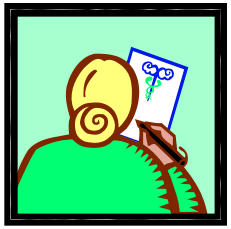
PHARMACOGENETICS
BASIC PRINCIPLES

Current Therapeutic Approach

PATHOLOGY AND / OR SYMPTOMS



1st choice drug

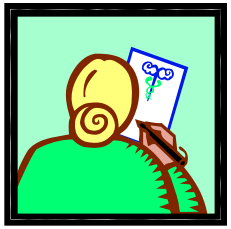
EFFICACY

Failure

Adverse Effects

Current Therapeutic Approach

PATHOLOGY AND / OR SYMPTOMS



1st choice drug

EFFICACY

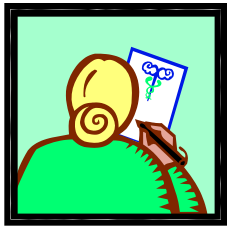
Failure

Adverse Effects

2nd choice drug

Current Therapeutic Approach

PATHOLOGY AND / OR SYMPTOMS



1st choice drug

EFFICACY

Failure

Adverse Effects

2nd choice drug

EFFICACY

Patient group

Same diagnosis

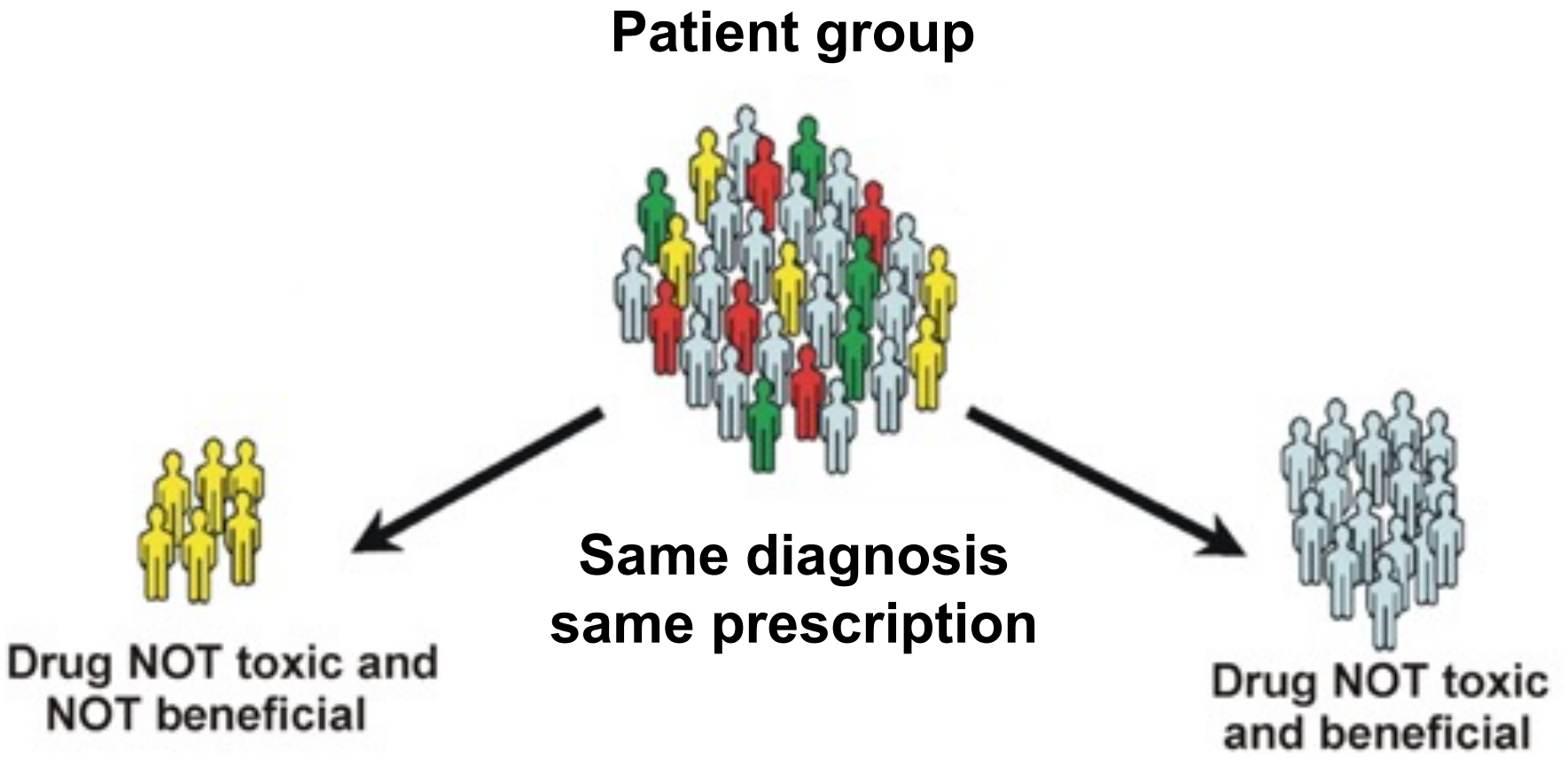
Patient group

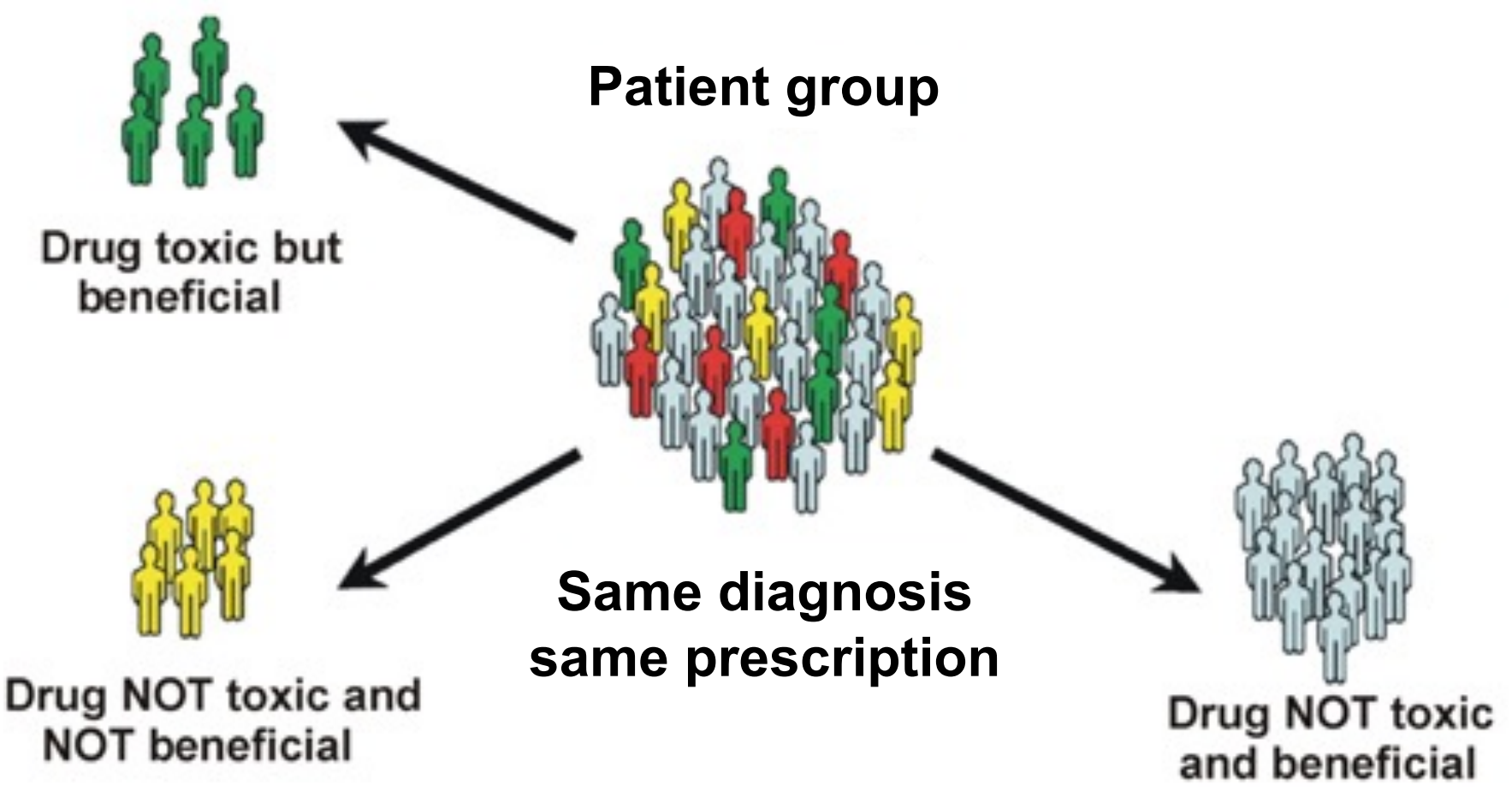
Same diagnosis
same prescription

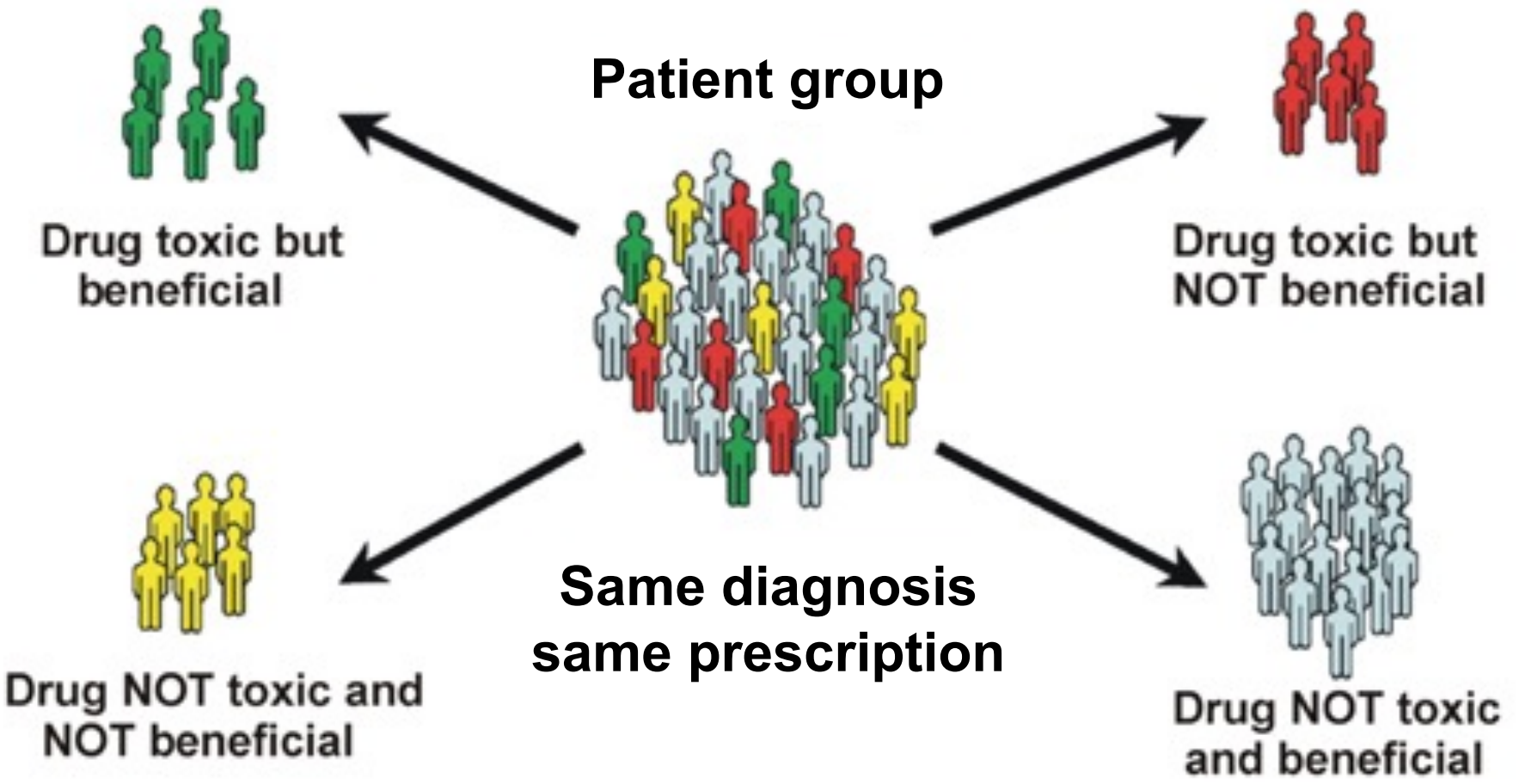
Patient group

Same diagnosis
same prescription

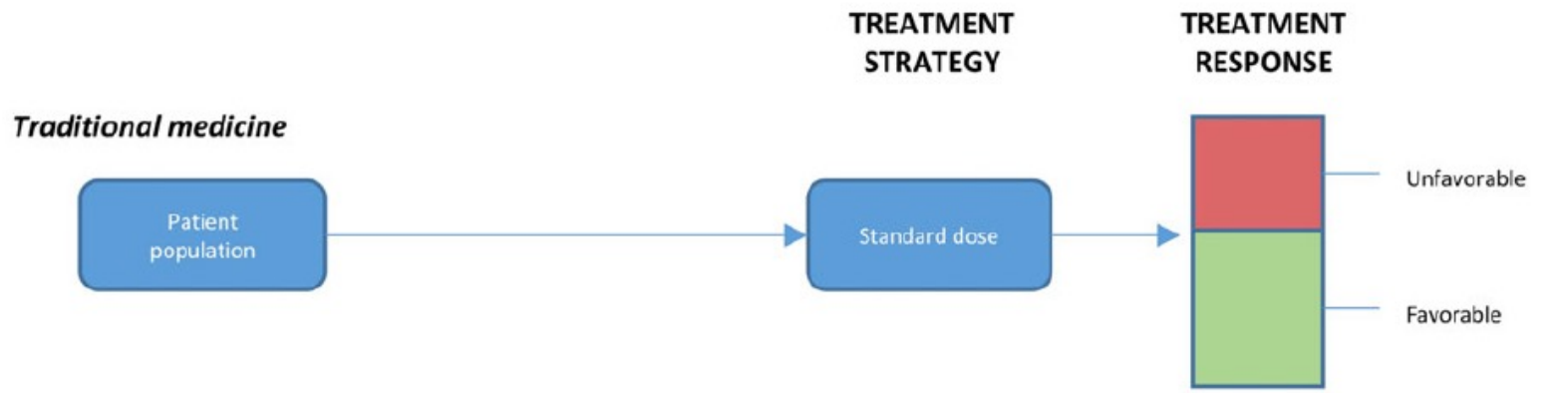
Drug NOT toxic and beneficial


Patient group
Same diagnosis
same prescription
Drug NOT toxic and
NOT beneficial
Drug NOT toxic
and beneficial


Patient group
Drug toxic but beneficial
Same diagnosis same prescription
Drug NOT toxic and NOT beneficial
Drug NOT toxic and beneficial


Patient group
Drug toxic but beneficial
Drug toxic but NOT beneficial
Same diagnosis same prescription
Drug NOT toxic and NOT beneficial
Drug NOT toxic and beneficial

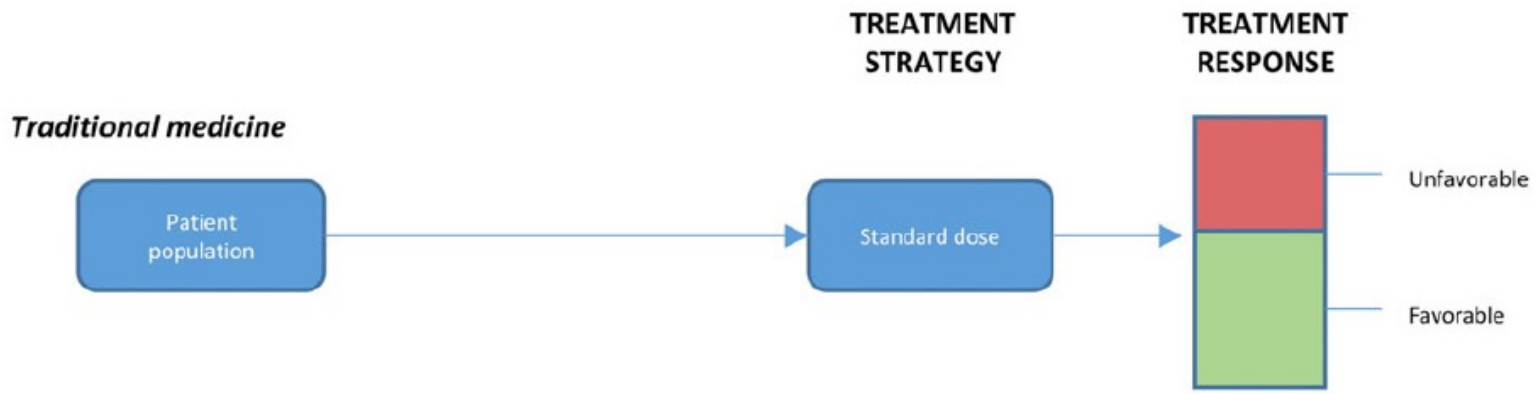
Inter-individual variability in response to drug treatment



EFFICACY OF DRUGS

«*the vast majority of drugs – more than 90%- only work in 30 or 50% of the people*».

Allen Roses past vice president of GlaxoSmithKline



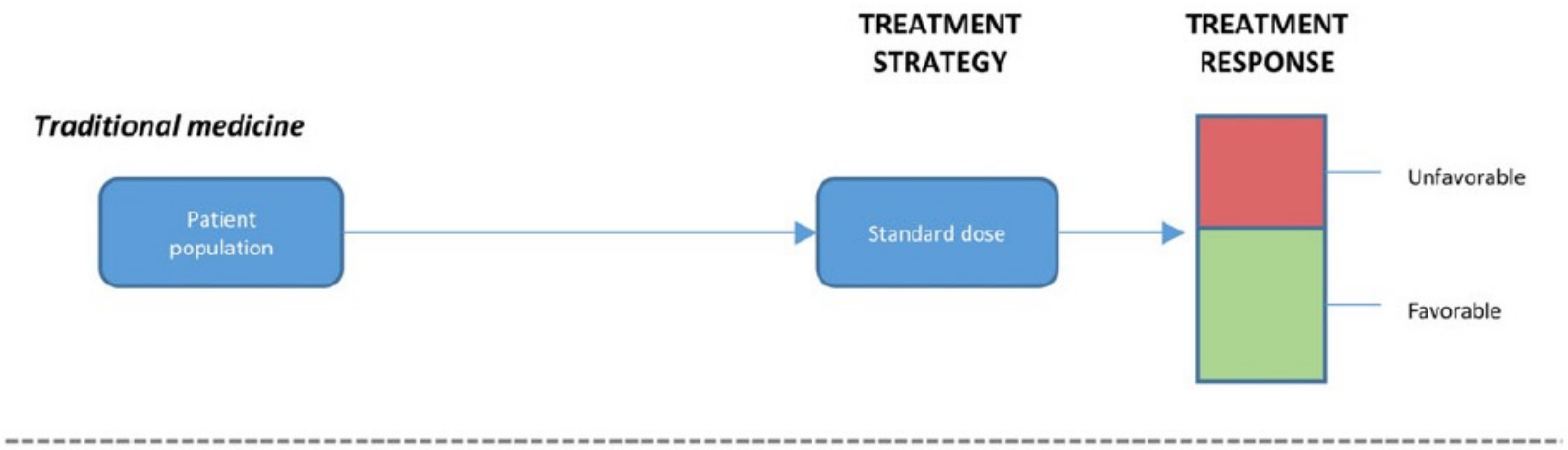
EFFICACY OF DRUGS

«*the vast majority of drugs – more than 90%
only work in 30 or 50% of the people*».

