- Does **genotype** influence **time to response**? (Study R-0552)
  - 8 week, double-blind, placebo-controlled study of **sertraline** in elderly depressed **outpatients** with DSM-IV major depression
    - 66 sites within the US
    - Anonymized DNA samples collected to test **for genotype effect on time-to-response to sertraline**
    - 4-14 day washout period prior to randomization
    - Age > 60
    - HAM-D ≥18
    - HAM-D and **CGI-I measures of response**
    - Predominantly Caucasian (95%)

Case Control Evaluation

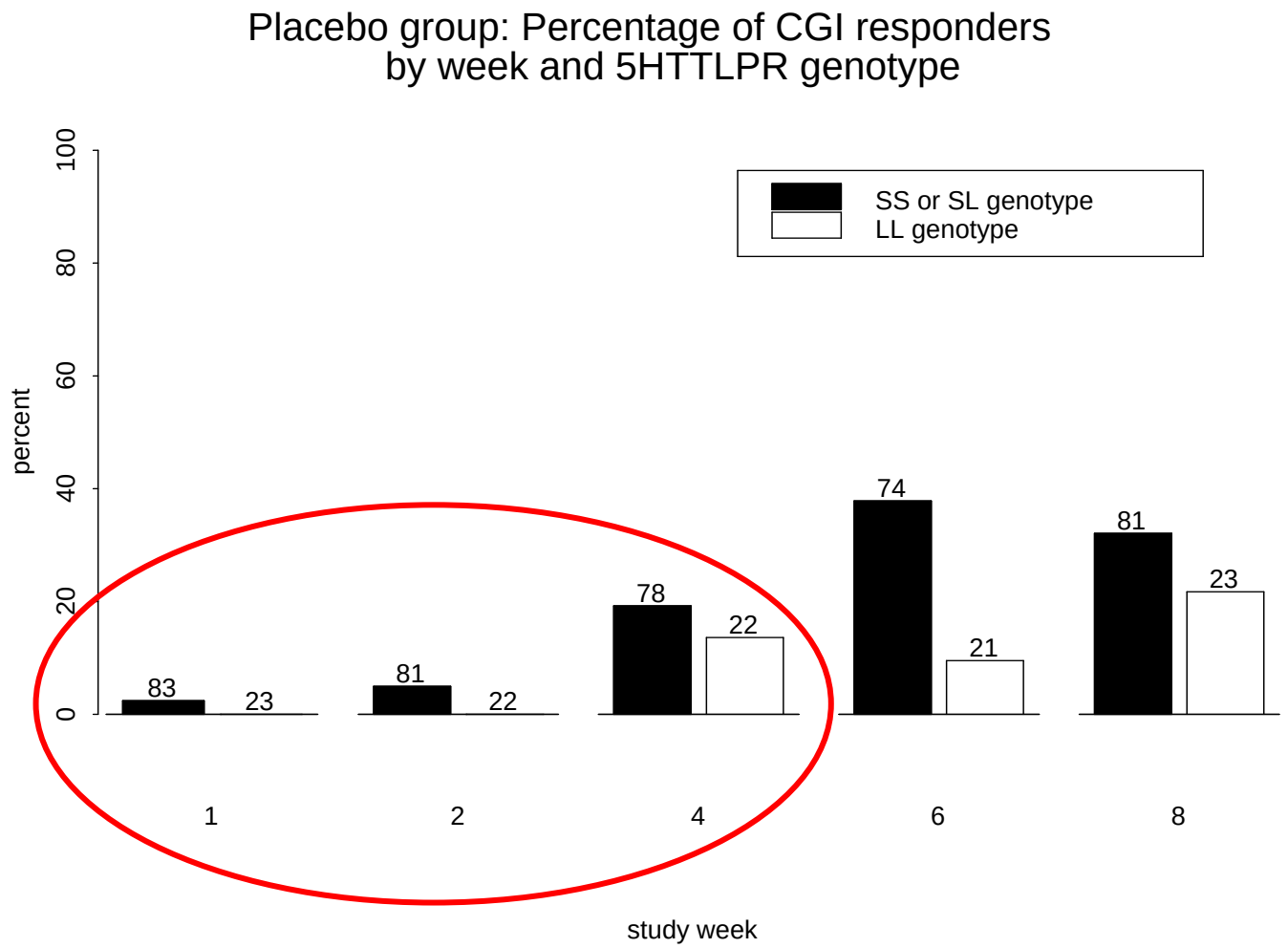
- Responders defined as
  - HAM-D
    - ≥ **50% reduction** in HAM-D from baseline
  - CGI-I
    - Individual with **a score of 1 or 2**

- Response defined at each time point post-baseline and evaluated for **a significant difference** in response **between the LL and SL/SS groups**
  - Direct association testing **a functional polymorphism** for effect on response

L/L Genotypes Respond More Rapidly to Sertraline



Response Time to Placebo Not Significant



Pharmacogenomics I

- **Drug response variability**
  - Diseases
  - Demographic Traits
    - 人口統計學
    - Age, race, gender
  - General Health
    - Nutritional status, organ function, *esp.* **liver** & **kidney**
  - Drug Traits
    - **Concomitant** treatments, interactions with drugs or food
- **Principles**
  - Genotypes
  - Drug **response**
  - Drug **metabolism**
  - Disease subpopulation
  - Diagnostic needs

Pharmacogenomics II - SNPs (1)

- Single Nucleotide Polymorphisms (SNPs)
- **Mutations** in genetic code
  - Changes, deletions, insertions (nucleic acids)
    - Protein profile changes
    - Its **actions** or **reactions** to drugs change
  - SNPs – over 1.42 million in human genome
  - SNPs – in excess (DNA coding regions) about 60,000

Pharmacogenomics II - SNPs (2)

- Genetic change in enzymes, **transporters**, receptors, intracellular signal transduction proteins, cell cycle proteins
  - Alter the desired or adverse effects of drugs and biologics
- SNPs
  - 50 years ago
  - Changes in **adverse events** related drug metabolism

Pharmacogenomics II- SNPs (3)

- **Acetylation variation** with ***isoniazid*** 異菸鹼硫胼 (治肺病之藥) and ***hydalazine*** led to different **neuropathies** and lupus reactions, cutaneous or organ function, among patients receiving the same therapy
  - Slower actylators

- **Sulfonamides**
  - Different **hypersensitivity** reactions between patients
    - Based on **differences in metabolism**

Pharmacogenomics II - SNPs (4)

- **SNPs' effects**
  - Early stop codons
  - Nucleotide repeats
  - Gene duplications
  - Exon skipping
  - Deletions of major amino acids
  - No transcripts
  - Genetic mutations in promoter SNPs, regulatory SNPs
  - More minor amino acid substitutions or deletions

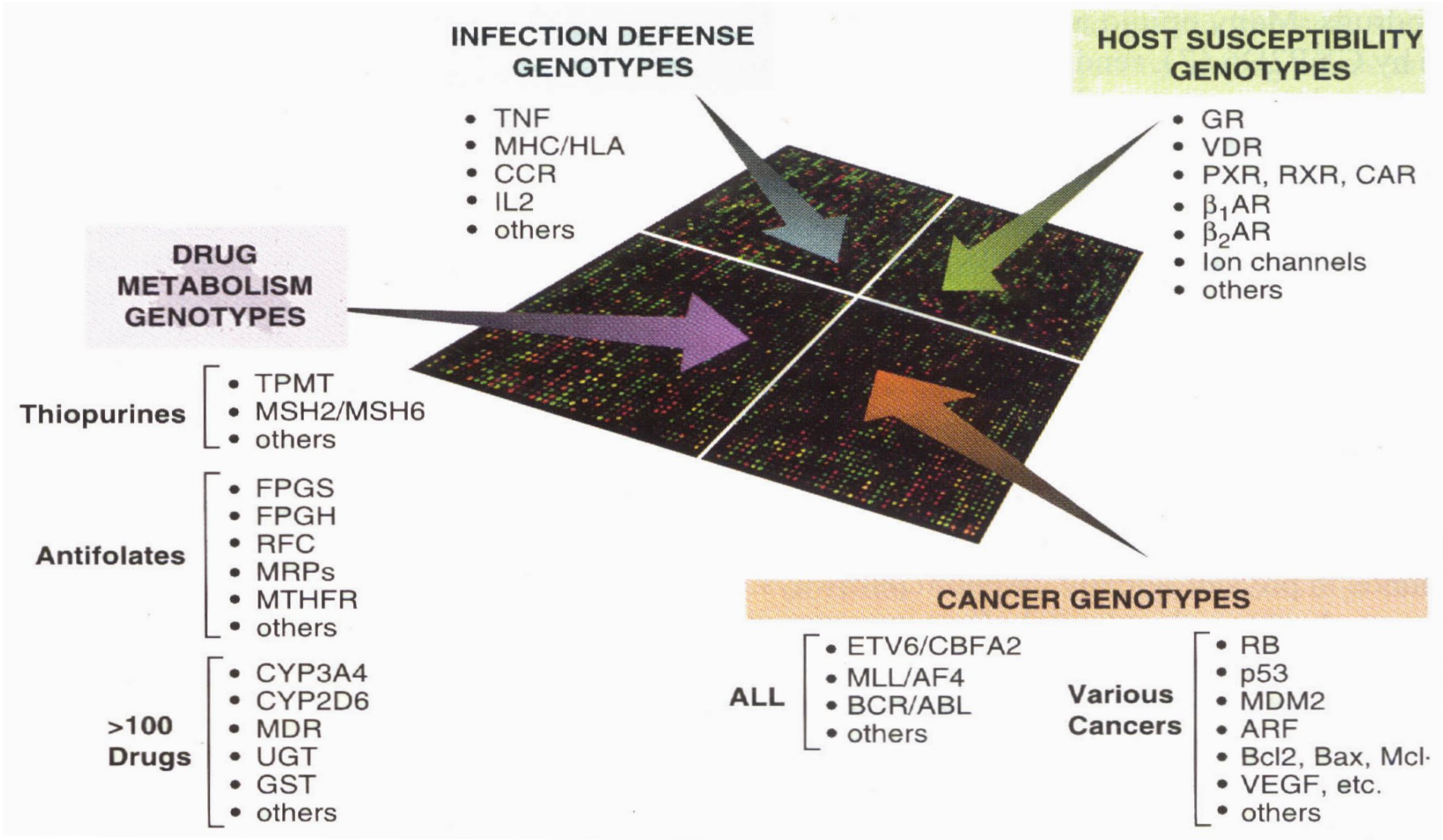
Pharmacogenomics IV
Outcomes – Efficacy & Safety

- Dose of drug **increase** (**metabolism**, more drug **destruction**; drug-***enalapril***; enzyme - ***ACE*** SNPs)
- Dose of drug **decrease** (**metabolism**, more drug **activation**; ***codeine***; ***CYP2D6*** SNPs)

- **Toxicity** of drugs (**adverse events**; anti-depressants ***Imipramine*** & ***CYP2D6*** SNPs)
- Response to **drug changes** (**targets**, FEV1 variation; Albuterol changes with SNPs in *beta-2 adrenergic receptor* = ***ADRB2***) – forced expiratory volume in one second

- **Disease subtypes**, drug response (**disease response change**; ***Herceptin***; and ***Her2neu***)
  - Breast cancer subtype

Pharmacogenomics V
Complexity of Genetic Variations



D528–D532 *Nucleic Acids Research, 2004, Vol. 32, Database issue*
DOI: 10.1093/nar/gkh005

SNP500Cancer: a public resource for sequence validation and assay development for genetic variation in candidate genes

Bernice R. Packer*, Meredith Yeager, Brian Staats, Robert Welch, Andrew Crenshaw, Maureen Kiley, Andrew Eckert, Michael Beerman, Edward Miller, Andrew Bergen[1], Nathaniel Rothman[1], Robert Strausberg[2] and Stephen J. Chanock[3]

Intramural Research Support Program, SAIC-Frederick, NCI-FCRDC, Frederick, MD, USA, [1]Division of Cancer Epidemiology and Genetics, [2]Office of Cancer Genomics, National Cancer Institute, Bethesda, MD, USA and [3]Section on Genomic Variation, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Gaithersburg, MD, USA