Allen Roses past vice president of GlaxoSmi

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Spear, B.B. et al. Trends Mol Med 2001;7:201-204.



ADVERSE DRUG REACTIONS (ADR)

ADRs were between the forth and sixth most common cause of death in the USA in 1994. (more than 2 million of cases, 100,000 fatal).

Estimated cost up to $4 billion per year in the United States and £1 billion per year in the United Kingdom.

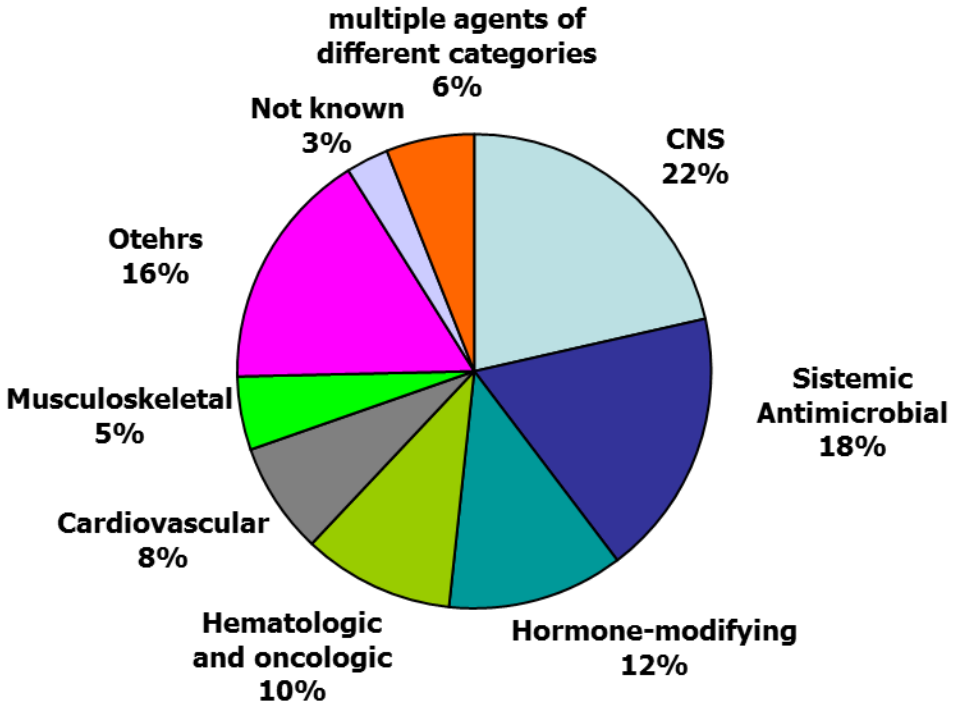
Lazarou J, et al. *Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies*. JAMA 1998.

Pirmohamed et al., *Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18820 patients* BMJ 2004

(NEISS-CADES) National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance Project USA

National surveillance of emergency department visits for outpatient adverse drug events (n=21298) period 01 / 04-12 / 05 in 63 hospitals

Budnitz DS et al., JAMA. 2006



(NEISS-CADES) USA

Table 4. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated In Emergency Departments by Drug Class—United States, 2004-2005

Therapeutic Category (Drug Class)*	Adverse Drug Events†	
	Cases	Annual Estimate, No. (%)
Central nervous system agents	4698	150 257 (21.4)
Opioid-containing analgesics	1167	41 421 (5.9)
Non–opioid-containing analgesics	715	20 887 (3.0)
Antidepressants and mood stabilizers	591	19 817 (2.8)
Anticonvulsants	588	17 887 (2.6)
Antipsychotics	443	13 635 (1.9)
Benzodiazepines	288	9299 (1.3)
Non–benzodiazepine-derived sedatives	182	6375 (0.9)
Stimulants	177	4152 (0.6)
Anesthetics	92	3176 (0.5)
Other central nervous system agents or central nervous system agents from different classes	455	13 608 (1.9)
Systemic antimicrobial agents	3867	127 807 (18.2)
Amoxicillin-containing agents	1150	35 228 (5.0)
Quinolones	445	16 074 (2.3)
Sulfonamide-containing agents	446	15 593 (2.2)
Cephalosporins	454	15 369 (2.2)
Erythromycins and macrolides	329	11 833 (1.7)
Penicillin	233	7848 (1.1)
Antivirals, antiparasitics, and antifungals	141	4338 (0.6)
Tetracyclines	106	3662 (0.5)
Lincomycins	100	3332 (0.5)
Metronidazole	59	1815 (0.3)
Other antimicrobial agents, unspecified antimicrobials, or drugs from different classes of antimicrobial agents	404	12 715 (1.8)

(NEISS-CADES) USA

Table 4. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated In Emergency Departments by Drug Class—United States, 2004-2005

Therapeutic Category (Drug Class)*	Adverse Drug Events†	
	Cases	Annual Estimate, No. (%)
Hormone-modifying agents	2345	84 098 (12.0)
Insulins	1494	53 030 (7.6)
Oral hypoglycemic agents	374	14 528 (2.1)‡
Glucocorticoids	182	6575 (0.9)
Estrogens and progesterones	91	2588 (0.4)
Other hormone-modifying agents or drugs from different classes of hormone-modifying agents	204	7377 (1.1)
Hematologic and oncologic agents	2120	72 029 (10.3)
Anticoagulants	1045	36 110 (5.1)‡
Platelet inhibitors	407	17 258 (2.5)‡
Antineoplastic agents	481	12 129 (1.7)‡
Other hematologic and oncologic agents or drugs from different classes of blood-modifying agents	187	6532 (0.9)‡
Cardiovascular agents	1498	53 457 (7.6)
ACE inhibitors/ARBs	306	10 392 (1.5)
Lipid-lowering agents	214	8828 (1.3)
β-Blockers	189	6596 (0.9)
Digitalis glycosides	131	5318 (0.8)‡
Diuretics	142	5108 (0.7)
Calcium channel blockers	138	5004 (0.7)
Nitrates/antiarrhythmics	69	2582 (0.4)
Centrally acting antiadrenergics	82	2162 (0.3)
Other cardiovascular drugs or drugs from different classes of cardiovascular agents	227	7467 (1.1)

(NEISS-CADES) USA

Table 4. Number of Cases and Annual Estimate of Individuals With Adverse Drug Events Treated In Emergency Departments by Drug Class—United States, 2004-2005

Therapeutic Category (Drug Class)*	Adverse Drug Events†	
	Cases	Annual Estimate, No. (%)
Musculoskeletal agents	1043	35 177 (5.0)
Nonselective nonsteroidal anti-inflammatory drugs	727	23 394 (3.3)
Muscle relaxants	133	4616 (0.7)
COX-2 selective nonsteroidal anti-inflammatory drugs	101	4587 (0.7)
Other musculoskeletal drugs or drugs from different classes of musculoskeletal agents	82	2580 (0.4)
Antihistamines, decongestants, expectorants, antitussives, and combination cold remedies	924	28 403 (4.0)
Vaccines	641	15 911 (2.3)
Gastrointestinal agents	385	12 477 (1.8)
Diagnostic agents	256	9726 (1.4)
Dermatologic agents	283	9459 (1.3)
Herbs, dietary supplements, and alternative agents	262	9423 (1.3)
Therapeutic nutrients, vitamins, minerals, and electrolytes	254	8445 (1.2)
Topical eye, ear, nose, and throat agents	195	6408 (0.9)
Autonomic agents	148	4302 (0.6)
Respiratory tract agents	127	3812 (0.5)
Immune-modifying agents	116	3654 (0.5)
Other agents	114	4547 (0.6)
Drugs not stated or not known	650	20 022 (2.9)
Drugs from more than 1 therapeutic category	1372	42 136 (6.0)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COX, cyclooxygenase.
*For 18 315 cases (annual estimate, 607 245; 86.6%) a single drug was implicated in the adverse event. For 1611 cases (annual estimate, 52 167; 7.4%) drugs from the same therapeutic category were implicated. For the remaining cases drugs from more than 1 therapeutic category were implicated and these are listed in a separate category.
†Annual estimates and percentages may not total 100% due to rounding.
‡Estimates with coefficient of variation >30%: oral hypoglycemic agents, 31.1%; anticoagulants, 33.3%; platelet inhibitors, 32.2%; antineoplastic agents, 36.3%; other hematologic and oncologic agents or drugs from different classes of blood-modifying agents, 33.8%; and digitalis glycosides, 33.5%.

(NEISS-CADES) USA

Table 5. Number of Cases and Annual Estimate of Drugs Most Commonly Implicated in Adverse Events Treated in Emergency Departments—United States, 2004-2005*

Drug	Adverse Drug Events	
	Cases, No.	Annual Estimate, No. (%)
Insulins	1577	55 819 (8.0)
Warfarin	1234	43 401 (6.2)†
Amoxicillin	1022	30 135 (4.3)
Aspirin	473	17 734 (2.5)
Trimethoprim-sulfamethoxazole	447	15 291 (2.2)
Hydrocodone-acetaminophen	420	15 512 (2.2)
Ibuprofen	526	14 852 (2.1)
Acetaminophen	497	12 832 (1.8)
Clopidogrel	241	10 931 (1.6)†
Cephalexin	293	10 628 (1.5)
Penicillin	270	9275 (1.3)
Amoxicillin-clavulanate	274	8959 (1.3)
Azithromycin	255	8794 (1.3)
Levofloxacin	230	8682 (1.2)
Naproxen	245	8634 (1.2)
Phenytoin	238	7937 (1.1)
Oxycodone-acetaminophen	227	7328 (1.0)
Metformin	179	6678 (1.0)

*Drugs implicated in ≥1% of adverse events. For 434 cases (annual estimate, 15 784 [2.2%]) 2 of these 18 drugs were implicated in the adverse event. Therefore, these 18 drugs accounted for adverse drug events in 8214 cases (annual estimate, 277 636 [39.6%]).

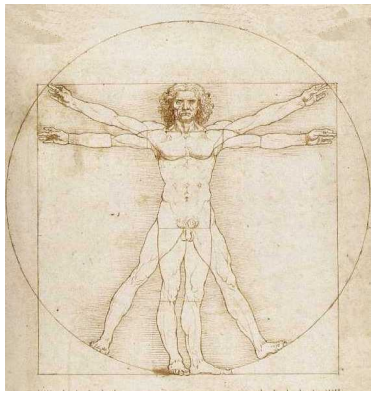
†Estimates with coefficient of variation >30%: warfarin, 32.5%; clopidogrel, 36.6%.

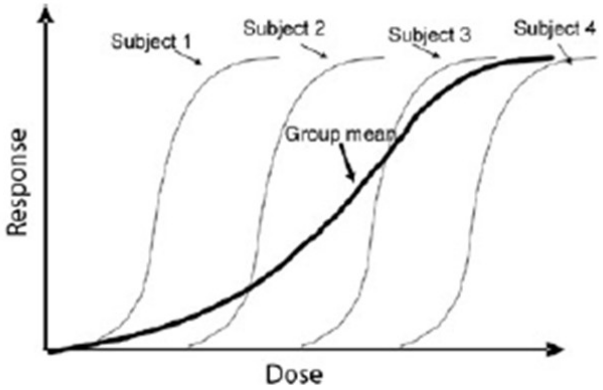
In Italy?

- 22 hospitals involved for a period of 10 days in 2000.
- 18854 patients admitted to the emergency room.
- 629 (3.3%) affected by ADE.
- Patients with ADE accounted for 4.3% of subsequently hospitalized patients.

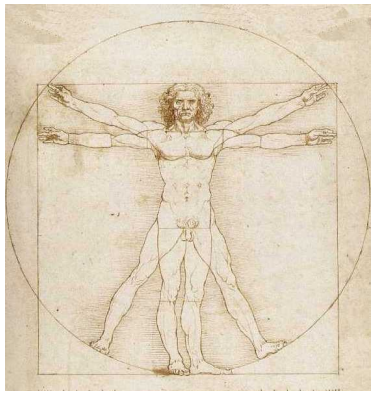
Trifirò G et al., Pharmacoepid Drug Saf. 2005.

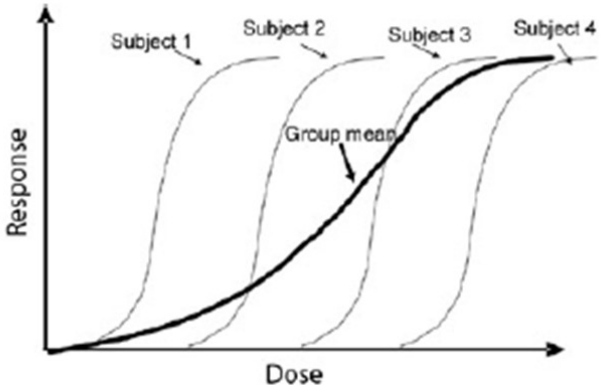
Response to the drug: factors involved





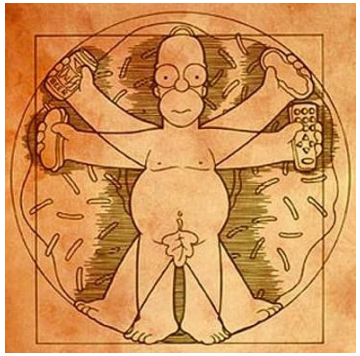
Response to the drug: factors involved



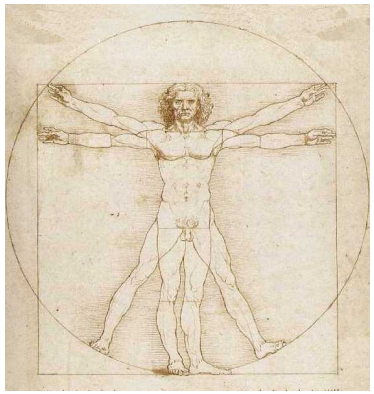


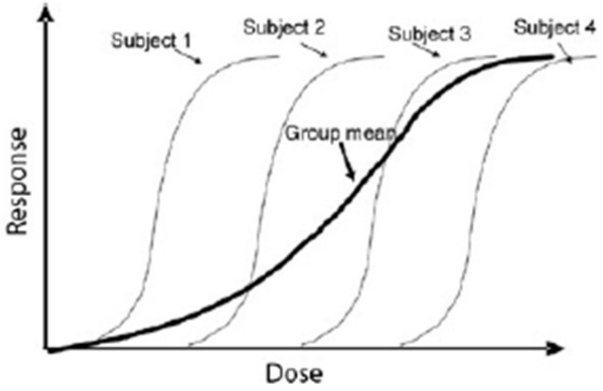
Extrinsic Factors

Smoke
Diet
Alcohol Consumption
Drugs Interaction
Other



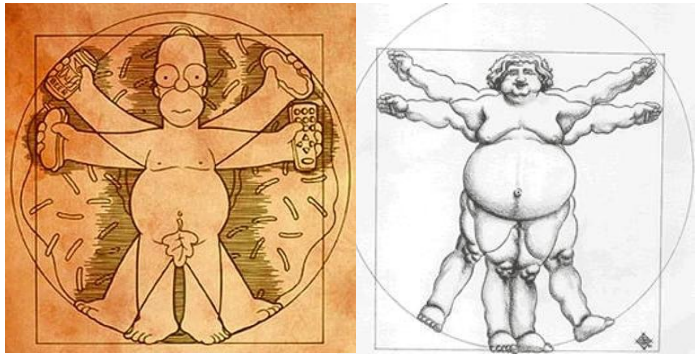
Response to the drug: factors involved





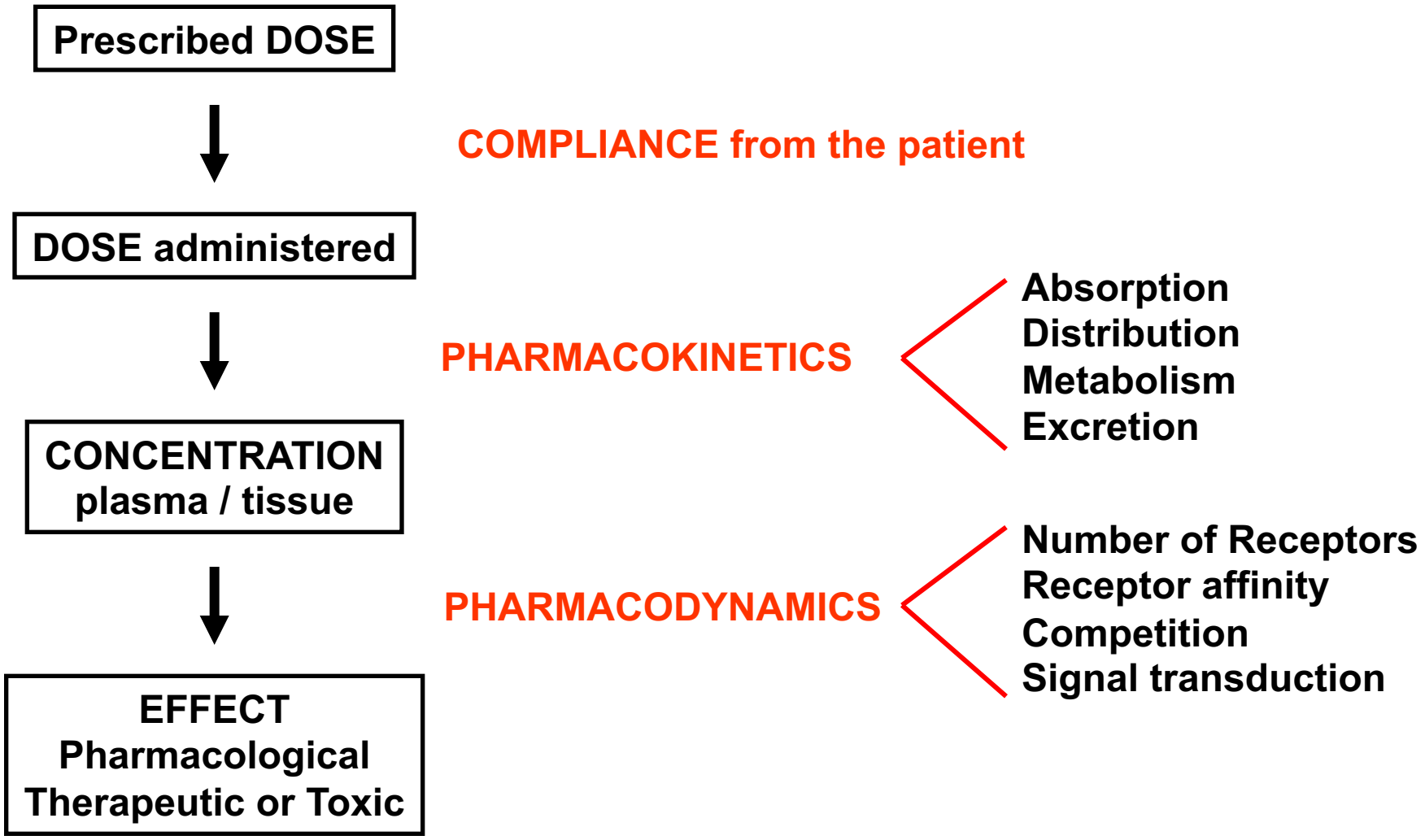
Extrinsic Factors

Smoke
Diet
Alcohol Consumption
Drugs Interaction
Other



Intrinsic Factors

Age - Sex - Race
BSA
Pregnancy / Breastfeeding
Organ dysfunctions
Pathologies
Genetics