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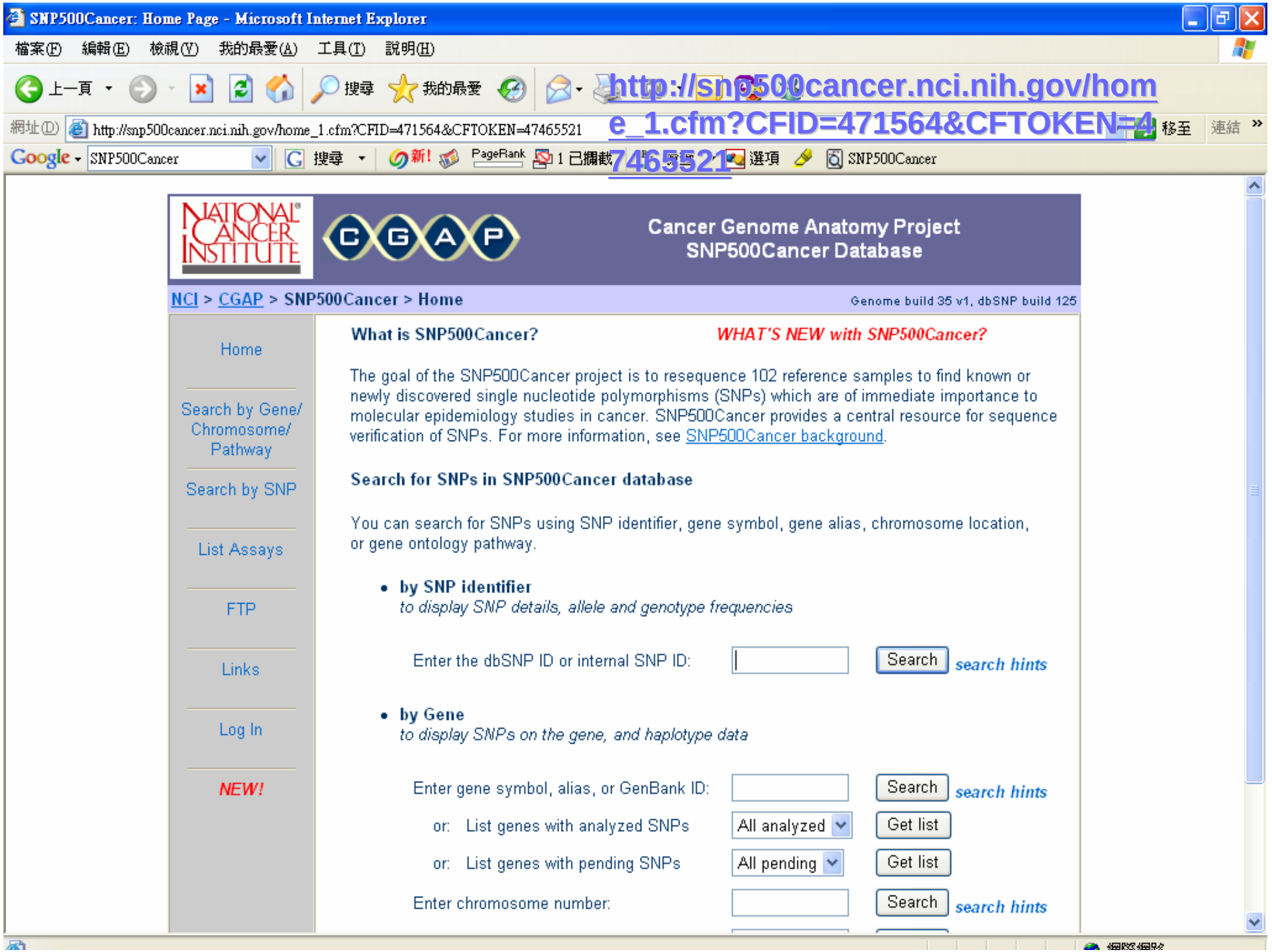
SNP500Cancer: Home Page - Microsoft Internet Explorer
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網址(D) http://snp500cancer.nci.nih.gov/home_1.cfm?CFID=471564&CFTOKEN=47465521
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NATIONAL CANCER INSTITUTE
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Genome build 35 v1, dbSNP build 125
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Search by Gene/ Chromosome/ Pathway
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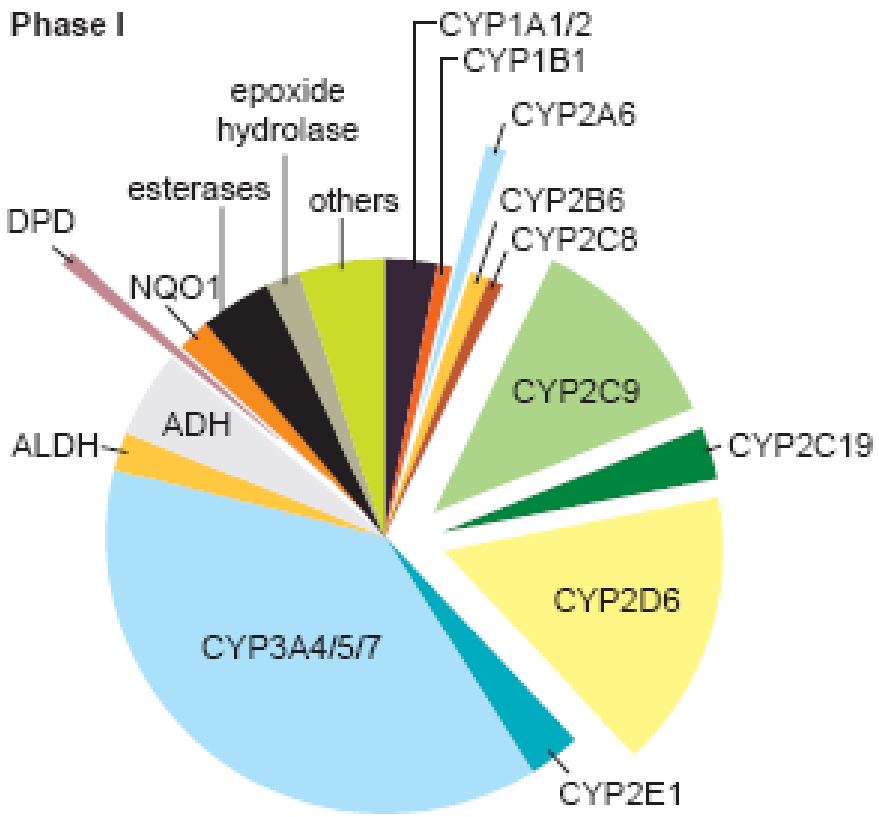
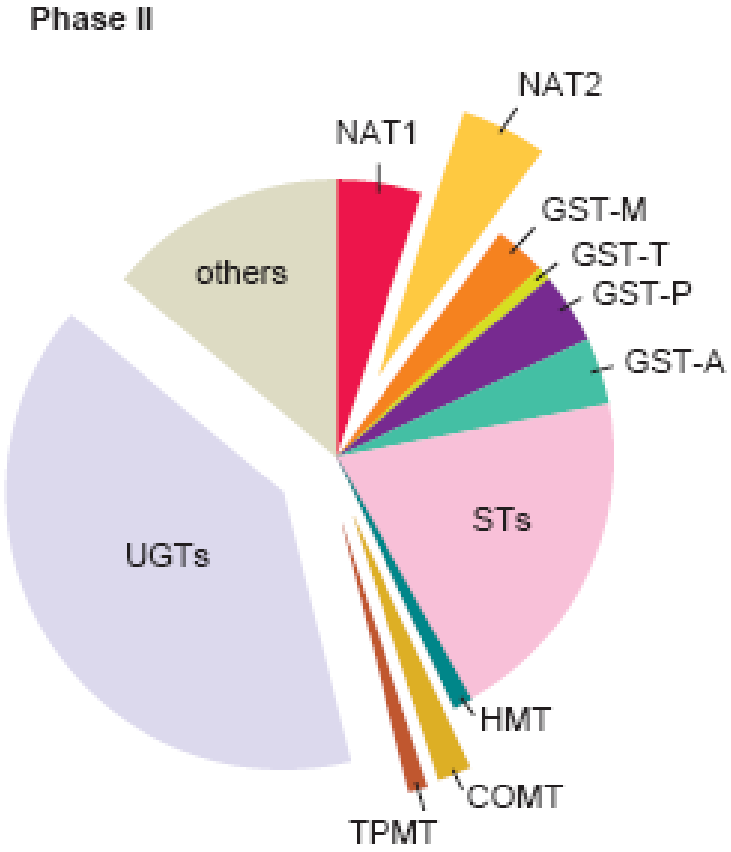
NEW!
What is SNP500Cancer?
WHAT'S NEW with SNP500Cancer?
The goal of the SNP500Cancer project is to resequence 102 reference samples to find known or newly discovered single nucleotide polymorphisms (SNPs) which are of immediate importance to molecular epidemiology studies in cancer. SNP500Cancer provides a central resource for sequence verification of SNPs. For more information, see SNP500Cancer background.
Search for SNPs in SNP500Cancer database
You can search for SNPs using SNP identifier, gene symbol, gene alias, chromosome location, or gene ontology pathway.
by SNP identifier
to display SNP details, allele and genotype frequencies
Enter the dbSNP ID or internal SNP ID:
Search
search hints
by Gene
to display SNPs on the gene, and haplotype data
Enter gene symbol, alias, or GenBank ID:
Search
search hints
or: List genes with analyzed SNPs
All analyzed
Get list
or: List genes with pending SNPs
All pending
Get list
Enter chromosome number:
Search
search hints

Phase I: Major human enzymes responsible for modification of functional groups

Phase II: Conjugation with endogenous substitutents (置換基) or Phase I metabolites that are readily excreted in the urine or bile





Genetic Variations in Drug-metabolizing Enzymes (1)

- At least one of these allele → alters the **activity** of the encoded protein
  - **Cytochrome P450 genes** (*CYP2D6*, *CYP3A4*)
    - Specify enzymes responsible for drug metabolism in the liver
    - ***Terfenidine*** **is metabolized by P450 enzymes CYP2D6 & CYP3A4**
      - 6-10% Caucasian population; **homozygous for non-functional *CYP2D6* mutant alleles**
      - **Terfenidine** is metabolized by ***CYP3A4*** in these individuals
    - ***CYP3A4***: is **inhibited** by
      - Several commonly **prescribed antibiotics**
      - **Grapefruit juice**

Genetic Variations in Drug-metabolizing Enzymes (2)

- ***Terfenidine*** is administered with a *CYP3A4* inhibitor
  - High levels of *terfenidine* accumulate → life-threatening cardiac arrhythmia (心率不整)
  - Has been removed from the US market (Kurth 2000)

SNPs in Drug-metabolizing Enzymes

- *CYP2D6*
  - Mutant alleles: responsible for individual variability in pain relief by opioid analgesics (止痛劑)
    - *E.g.*, **Codeine** (可待因)
      - Require **activation by *CYP2D6***
    - Individuals with non-functional *CYP2D6* mutant alleles → resistant to the effects of opioid analgesics
    - Several mutant alleles of the *CYP2D6* gene coding for **debrisoquine 4-hydroxyase** predispose to **toxicity** with
      - Metaprolol, timolol, nortriptyline, perhexeline, propafenone and **codeine**
  - Genetic tests (**genotyping**): to prevent potential toxicity by lowering dosages or **not** prescribing certain drugs → selection of optimal drug therapy

Cytochrome P-450 Multiplicity (1)

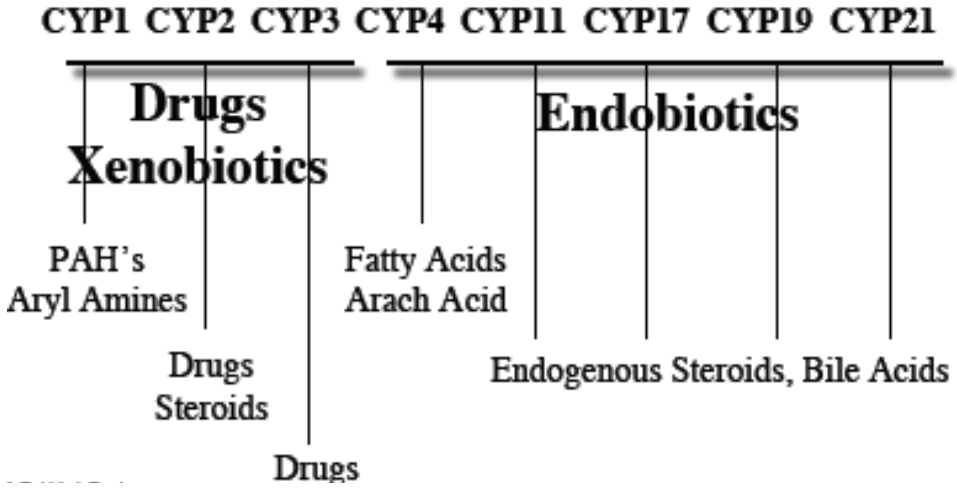
- **Superfamily**: current estimates > 1,000 genes
- Some of these are "pseudogenes"
- Humans: current estimates
  - ~57 distinct P450's in 17 families
  - Initially simple P-450's cholesterol & FA's form membranes
  - Millions of years, evolved endogenous ⇨ endogenous + exogenous compounds