Prescribed DOSE
COMPLIANCE from the patient
DOSE administered
PHARMACOKINETICS
Absorption
Distribution
Metabolism
Excretion
CONCENTRATION
plasma / tissue
PHARMACODYNAMICS
Number of Receptors
Receptor affinity
Competition
Signal transduction
EFFECT
Pharmacological
Therapeutic or Toxic

Importance of Genetics in Adverse Drug Reactions (ADE)

Frequency in their metabolism of enzymes with possible inactive allelic variants (PM)

Randomly Selected drugs

7% - 22%

***Range P*=.006-*P*.001**

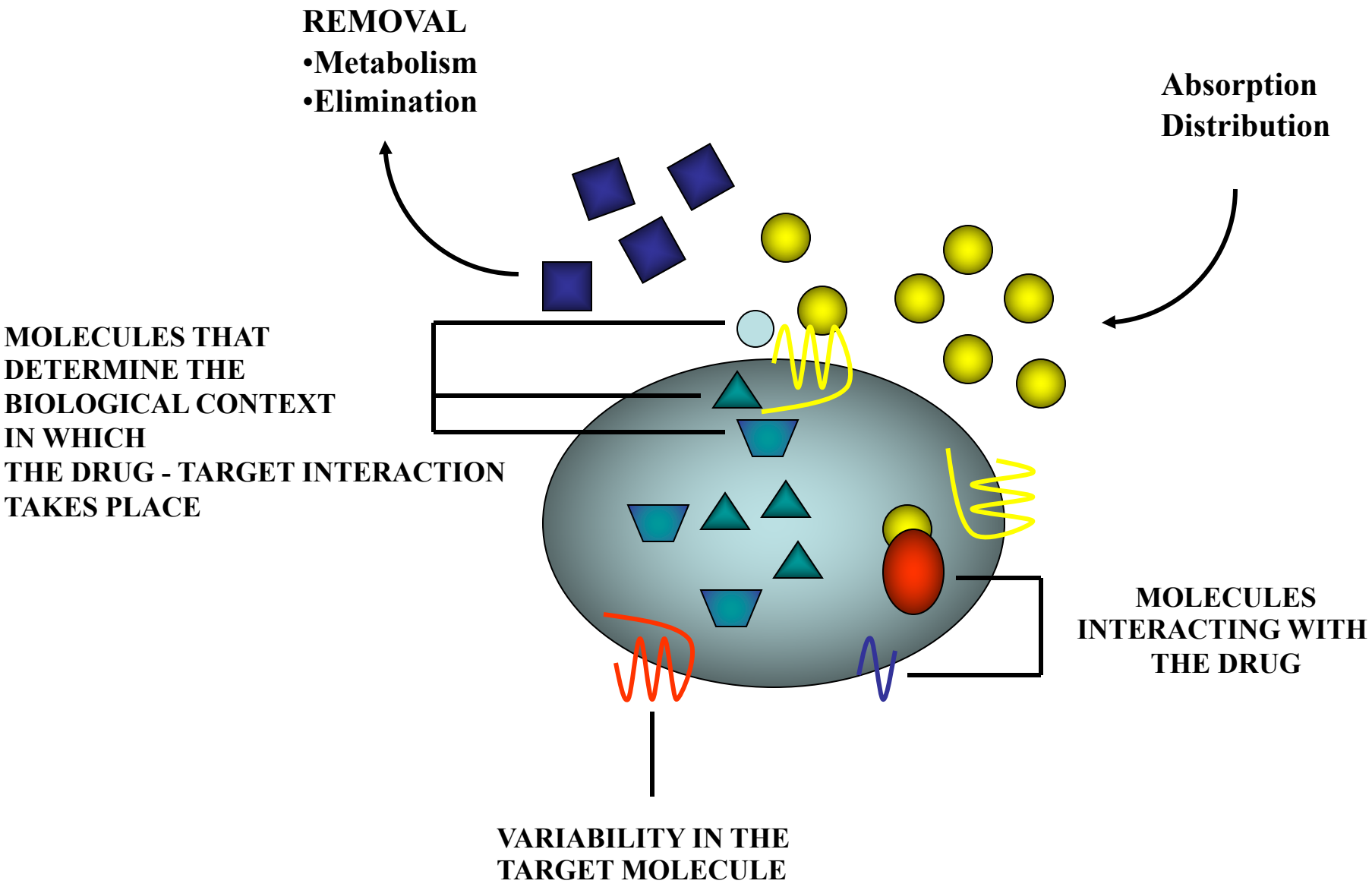
Drugs Frequently cause of ADE

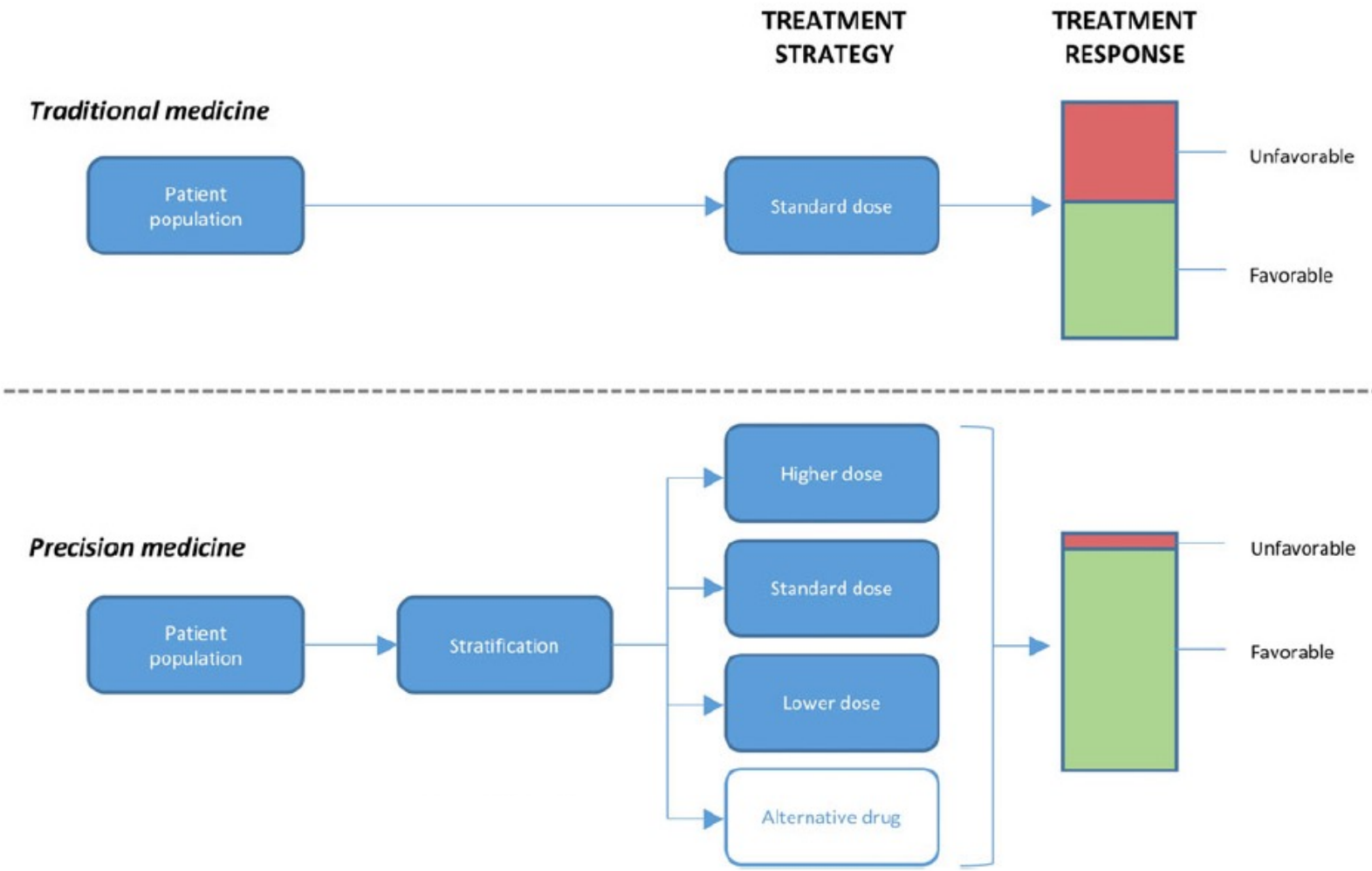
59%

JAMA. 2001;286:2270-2279

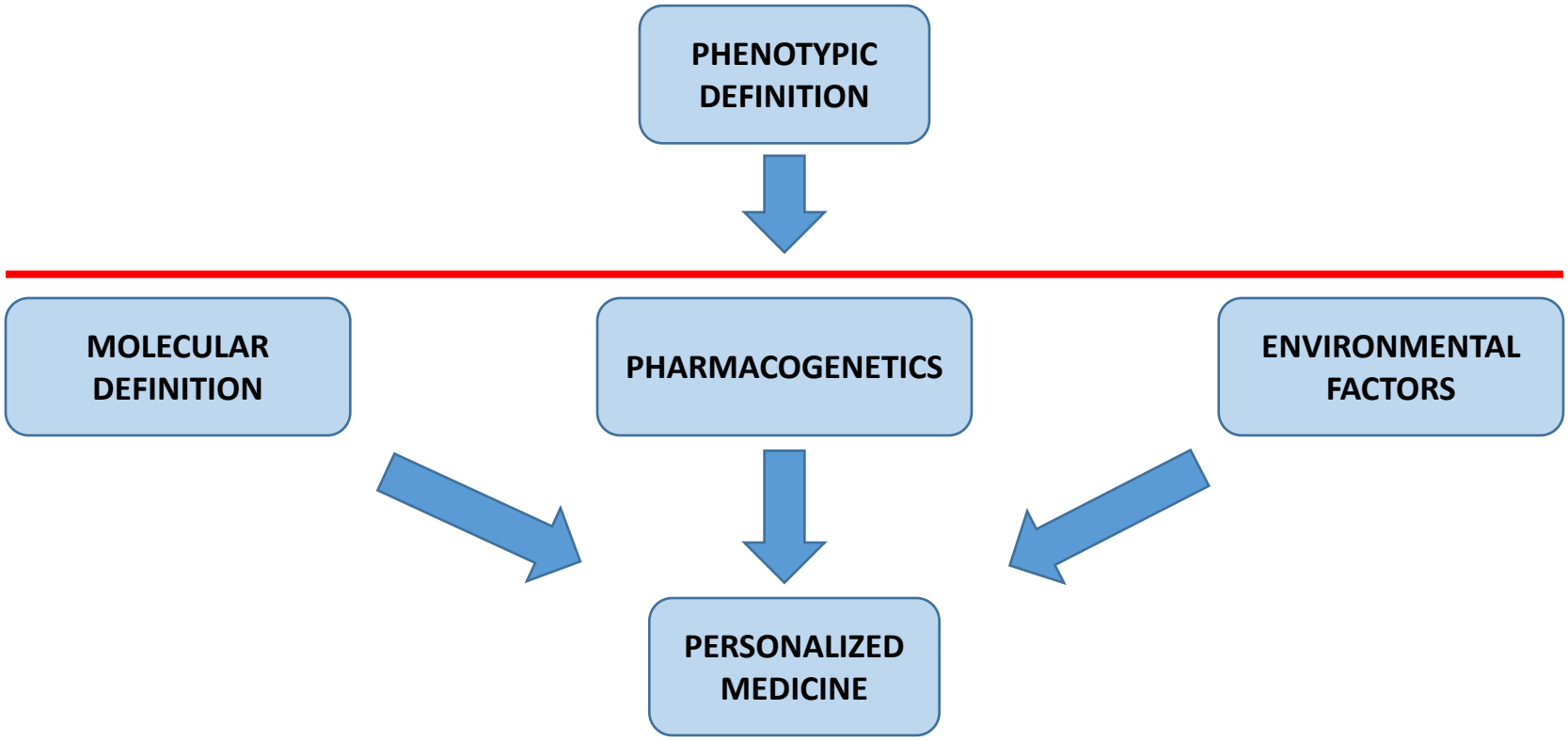
Pharmacogenetics

Interindividual variability in the sequence of genes that code for proteins involved in the modulation of drug response.




TREATMENT STRATEGY
TREATMENT RESPONSE
Traditional medicine
Patient population
Standard dose
Unfavorable
Favorable
Precision medicine
Patient population
Stratification
Higher dose
Standard dose
Lower dose
Alternative drug
Unfavorable
Favorable

PERSONALIZED MEDICINE: *THE ROLE OF PHARMACOGENETICS*



PERSONALIZED DRUG THERAPY

GOALS

- the right drug
- at the right dose
- for the right patients
- at the right time

PERSONALIZED DRUG THERAPY: STRATEGIES

«A POSTERIORI» METHOD	**MONITORING**	of the plasma concentrations of the specific drug (TDM)
«A PRIORI» METHODS	**PHENOTYPING**	of enzymatic activities by means of “probe drugs”
	GENOTYPING	of the variants of the genes involved in the modulation of the response to drugs

END POINTS OF PHARMACOGENETIC TESTS

- *A priori* assessment of the risk of adverse events (safety)
- *A priori* customization of the dosage / pharmacological posology on a genetic basis (dosing)
- *A priori* determination of the most effective therapy for individual patients (efficacy)

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

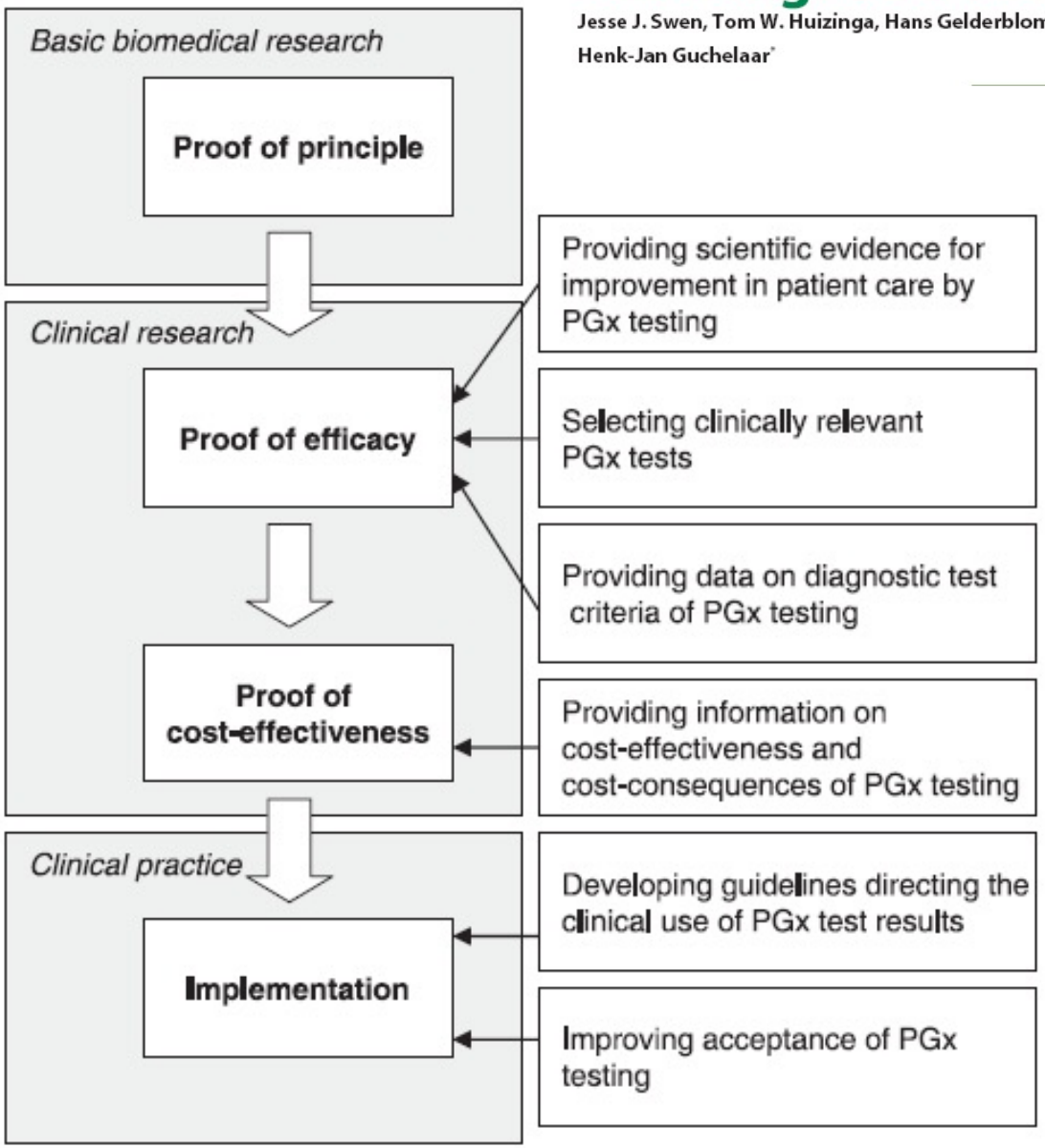
Therein, a valid biomarker is described as a "biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results." The classification of biomarkers is context specific.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