Cytochrome P-450 Multiplicity (2)

- Superfamily nomenclature
- *CYP2D6*
  - C: Cyt P450
  - 2: Family (>40% homology)
  - D: subfamily (>55% homology)
  - 6: individual form

Human P-450 Multiplicity

CYP1	CYP2	CYP3	CYP4	CYP11	CYP17	CYP19	CYP21
1A1	2A6	3A3	4A9	11A1			21A2
1A2	2A7	3A4	4A11	11B1			
	2B6	3A5	4B1	11B2			
	2C8	3A7	4F2				
	2C9		4F3				
	2C10						
	2C18						
	2C19						
	2D6						
	2E1						



Genetic Variations in Drug-metabolizing Enzymes (3)

- Some drugs require **metabolism** before exerting their **effect**, *e.g.*,
  - **Antileukemic agents**
    - Mercaptopurine (MP)
    - Thioguanine (TG)
  - **Immunosuppressant**
    - Azathiopurine
  - Polymorphisms in genes encoding the metabolizing enzymes may produce **adverse drug effects**

Genetic Variations in Drug-metabolizing Enzymes (4)

- **MP & TG ∈ inactive prodrugs**
  - Require metabolism to **thiopurine nucleotides** to exert **cytotoxicity**
    - Undergo S-methylation catalyzed by thiopurine S-methyltransferase (*TPMT*)
    - High TPMT activity results in less activation to **thioguanosine phosphates** (TGNs), a competitive metabolic pathway
    - Patients with **inactivating TPMT mutation** (1/300 inherited deficiency)
      - Accumulate **high TGNs concentration** in **erythrocytes** ⇨ potentially **fatal hematopoietic** toxicity if full doses are administrated
      - 10% Caucasians & African-Americans are **heterozygous** for **active TPMT** ⇨ at intermediate risk of thiopurine toxicity

Genetic Variations in Drug-metabolizing Enzymes (5)

- Genotyping (DNA microarray)
  - To identify ***TPMT*-deficient** patients → successful treatment **at a reduced thiopurine dosage**

- Most **drug-metabolizing enzymes** exhibit clinical relevant genetic polymorphisms (next slide)

Gene/Enzyme	Drug	Quantitative Effect
CYP2C9	Tolbutamide, warfarin, Phenytoin, nonsteroidal anti-inflammatoies	Anticoagulant effect of warfarin
CYP2D6	Beta blockers, **antidepressants**, antipsychotics, **codeine**, debrisoquin, dextromethorphan, encainide, flecainide, guanoxan, methoxyamphetamine, N-propylajmaline, perhexiline, phenacetin, phenformin, propafenone, sparteine	Tardive dyskinesia from antipsychotics; narcotic side effects, efficacy, & dependence; imipramine dose requirment; beta-blocker effect
Dihydropyrimidine dehydrogenase	Fluorouracil	Fluorouracil neurotoxicity
Thiopurine methyltransferase	Mercaptopurine, thioguanine, azathioprine	Thiopurine toxicity & efficacy; risk of second cancers
ACE	Enalapril, Lisinopril, captopril	Renoprotective effects, cardiac indices, blood pressure, immunoglobulin A nephropathy
Potassium channels		
HERG	Quinidine	Drug-induced long QT syndrome
KvLQT1	Cisapride Terfenadine, disopyramide, meflaquine	Drug-induced torsade de pointes Drug-induced long QT syndrome
hKCNE2	Clarithromycin	Drug-induced arrhythmia

Drug Target Polymorphisms (1)

- Affect drug
  - Pharmacodynamics
  - Efficacy

- **Genes** involve in
  - Determine the plasma concentration (extent of drug **activation**)
  - Determine the sensitivity of the **drug receptor** at any given concentration

Drug Target Polymorphisms (2)

- Drug-metabolizing enzymes
- Receptors

- Both homozygous wild-type
  - High probability of therapeutic efficacy
  - Low probability of drug toxicity

- Both homozygous mutants
  - Low probability of efficacy
  - High probability of drug toxicity

Receptor Polymorphisms (Example) (1)

- Kuivenhoven *et al.* (1998) N Engl J Med 8, 86-93.

- Background
  - **Higher high-density lipoprotein** (HDL) cholesterol concentration is inversely related to the risk of coronary artery disease
  - The **Cholesteryl Ester Transfer Protein (*CETP*)** has a central role **in the metabolism of HDL** → alter the susceptibility to atherosclerosis (動脈硬化症)

- ***CETP* polymorphisms**
  - B1 variant
  - B2 = without B1 variant

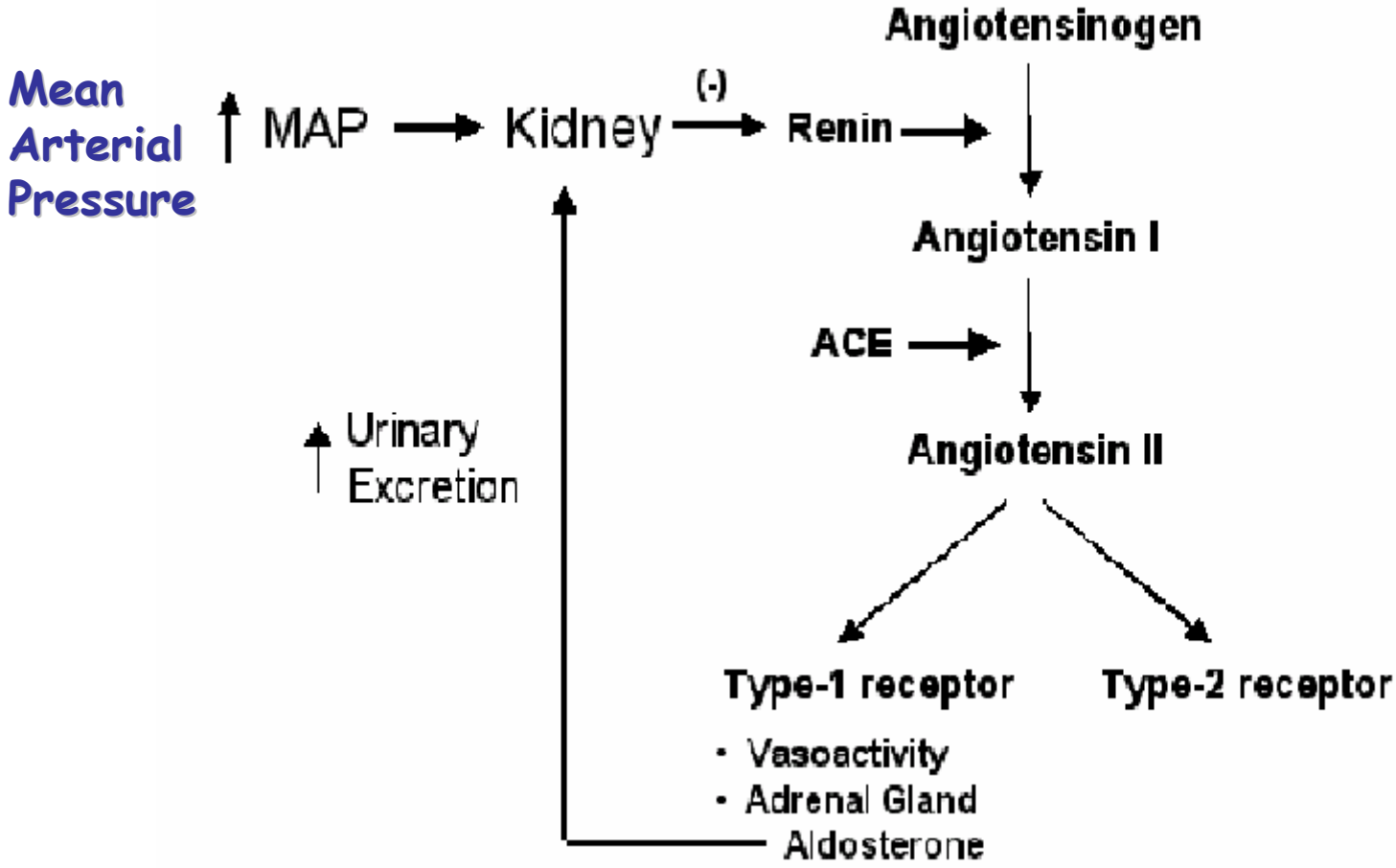
Receptor Polymorphisms (Example) (2)

- **807 patients**
  - Antiographically documented coronary atherosclerosis
  - Participated in **a cholesterol-lowing trial** designed to induced the regression of coronary atherosclerosis
    - Randomly assigned to treatment with either (2 years)
      - ***Pravastatin***
      - ***Placebo***
  - **B1 variant** of the *CETP* gene was associated with
    - Higher plasma CETP conc.
    - Lower HDL cholesterol conc.
  - ***Pravastatin*** therapy slowed the progression of coronary atherosclerosis **in *B1B1* carriers** but not in *B2B2* carriers

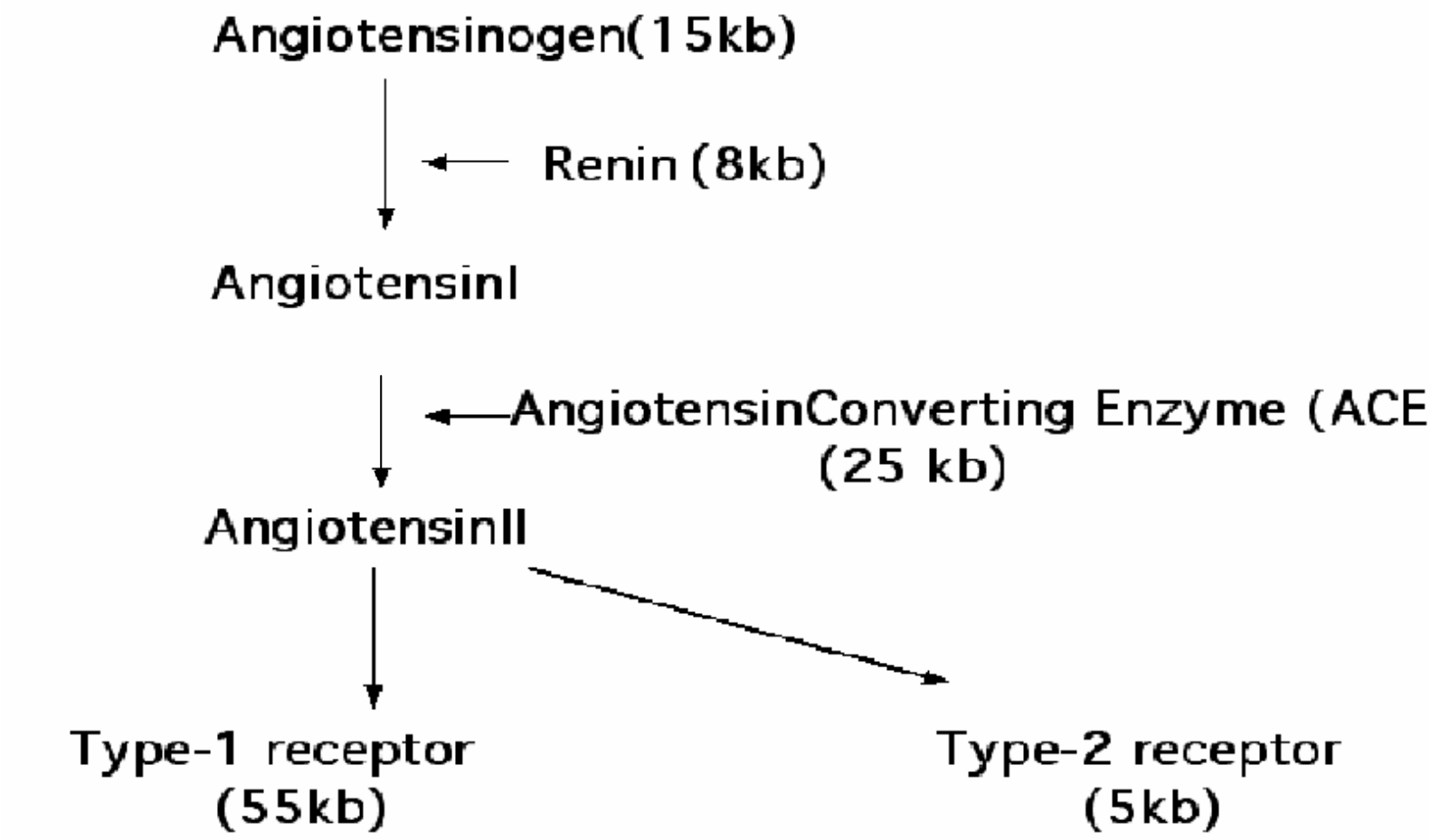
Example: *ACE*

- Patients **homozygous** for an allele with **a deletion in intron 16** of the gene for angiotensin-converting enzyme (*ACE*) showed **no** benefit from the **hypertension drug** ***enalapril*** while other patients did benefit