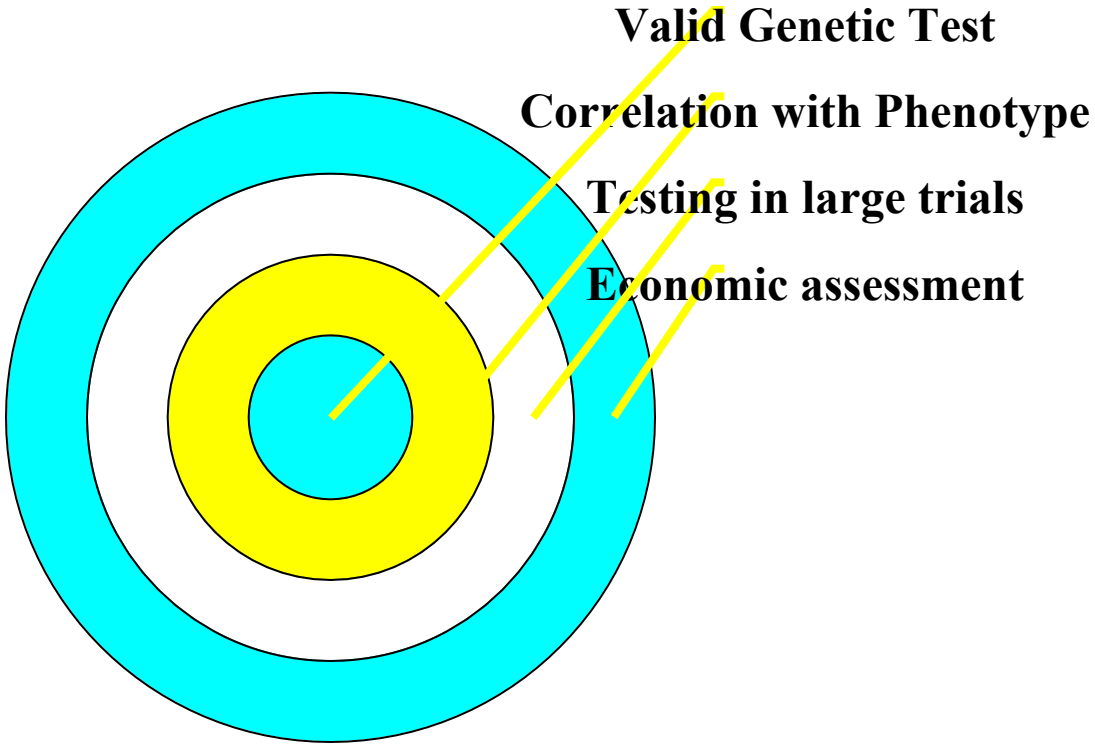
OPEN ACCESS Freely available online PLoS MEDICINE
Research In Translation

Translating Pharmacogenomics: Challenges on the Road to the Clinic

Jesse J. Swen, Tom W. Huizinga, Hans Gelderblom, Elisabeth G. E. de Vries, Willem J. J. Assendelft, Julia Kirchheiner, Henk-Jan Guchelaar*



Steps Toward Clinical Pharmacogenetic Labelling

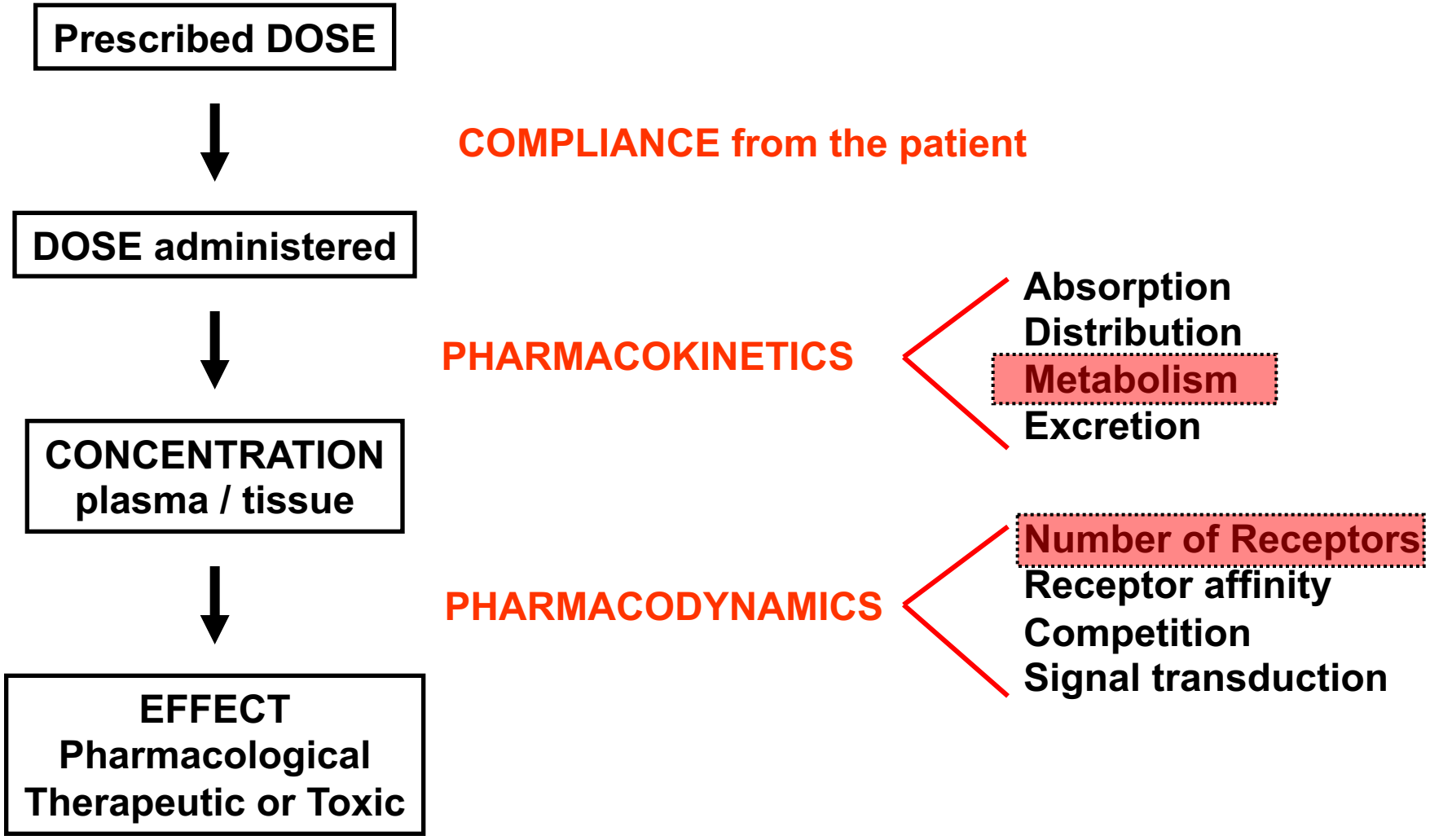


Valid Genomic Biomarkers in the Context of Approved Drug Labels FDA

DRUG	BIOMARKER	GOAL	STATUS
Azathioprine	TPMT	SAFETY	**recommended**
Abacavir	HLA-B*5701	SAFETY	**recommended**
Atomoxetine	2D6	SAFETY	**information only**
Irinotecan	UGT1A1	SAFETY	**recommended**
Warfarin	2C9 and VKORC1	SAFETY	**recommended**
Celecoxib	2C9	SAFETY	**Information only**
Codeine	2D6	SAFETY	**information only**
Panitumumab	K-ras	EFFICACY	**recommended**
Clopidogrel	2C19	EFFICACY	**information only**
Tamoxifen	2D6	EFFICACY	**Pending**

Valid Genomic Biomarkers in the Context of Approved Drug Labels FDA

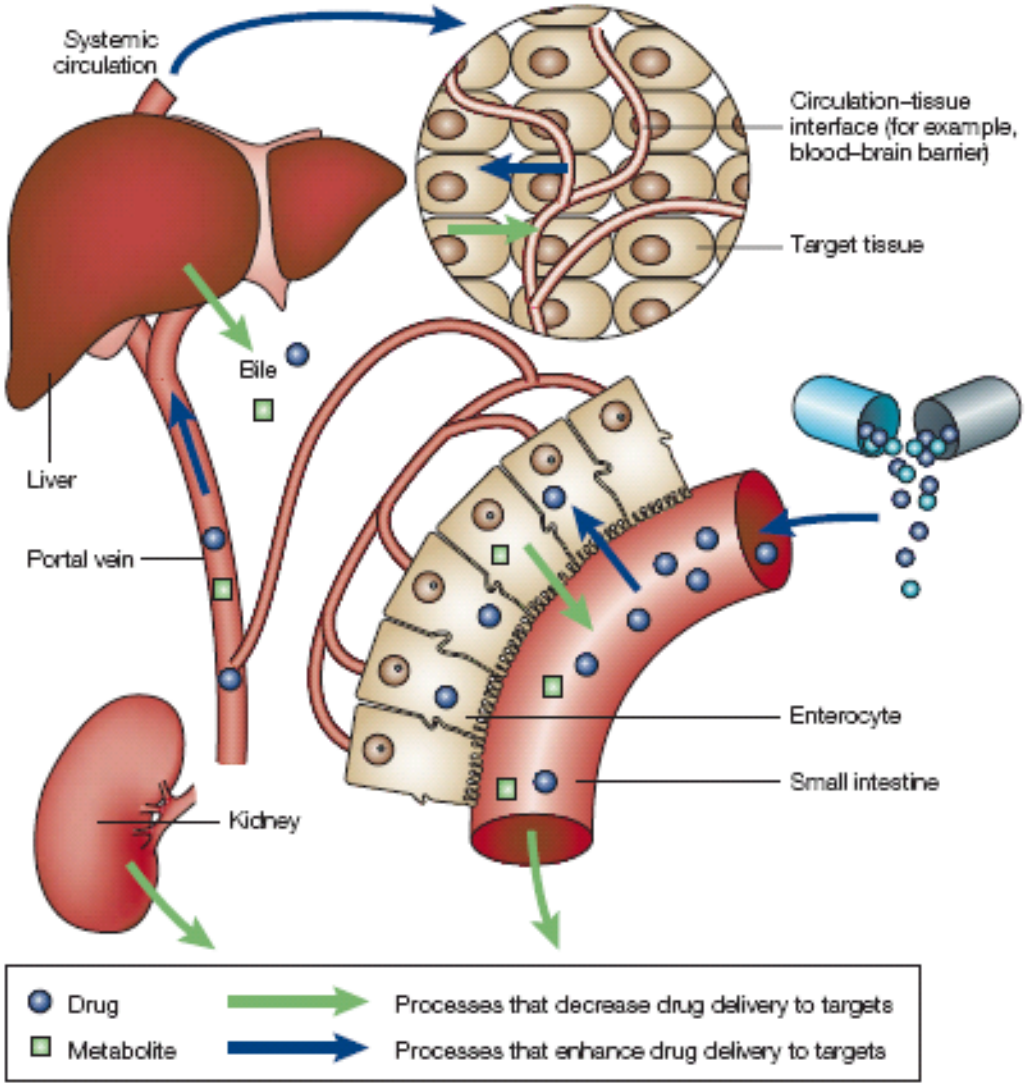
DRUG	BIOMARKER	GOAL	STATUS
Azathioprine	TPMT	SAFETY	**recommended**
Abacavir	HLA-B*5701	SAFETY	**recommended**
Atomoxetine	2D6	SAFETY	**information only**
Irinotecan	UGT1A1	SAFETY	**recommended**
Warfarin	2C9 and VKORC1	SAFETY	**recommended**
Celecoxib	2C9	SAFETY	**Information only**
Codeine	2D6	SAFETY	**information only**
Panitumumab	K-ras	EFFICACY	**recommended**
Clopidogrel	2C19	EFFICACY	**information only**
Tamoxifen	2D6	EFFICACY	**Pending**


Prescribed DOSE
COMPLIANCE from the patient
DOSE administered
PHARMACOKINETICS
Absorption
Distribution
Metabolism
Excretion
CONCENTRATION
plasma / tissue
PHARMACODYNAMICS
Number of Receptors
Receptor affinity
Competition
Signal transduction
EFFECT
Pharmacological
Therapeutic or Toxic

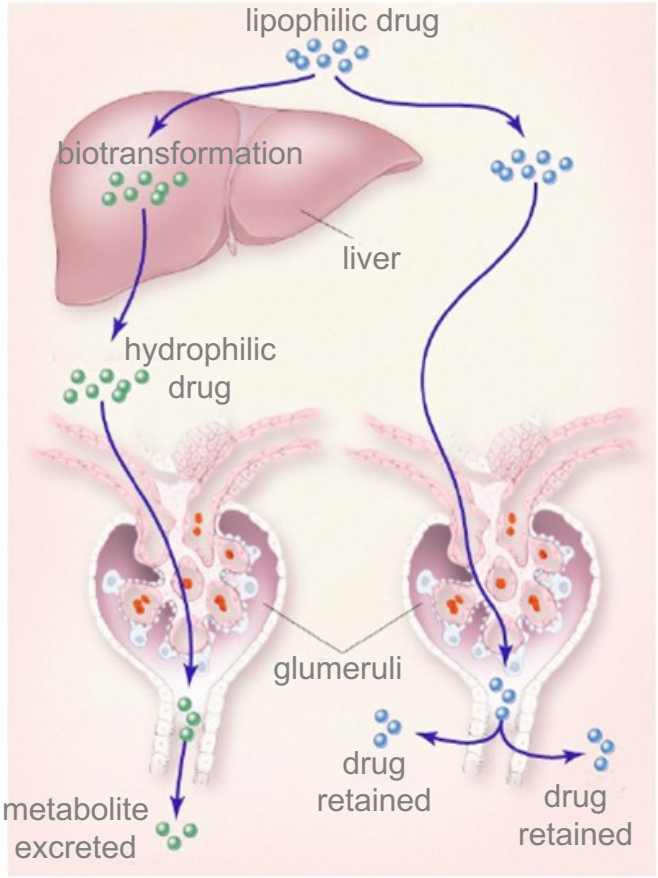
Pharmacokinetics

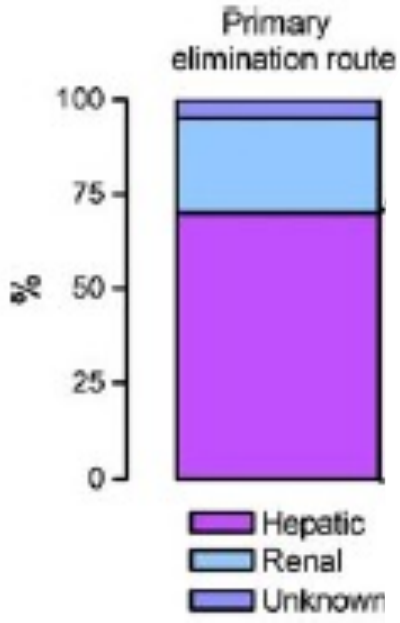
The bioavailability of a drug and / or its metabolites in the target tissue depends on :

1. Absorption
2. Distribution
3. Metabolism
4. Excretion



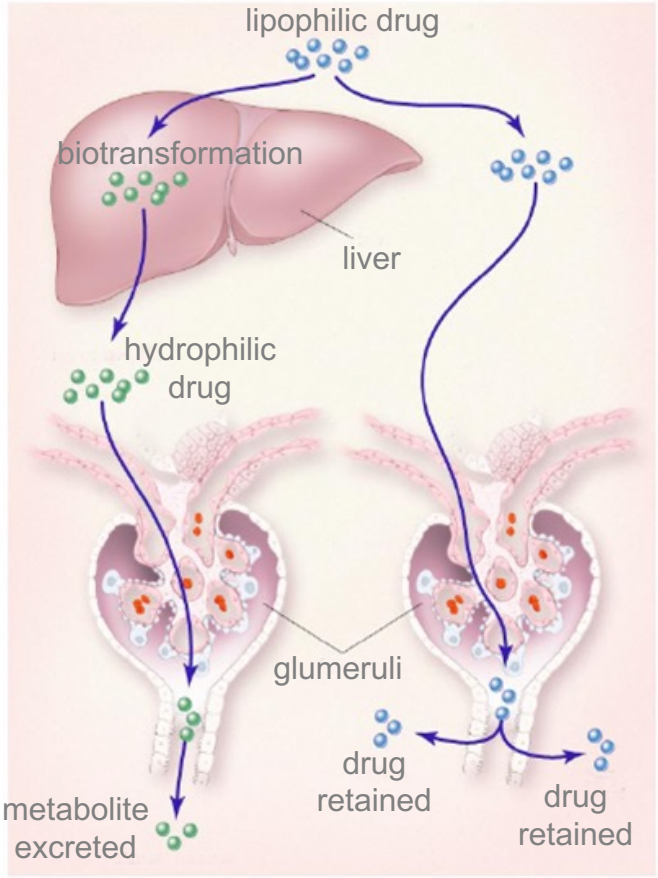
Elimination of the drug

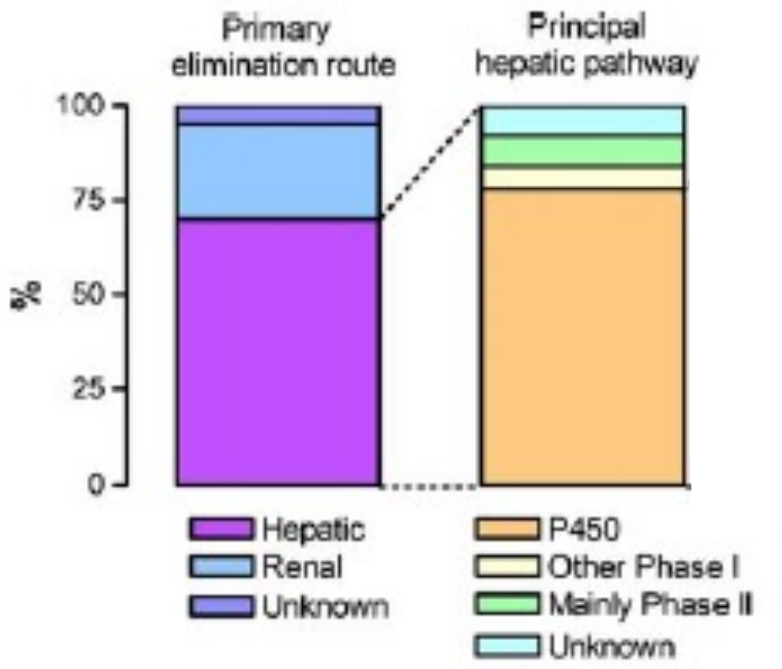




Zanger UM et al. Anal Bioanal Chem 2008

Eliminazione del Farmaco





Zanger UM et al. Anal Bioanal Chem 2008

DRUG METABOLISM

Phase 1 reactions

OXIDATIONS

REDUCTIONS

HYDROLYSIS

Phase 2 reactions

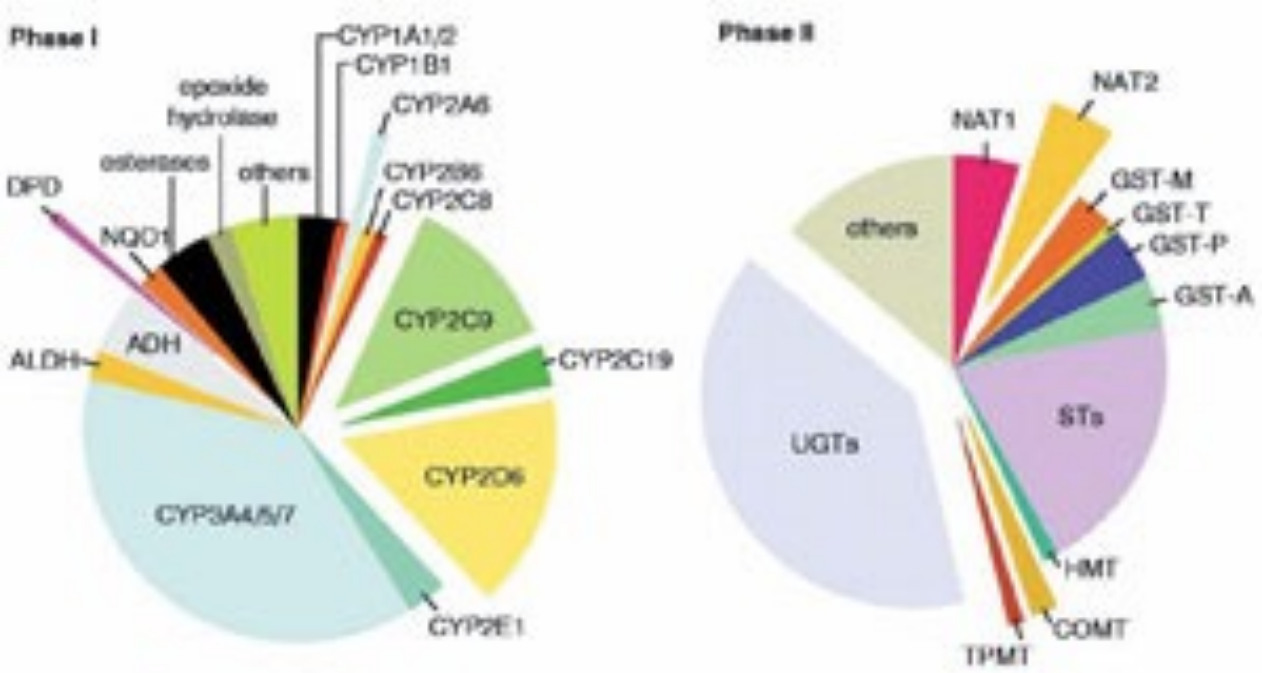
CONJUGATIONS

glucuronidation

acetylations

methylations

sulfatations



DRUG METABOLISM

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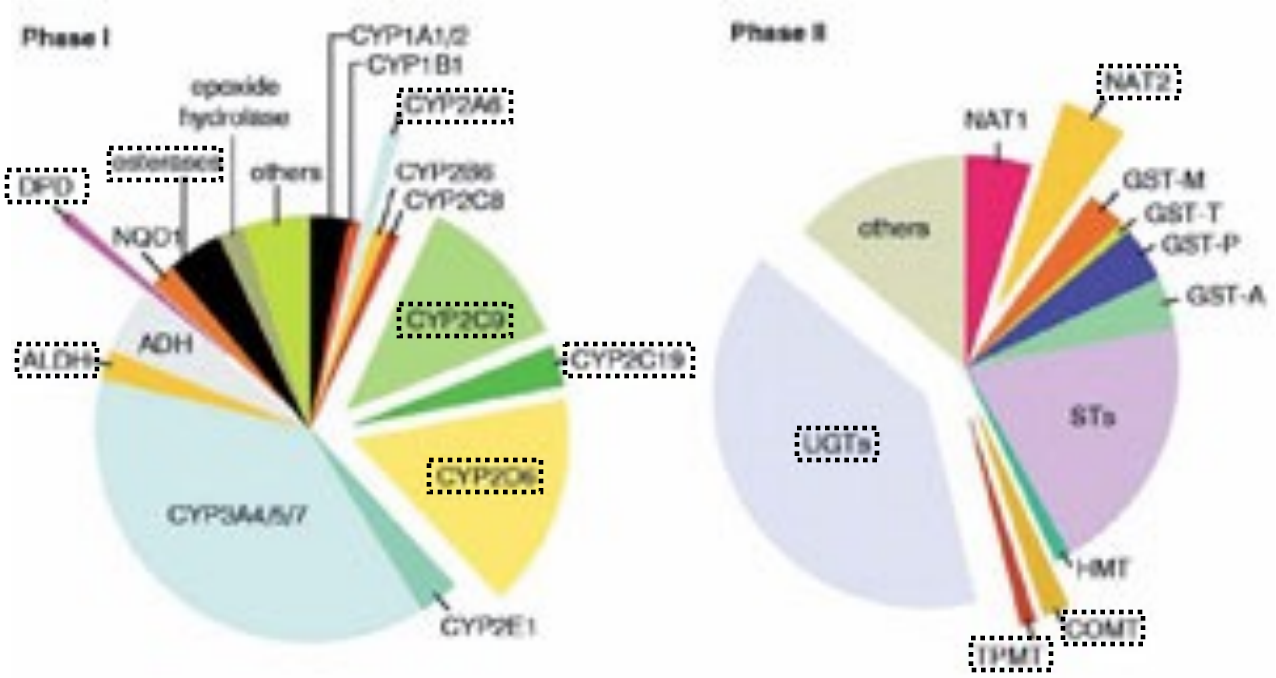
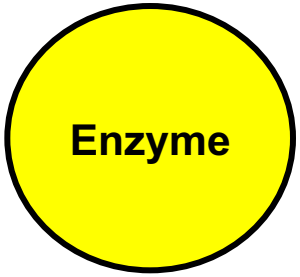


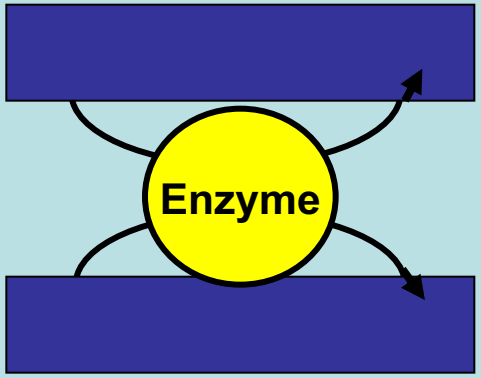
GENETIC POLYMORPHISMS OF PHASE 1 AND 2 ENZYMES: EFFECT ON ENZYMATIC ACTIVITY

Polymorphism	Enzymatic activity	
• Single nucleotide replacement (SNP)	Abolished	
• Deletion / insertion of some nucleotides	Reduced	
• Duplication of the entire gene	Increased	

"Normal" activity

Pro-drug

Drug



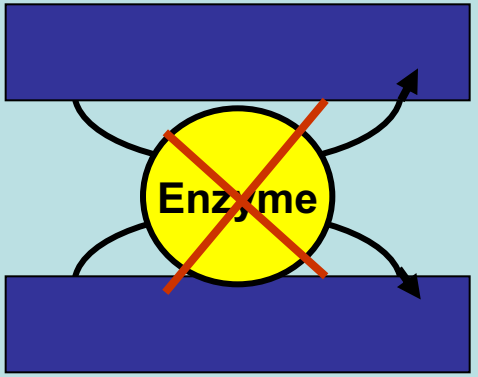
Drug

Inactivation

"Reduced" activity

Pro-Drug

Drug



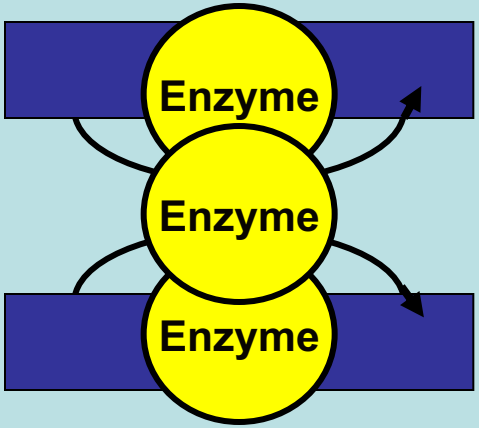
Drug

Inactivat.

"Ultra Rapid" Activity

Pro-Drug

Drug



Drug

Inactivat.

Phenotype and Metabolism of Drugs

Poor Metabolizers (PM)

Extensive Metabolizers (EM)

Ultrarapid Metabolizers (UM)

METABOLIC ACTIVITY

Phenotype and Metabolism of Drugs

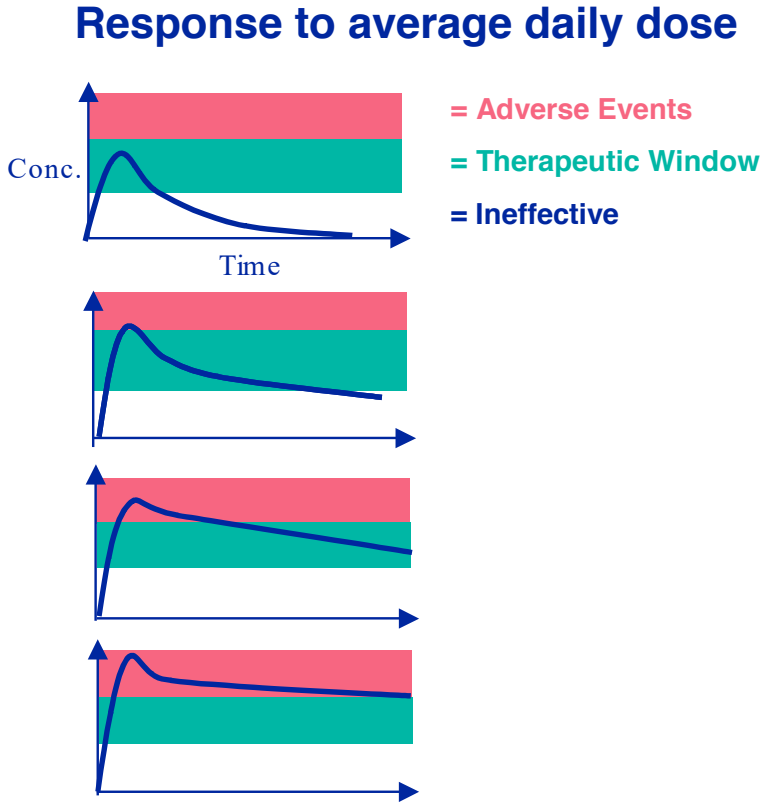
Intermediate Metabolizers (IM)

Poor Metabolizers (PM)	Extensive Metabolizers (EM)	Ultrarapid Metabolizers (UM)
		

METABOLIC ACTIVITY

Phenotype ⟷ Genotype

Phenotype	Genotype
Gene duplication	ULTRARAPID METABOLIZERS
	EXTENSIVE METABOLIZERS
	INTERMEDIATE METABOLIZERS
Homozygotes for non-functional genes or Gene deletion	POOR METABOLIZERS



Phenotype ⟷ Genotype

Phenotype **Genotype**

Gene duplication

ULTRARAPID METABOLIZERS

EXTENSIVE METABOLIZERS

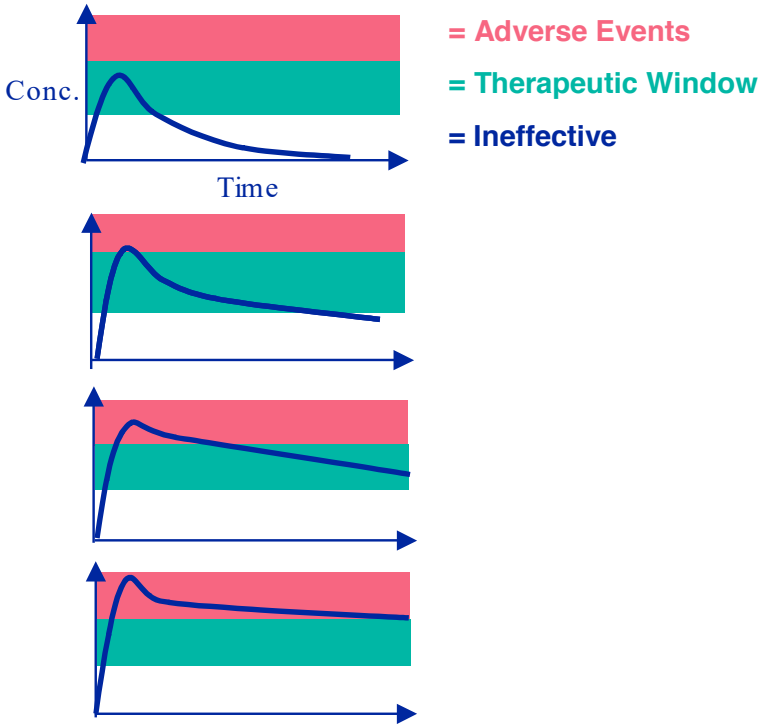
INTERMEDIATE METABOLIZERS

POOR METABOLIZERS

PHENOCOPY
Cytochrome inhibiting drugs / substances

Homozygotes for non-functional genes or Gene deletion

Response to average daily dose



Phenotype ⟷ Genotype

Phenotype **Genotype**

Duplicazione genica

ULTRARAPID METABOLIZERS

EXTENSIVE METABOLIZERS

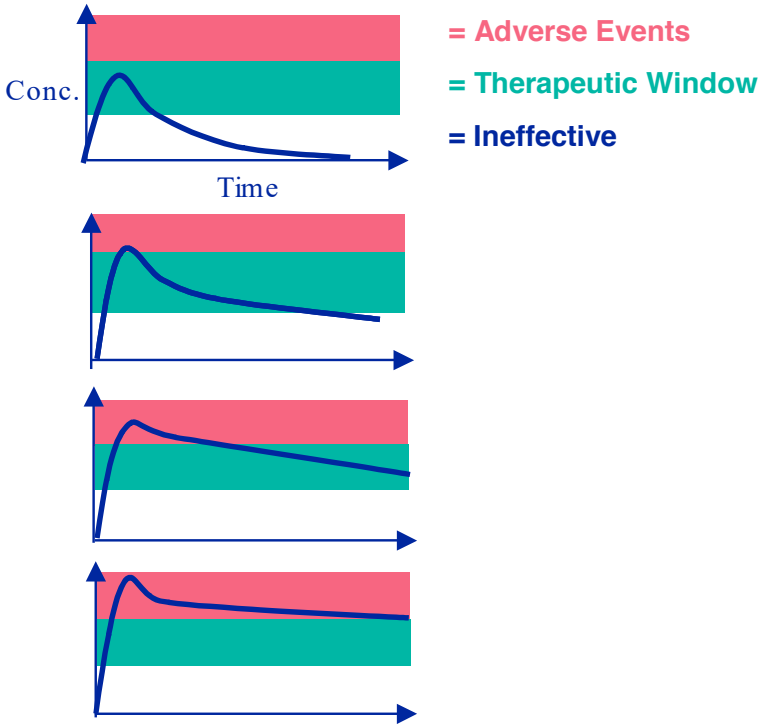
INTERMEDIATE METABOLIZERS

POOR METABOLIZERS

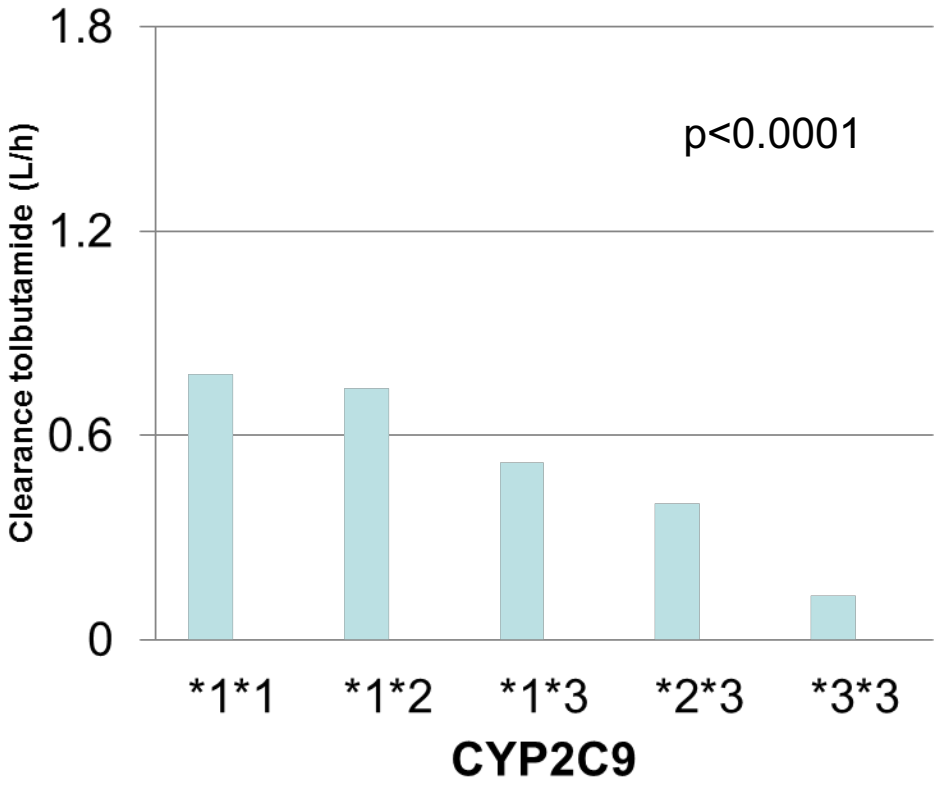
FENOCOPIA
Cytochrome inducing drugs / substances

Omozigoti per geni non funzionali o Delezione genica

Response to average daily dose



CYP2C9
GENOTYPE AND INDUCTION



Genetically determined increase in clearance (genotypes * 1 * 1 vs. * 3 * 3)

6.0

Vormfelde SV,et al.
Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers.
Clin Pharmacol Ther. 2009 Jul;86(1):54-61.