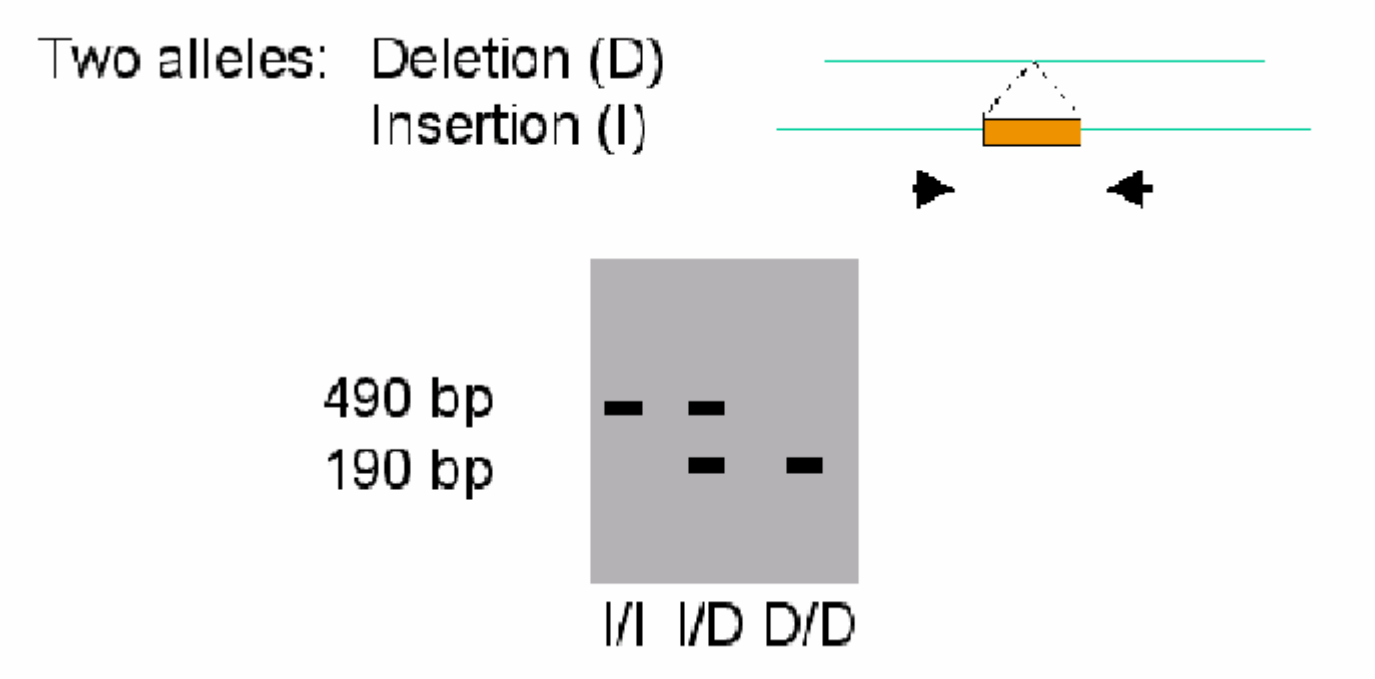
Renin-Angiotensin System: Physiology



Renin-Angiotensin System



ACE: Candidate Gene



- "D" allele: ↑enzyme activity, hypertension, LVH, CAD, renal disease, longevity
- "I" allele: ↑LV mass, elite endurance /athletic performance