CYP2C9
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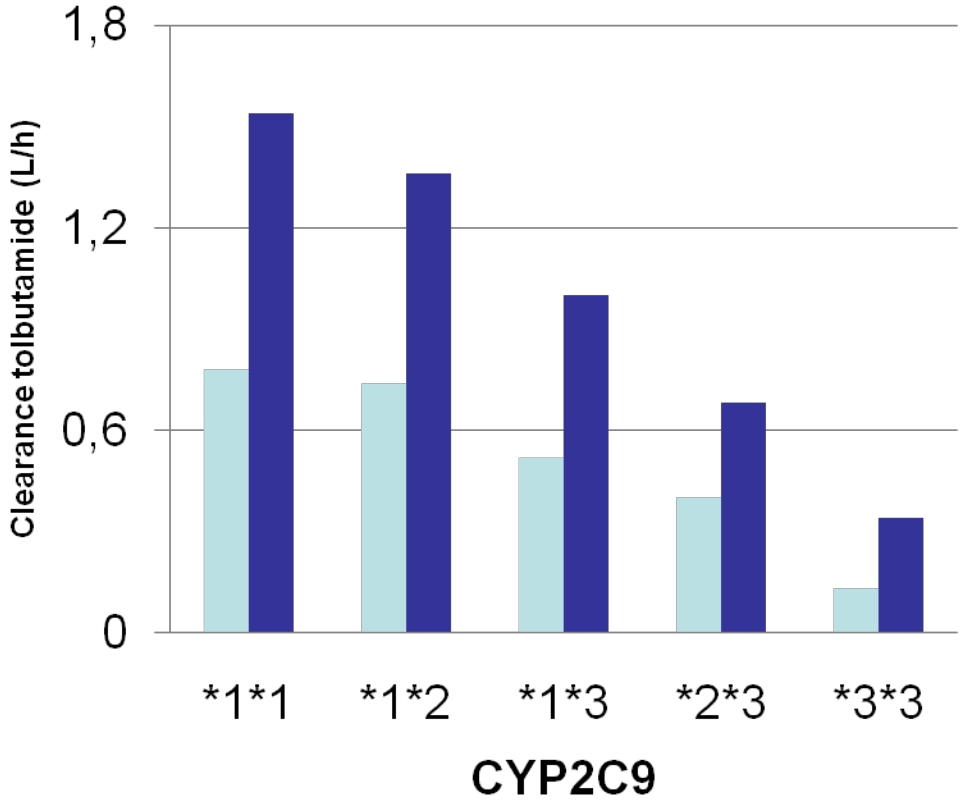


Genetically determined increase in clearance (genotypes * 1 * 1 vs. * 3 * 3)

6.0

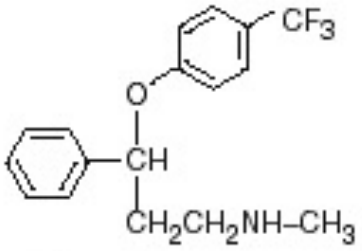
Increased clearance with rifampicin (median)

1.9

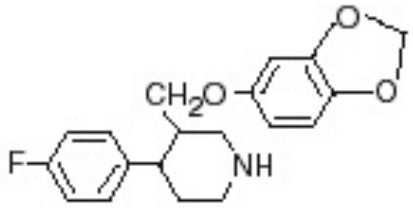
Vormfelde SV,et al.
Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers.
Clin Pharmacol Ther. 2009 Jul;86(1):54-61.

CYP2D6
GENOTYPE AND INHIBITION (SSRI)

HIGH

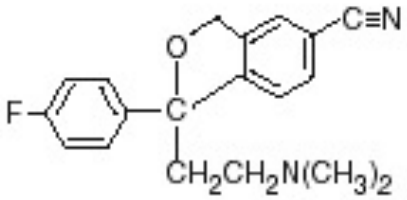


Fluoxetine **Prozac**

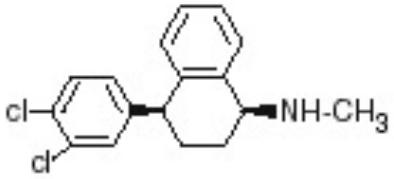


Paroxetine **Seroxat, Paxil, Aropax, Xetanor, ParoMerck, Rexetin**

INTERMEDIATE

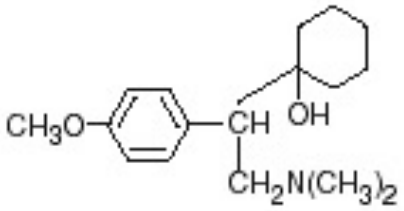


Citalopram **Citrol, Seropram, Talam**

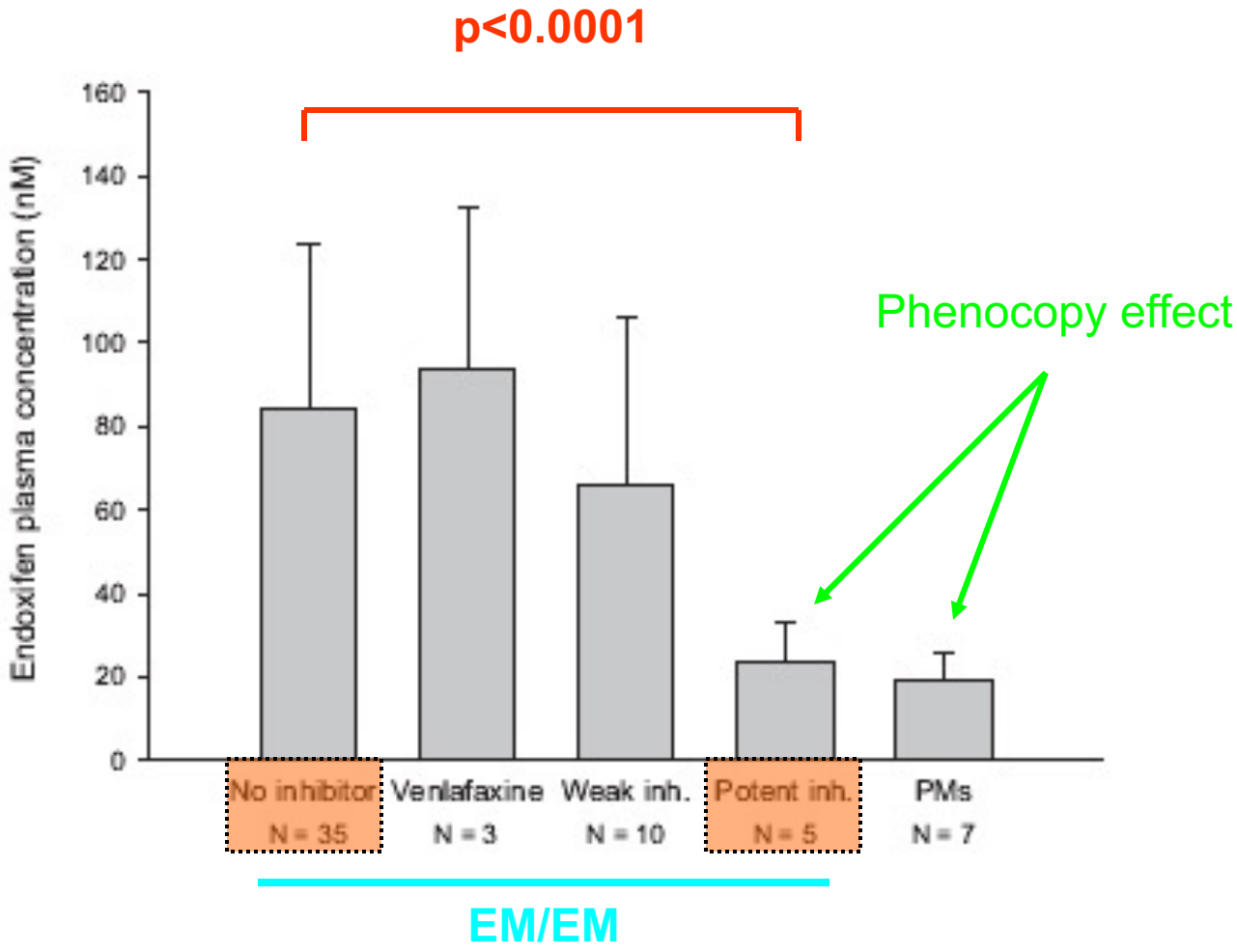


Sertraline **Zoloft, Lustral**

LOW



Venlafaxine **Efexor, Faxine**



Borges S et al. Clin Pharmacol Ther 2006

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Phase 2 reactions

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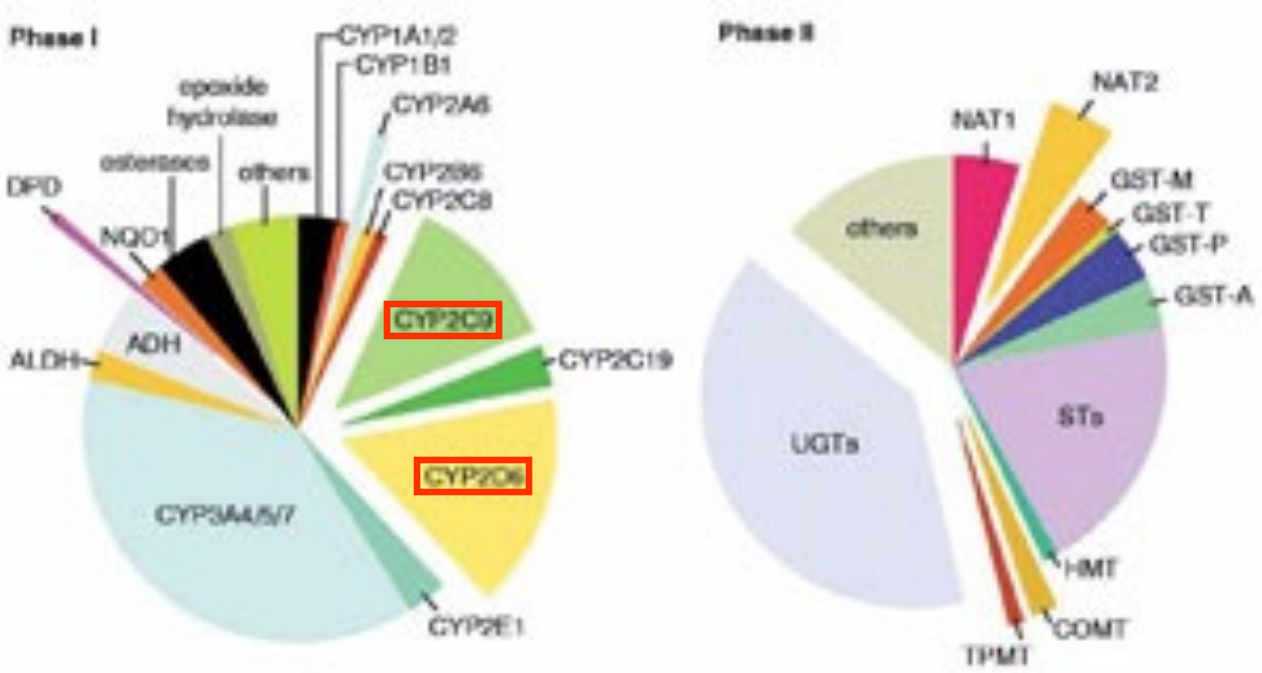
glucuronidation

acetylations

methylations

sulfatations



Cytochromes P-450 (CYPs)

- CYPs are a superfamily of microsomal enzymes relevant in the biosynthesis and degradation of endogenous compounds such as steroids, lipids and vitamins.

- CYPs metabolize many chemicals present in the diet, in the environment or taken as drugs.

- They mainly catalyze the oxidation of their substrates.

CYPs: site of action

- The metabolism of cytochromes takes place mainly in the liver, but also in the enterocytes of the small intestine epithelium.

- CYP3A, in particular, is present in enterocytes.

- Following the oral administration of a drug, CYPs, in the intestine and in the liver, can reduce the amount of drug that reaches the systemic circulation, thus influencing its effect. This is known as first pass metabolism.

CYPs are polymorphic

- To date, more than 57 active CYP450 genes and 58 pseudogenes are known in humans.
- Most of these genes are polymorphic.
- More than 434 different alleles of the genes coding for CYP450 have been described, moreover numerous functional SNPs have been identified for which the corresponding allele has not yet been defined.
- http://www.imm.ki.se/cypalleles/

CYPs: nomenclature

- **CYP** – abbreviation for cytochrome P450
- **Number** – family (sequence homology ≥ 40%)
- **Letter** – subfamily (sequence homology ≥ 55%)
- **Number** – specific gene / specific enzyme within the subfamily
- **Asterisk followed by a number and a letter**– allele of the gene
- **Example** : *CYP2D6*1A* allele *1A of CYP2D6 gene

CYP 2D6*1a

CYPs: role in drug metabolism

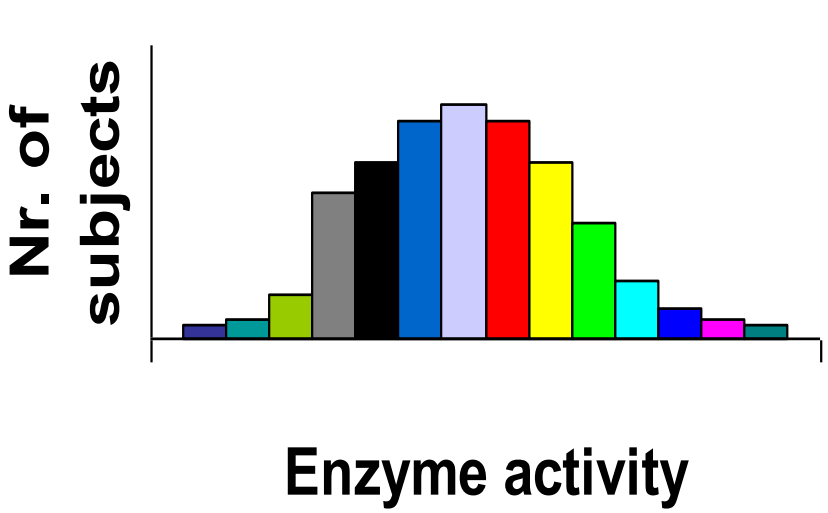
Enzyme	% of metabolised drugs	Main polymorphisms
CYP3A4	40 – 45%	Rari
CYP2D6	20 – 30%	*2xn, *4, *10, *17, *41
CYP2C9	10%	*2, *3
CYP2C19	5%	*2, *3
CYP1A2	5%	*1K
CYP2B6	2 – 4%	-
CYP2E1	2 – 4%	-
CYP2A6	2%	*4,*9
CYP2C8	1%	*3
CYP3A5	<1%	*3

CYPs: two classes of enzymes

Class I

- Well conserved.
- Without important
- functional polymorphisms.
- Active in the metabolism of procarcinogens and drugs.

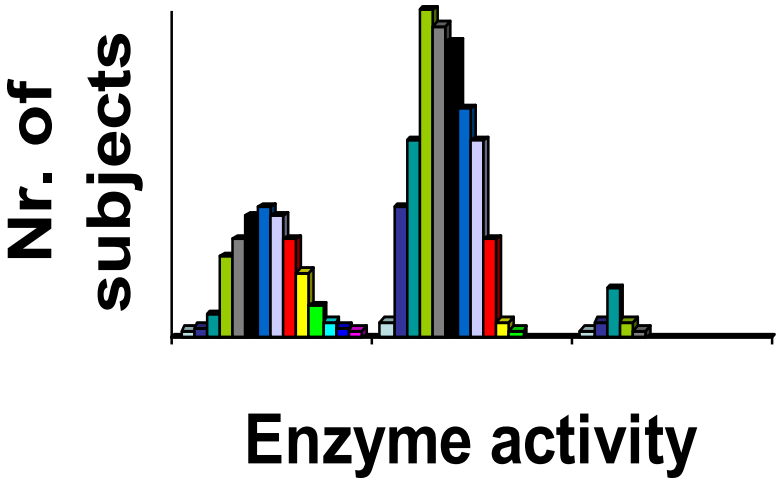
CYP1A1, CYP1A2, CYP2E1, CYP3A4



Class II

- Highly polymorphic.
- Active in the metabolism of drugs but not of procarcinogens.

CYP2B6, CYP2C9, CYP2C19, CYP2D6



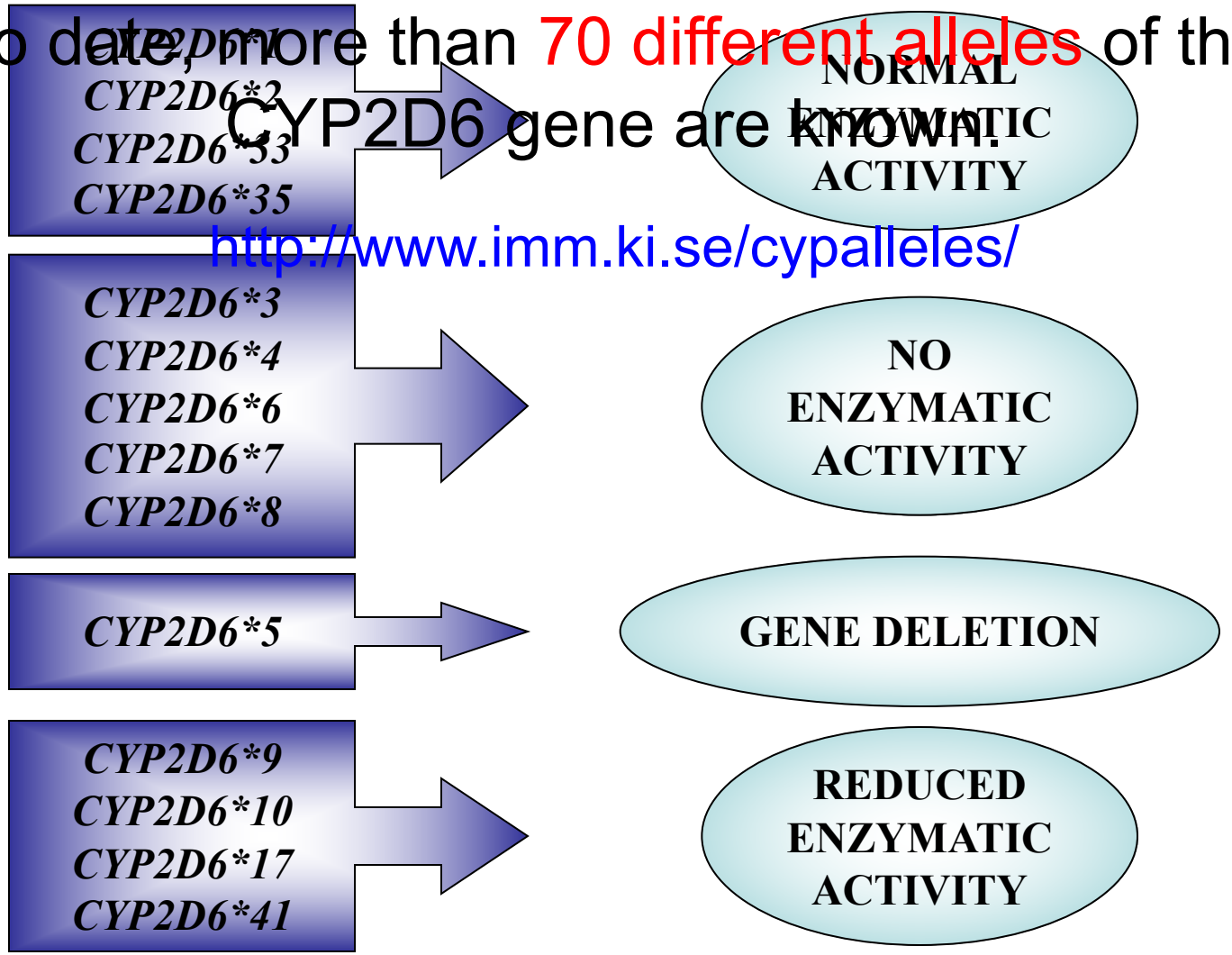
CYP2D6

- It is part of the superfamily of CYPs: microsomal enzymes relevant in the biosynthesis and degradation of endogenous compounds and in the metabolism of many xenobiotics
- Although CYP2D6 constitutes only between 2% and 5% of the total content of CYPs, approximately 20% of drugs are metabolized by CYP2D6.
- CYP2D6 has the largest number of genetic variants identified.