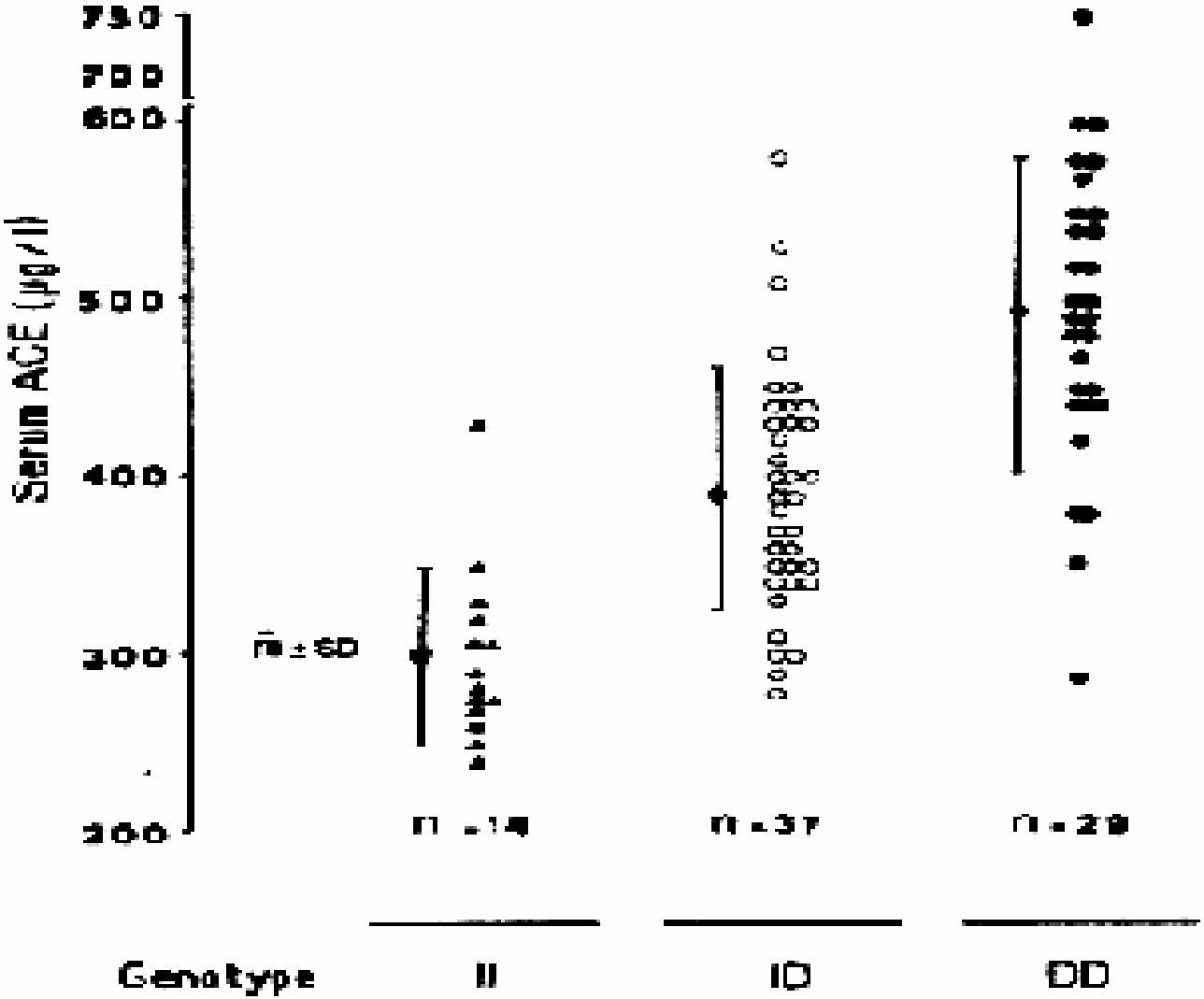


Figure 2. Serum immunoreactive ACE concentrations (μg/liter) for individual with the II, ID, and DD genotypes, respectively, shown in left, middle, and right panels. Solid vertical bars indicate mean concentration and standard deviation for each group.

Rigat et al. J. Clin. Invest. 1990

The Value of Pharmacogenomics

- Drug discovery: enhanced
- Patient drug therapy: optimized

- **Patient vary in drug response**
  - To identify polymorphisms in **drug-metabolizing** enzymes
  - To identify **drug targets** in order to tailor drug therapy

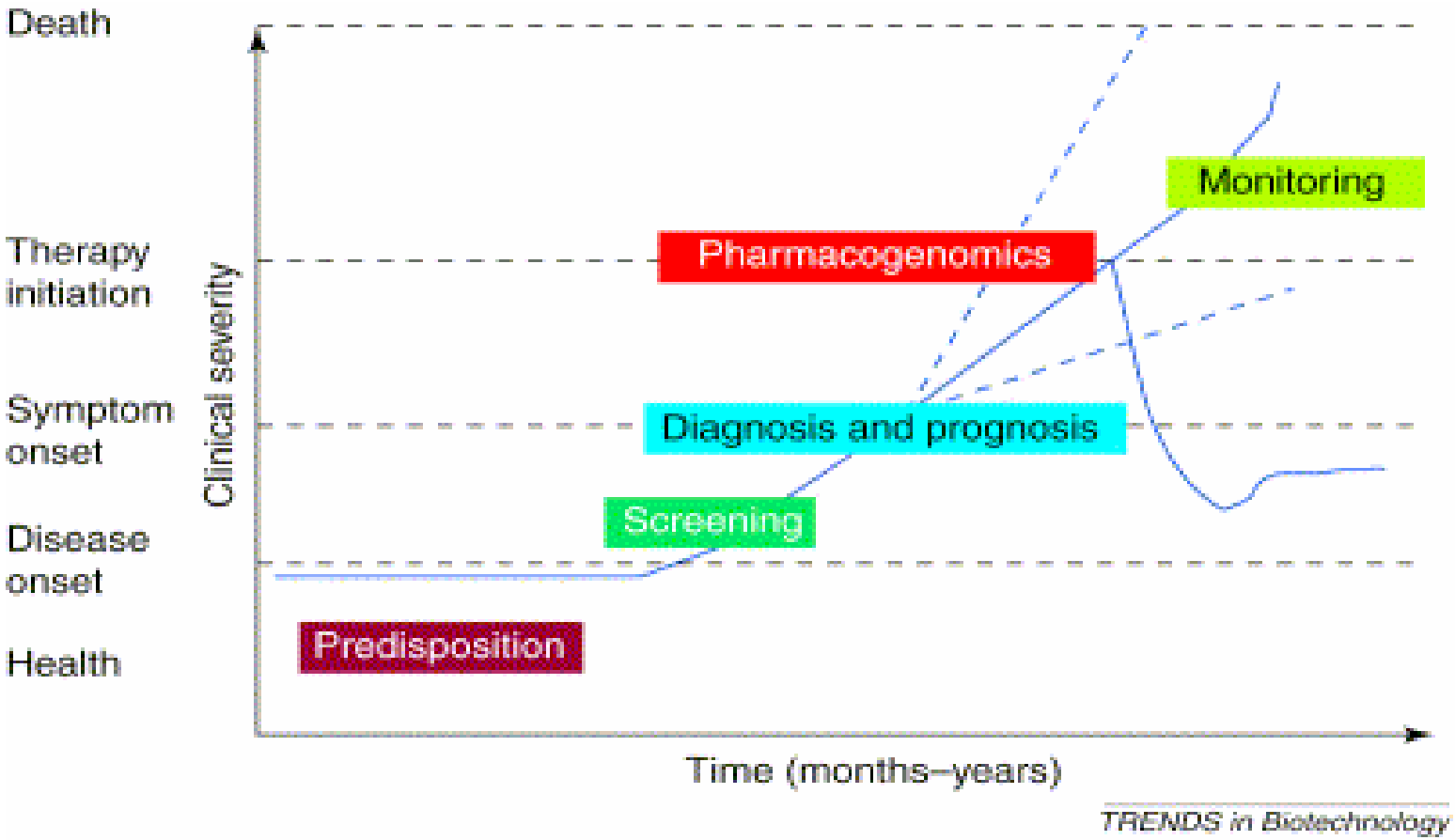
- Pharmacogenomics → to create small molecules with greater **specificity** and **efficacy**
  - **Rational drug design**
  - Combinatorial methods

Real World Applications

- Most of the major pharmaceutical companies are currently collecting **pharmacogenomic data** in their clinical trials
  - Data is yet to be published

- **Genetic indications** for drug use are **still a few years away**

Impact of Pharmacogenomics on Chronic Diseases



Trends Biotech. 19, 491-496 (2001)

Pharmacogenomics - A new Script for Prescriptions

- **Information**
  - Unique variations in an individuals's **genetic makeup**
  - Resulting highly variable **responses** to drug
    - Metabolism
    - Effectiveness
    - Toxicity
- **Everybody** must
  - **Get up and ready for pharmacogenomics**