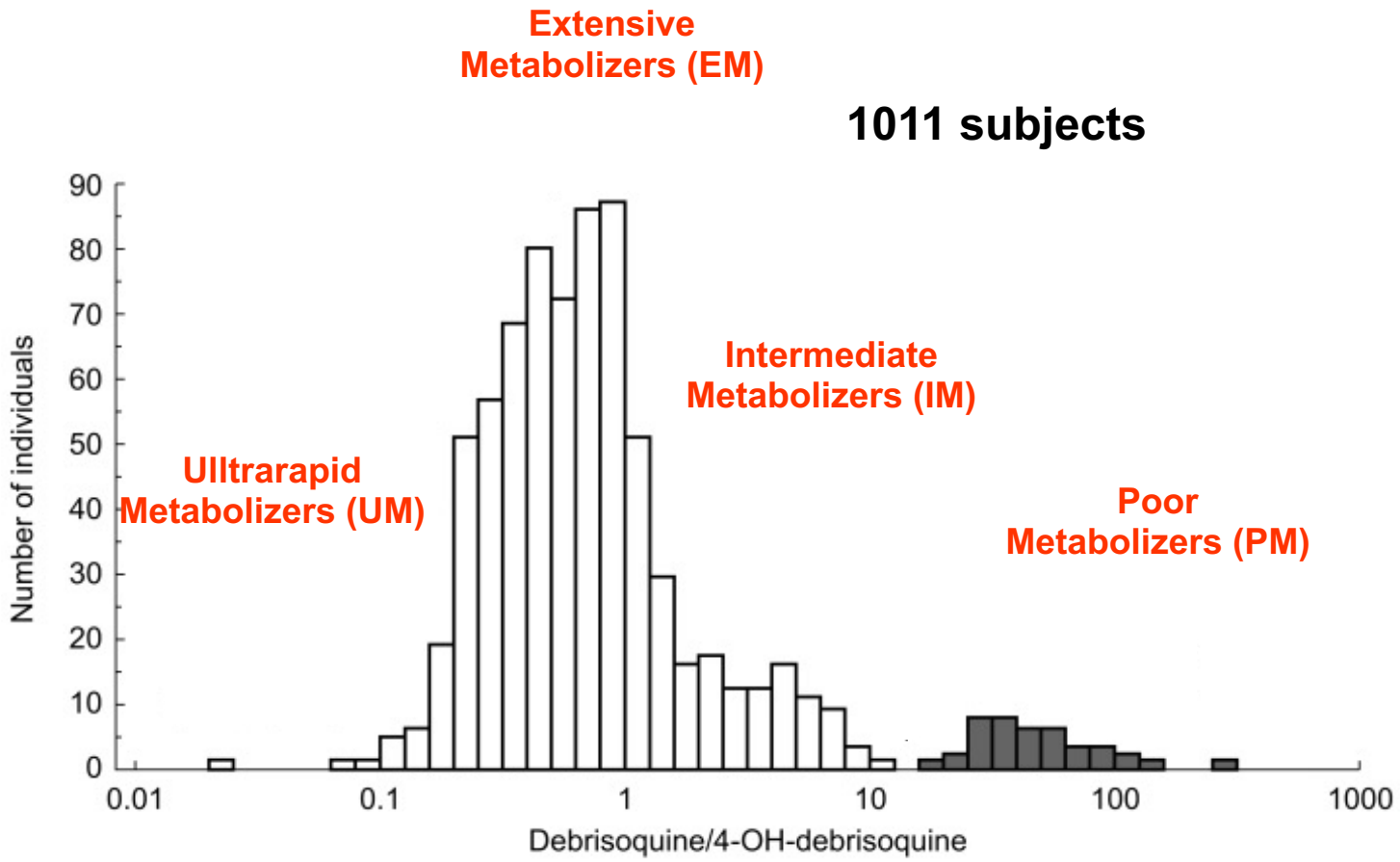
CYP2D6: alleles

To date, more than 70 different alleles of the CYP2D6 gene are KNOWN!

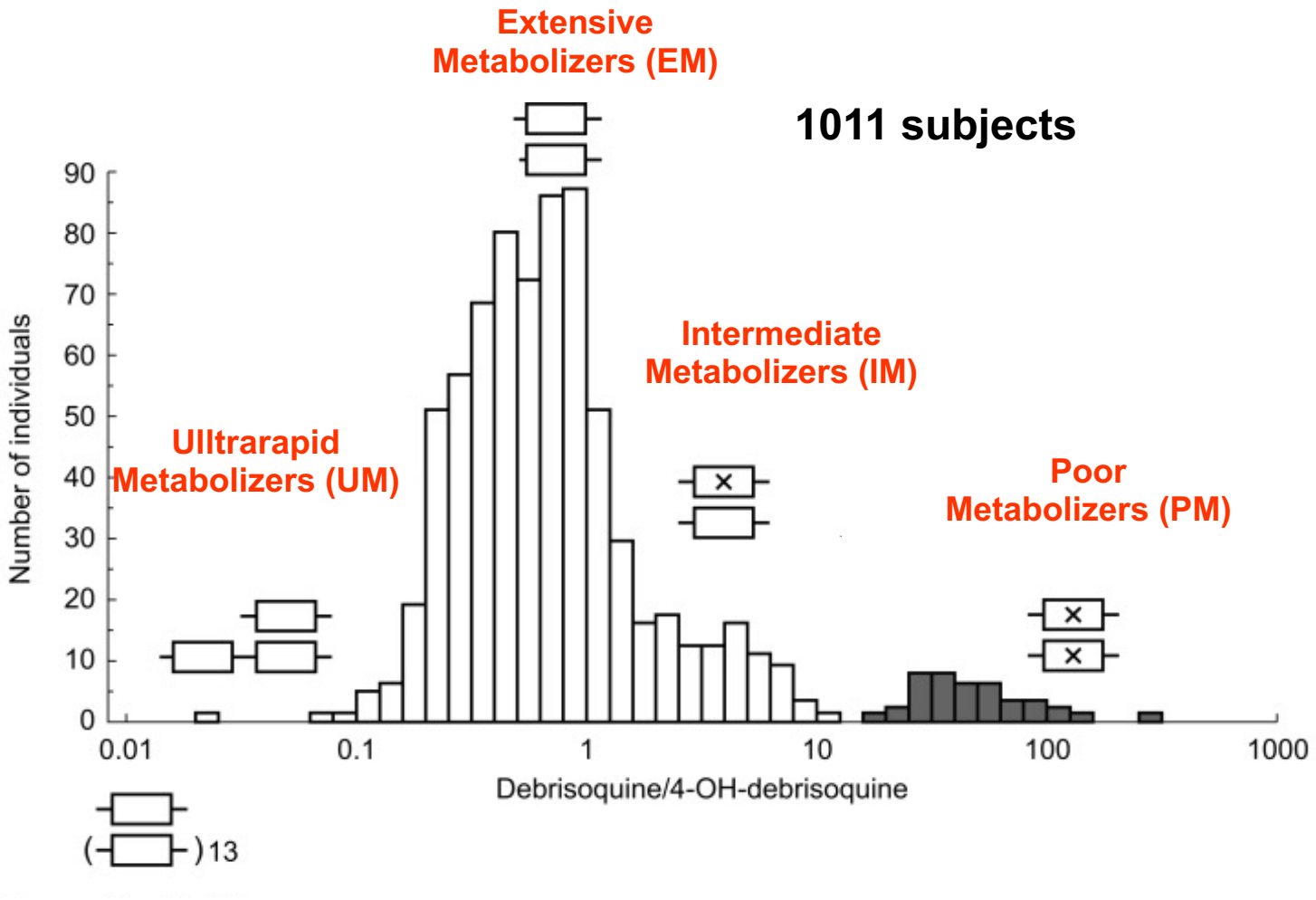
http://www.imm.ki.se/cypalleles/



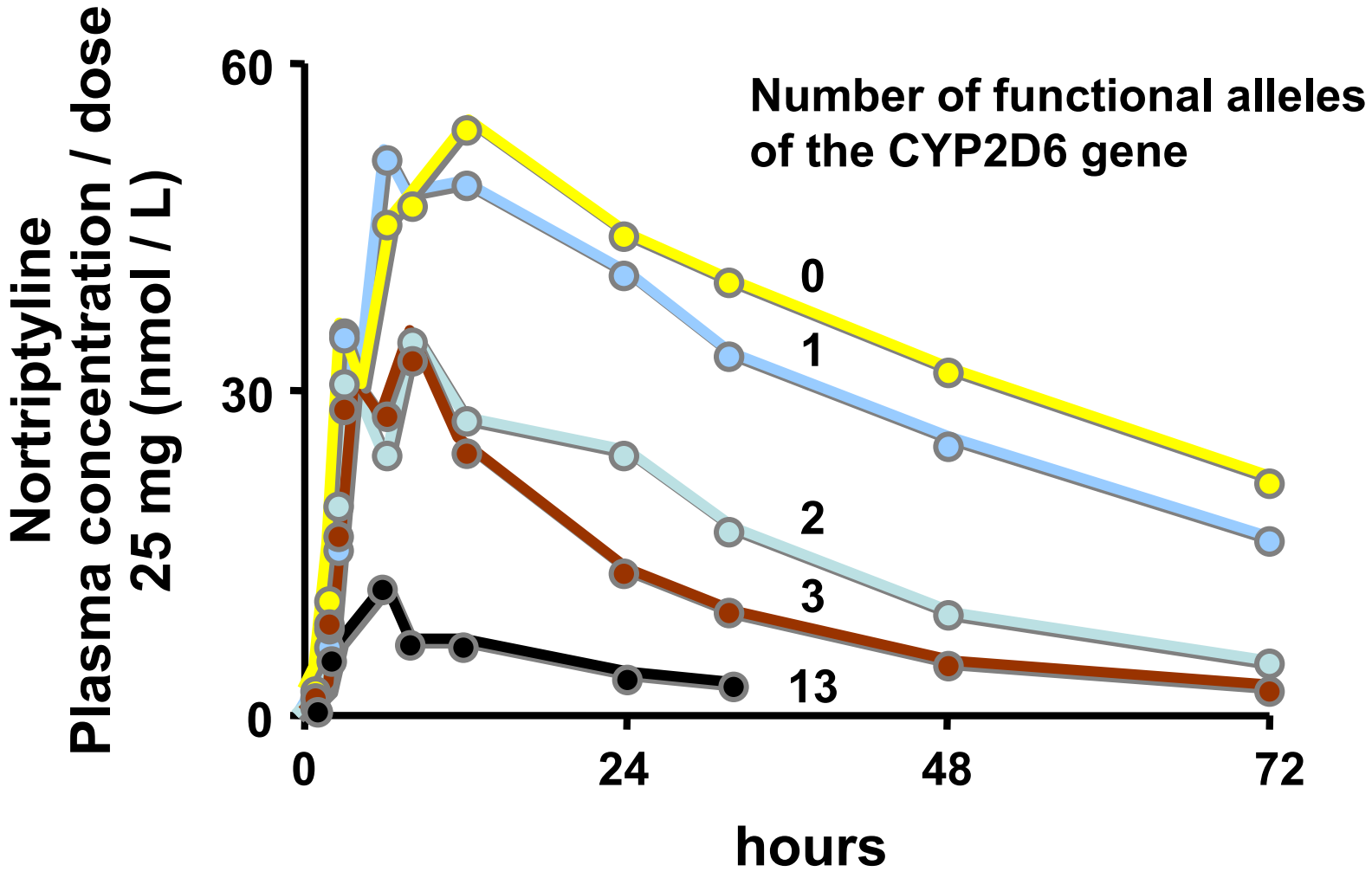
CYP2D6 activity: phenotypic variability

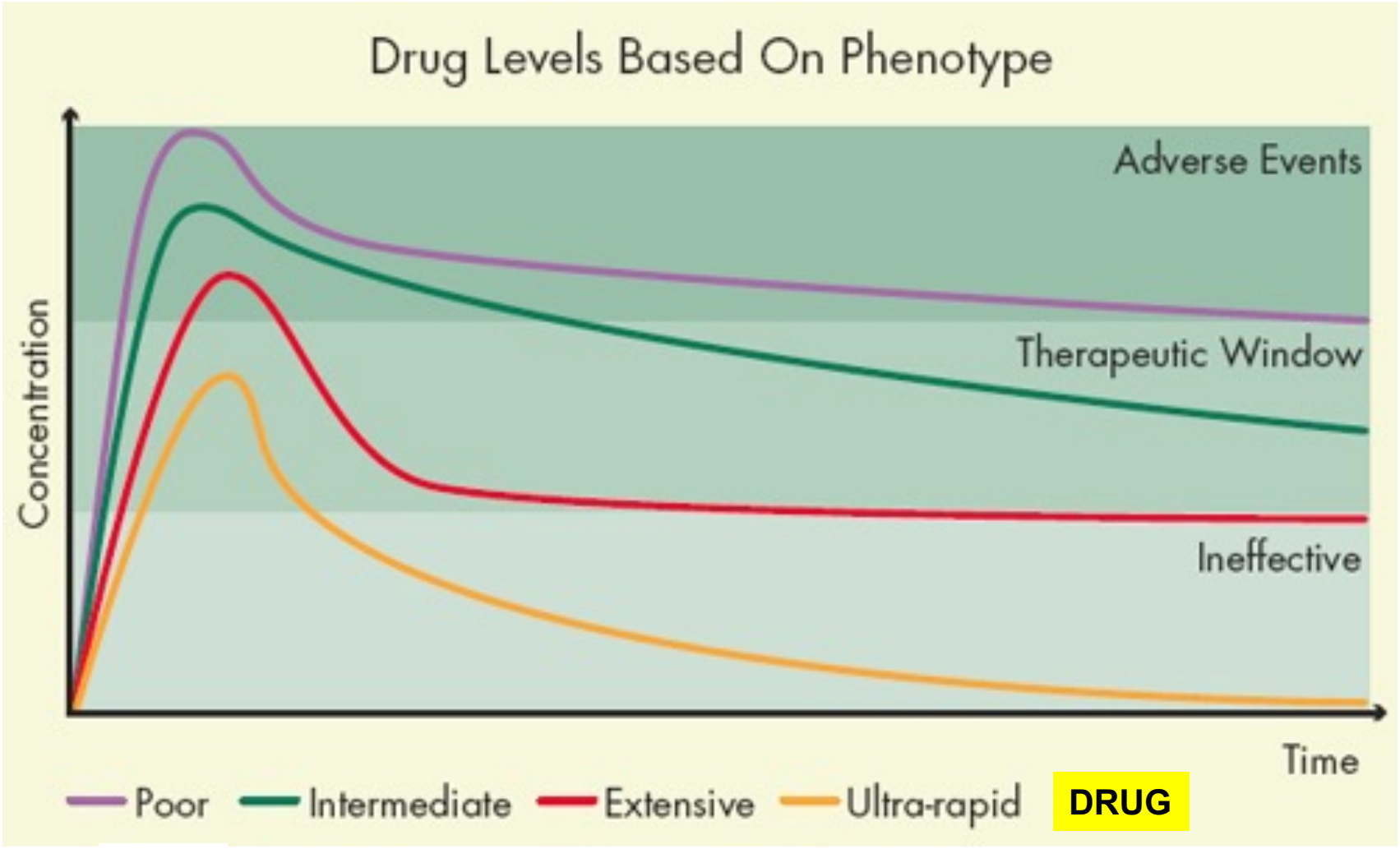


CYP2D6 activity: genetic basis of phenotypic variability



Dose effect of the number of CYP2D6 alleles





Ultra Rapid	Extensive	Intermediate	Poor	PRO-DRUG

Inter-ethnic variability of CYP2D6 phenotypes

Phenotypes	Caucasians	East Asians	African Americans	North Africa and Middle East	Mexican Americans
CYP2D6 PM	5-10	1	1-2	2	3
CYP2D6 UM	1-10	0-2	2	10-29	1
CYP2D6 Others	80-94	>90	96-97	69-88	96

PM and UM: effect on drug metabolism and number of such subjects in Europe

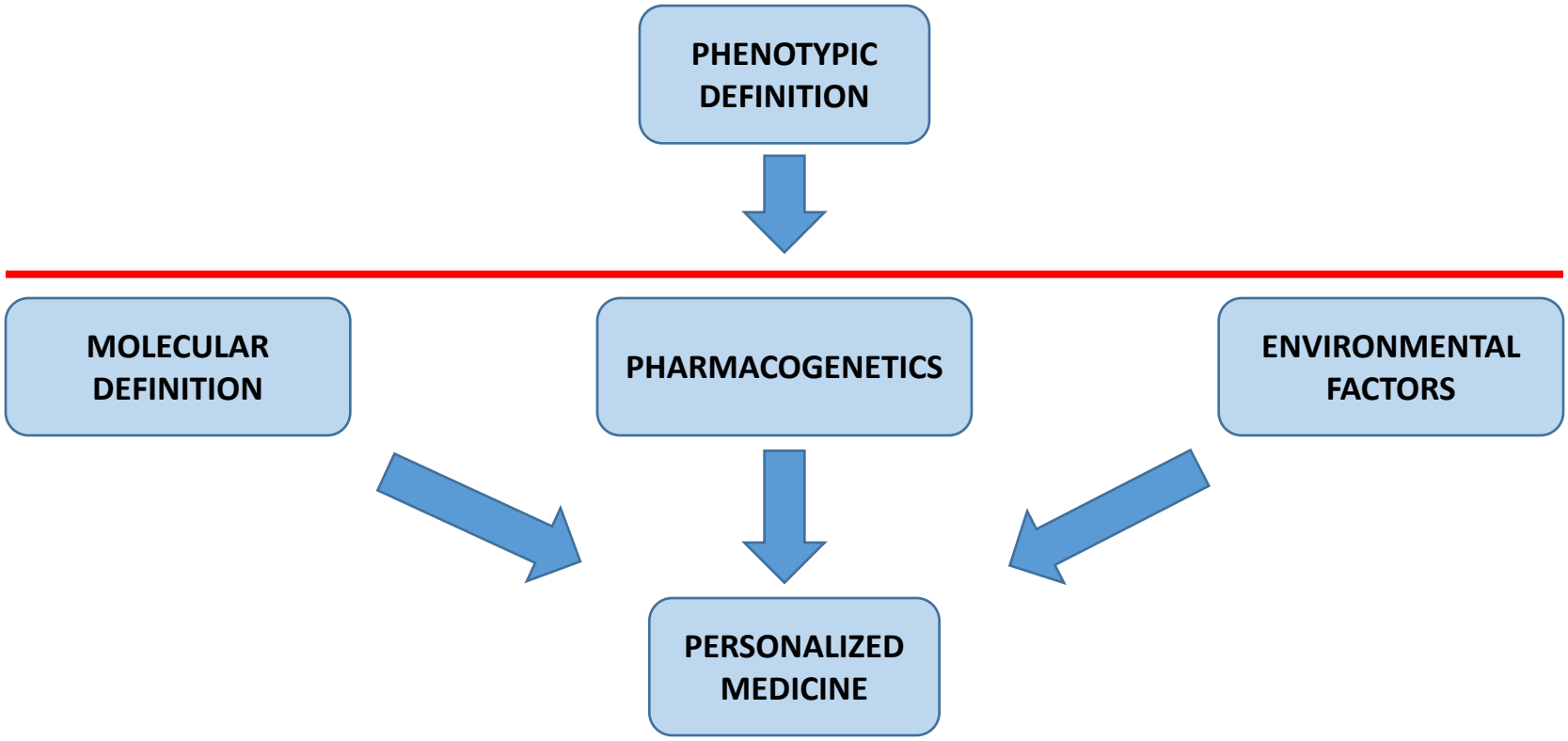
20-30 million CYP2D6 PM

- Reduced drug metabolism
- Circulating drug levels outside the standard dose therapeutic window
- Increased risk of adverse effects
- Failure to respond in case of pro-drug administration (e.g. codeine)

15-20 million CYP2D6 UM

- Accelerated drug metabolism
- Failure to respond to drug after administration of standard dosages (non-responders)

PERSONALIZED MEDICINE: *THE ROLE OF PHARMACOGENETICS*



European Heart Journal (2012) **33**, 1564–1570
doi:10.1093/eurheartj/ehs112

REVIEW

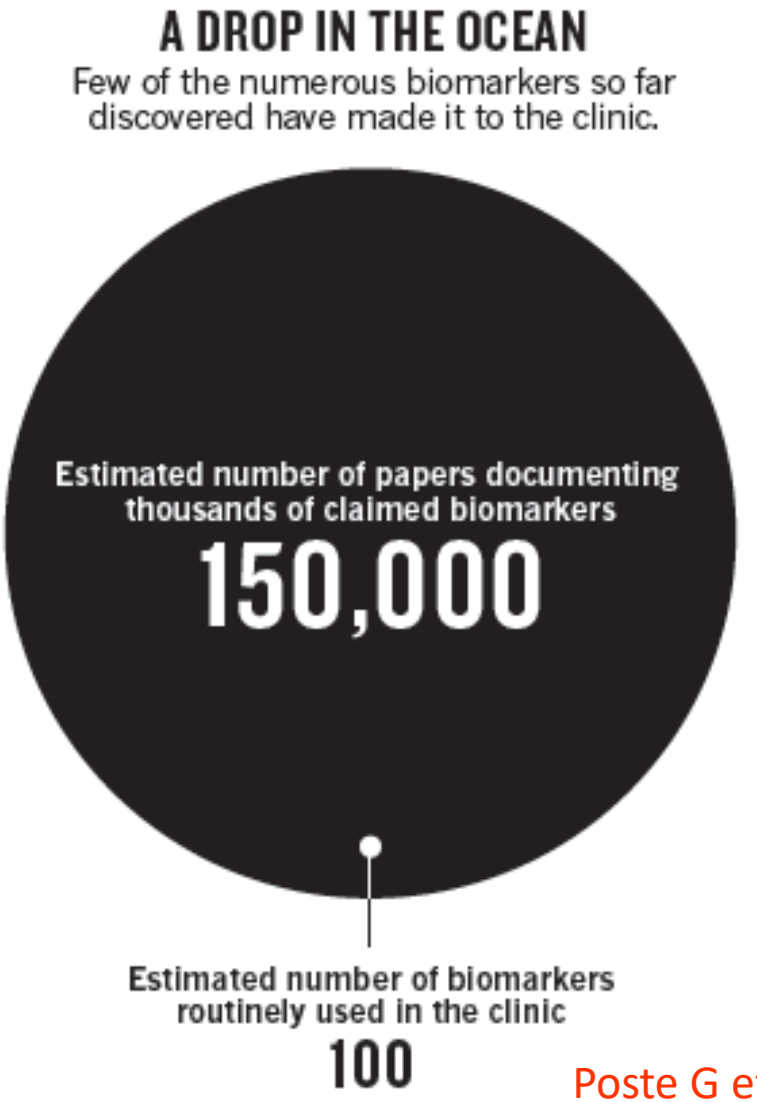
Frontiers in cardiovascular medicine

Personalized medicine: hope or hype?

Keyan Salari[1], Hugh Watkins[2], and Euan A. Ashley[3]*

[1]Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA; [2]Department of Cardiovascular Medicine, University of Oxford, Oxford, UK; and [3]Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine, Stanford University School of Medicine, Falk Cardiovascular Research Building, 300 Pasteur Drive, Stanford, CA 94305, USA

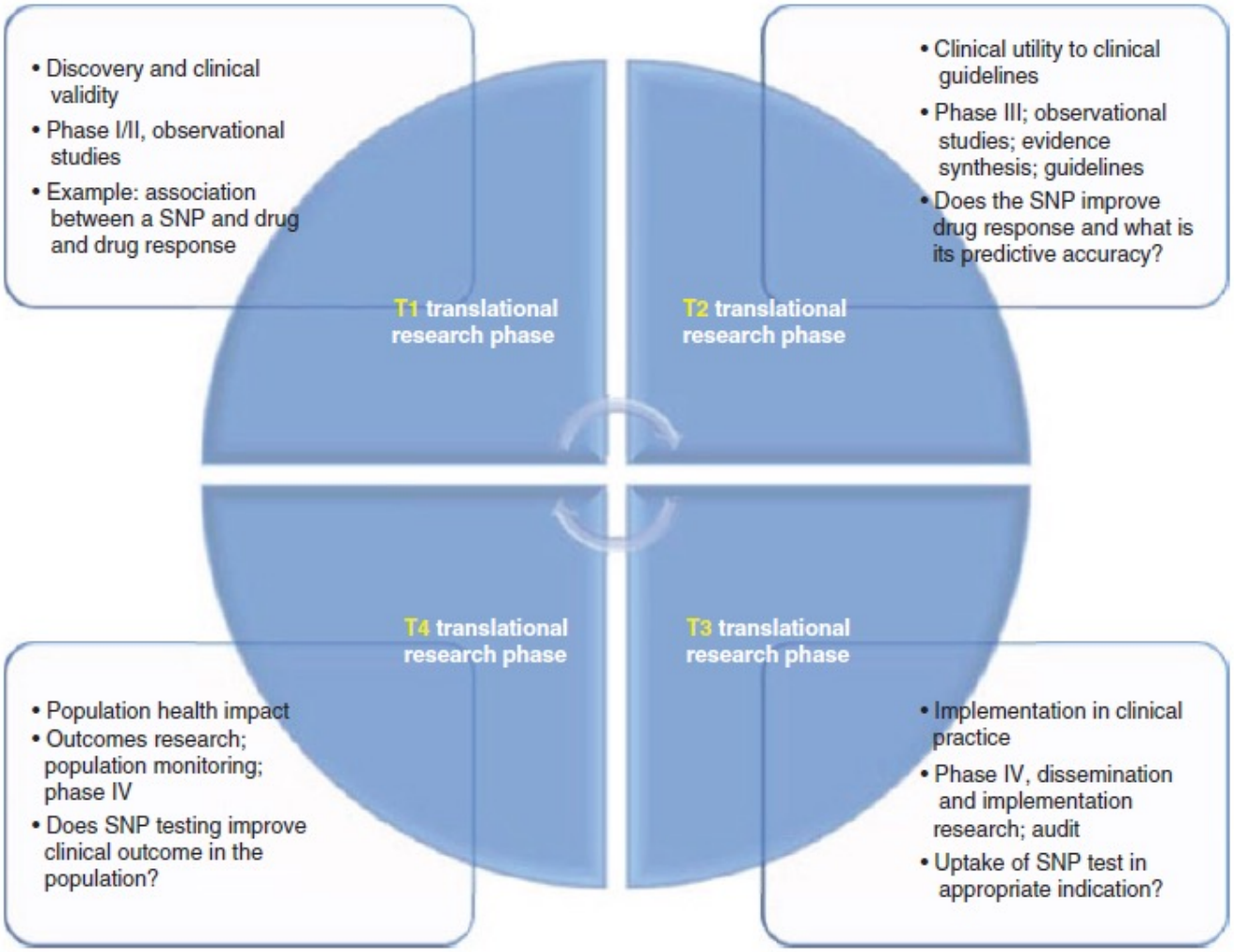
FROM BENCH TO BEDSIDE: *TRANSLATIONAL GAP*



Poste G et al., Nature 2011,469:156-157

FROM BENCH TO BEDSIDE:

A FOUR PHASES TRANSLATIONAL PATHWAY



ohamed M. Clin Pharmacol Ther. 2010 Dec;88(6):862-6

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Therein, a valid biomarker is described as a "biomarker that:

- is measured in an analytical test system with well established performance characteristics

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

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- for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results."

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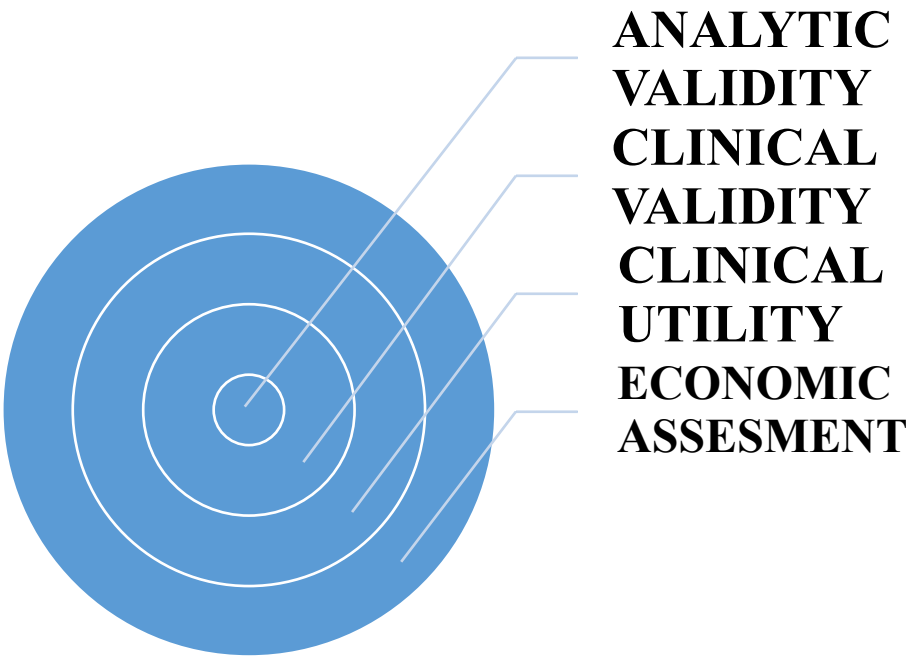
Steps Toward Clinical Pharmacogenetic Labelling



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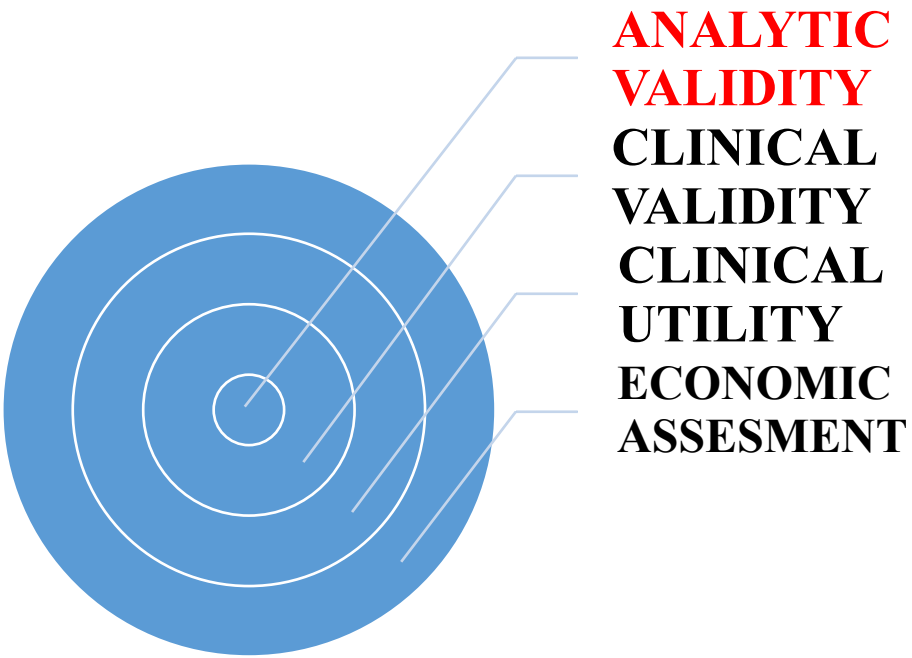
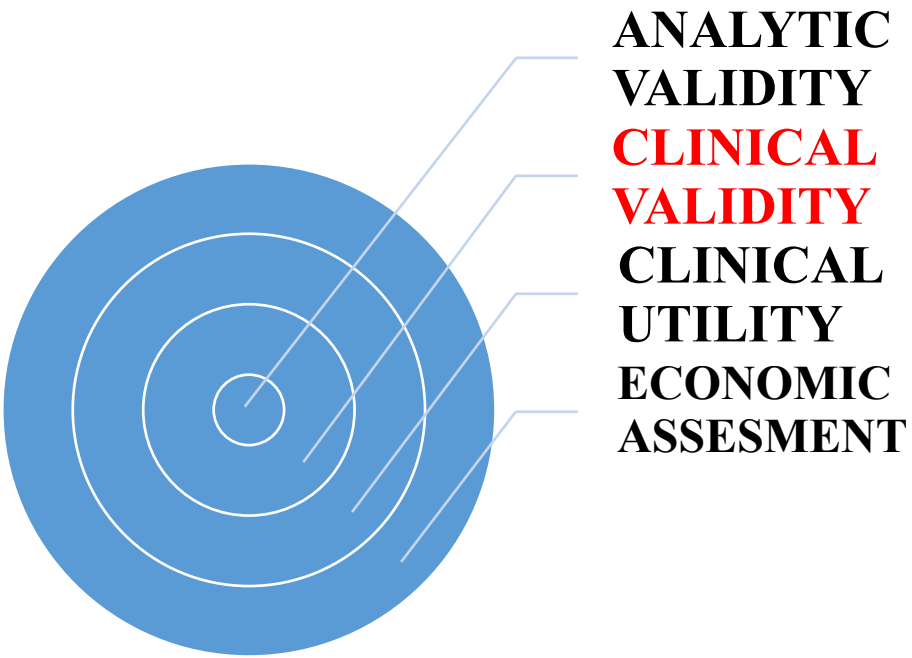


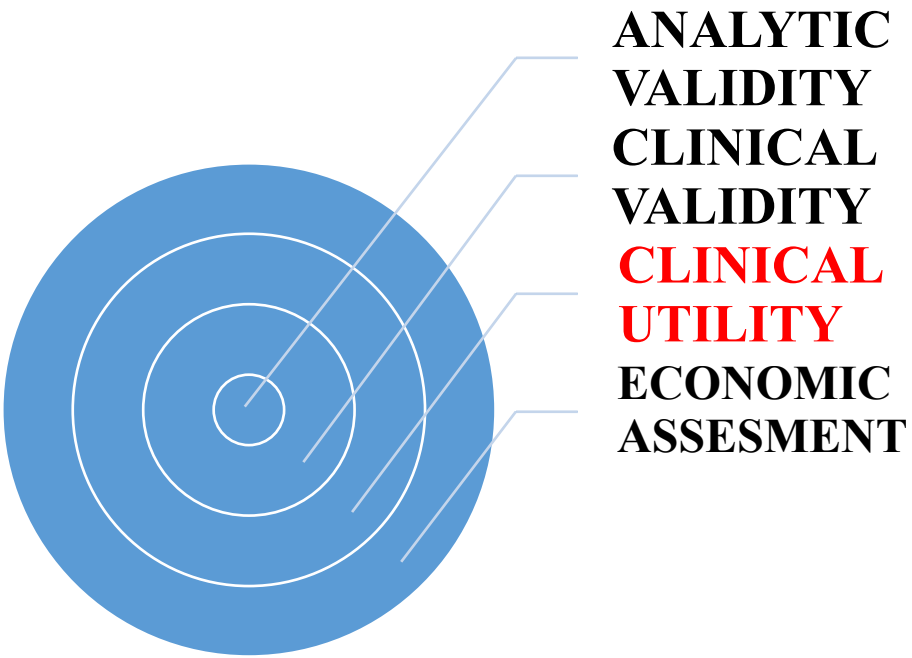
How accurately and reliably the test measures the genotype of interest

Steps Toward Clinical Pharmacogenetic Labelling



How consistently and strongly the genetic variants relate to the outcome of interest

Steps Toward Clinical Pharmacogenetic Labelling



How likely the test is to significantly improve patient outcomes

Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose.

Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling.
The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information.
Biomarkers in the table include but are not limited to germ-line or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities; selected protein biomarkers that are used to select patients for treatment are also included.

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The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information.
Biomarkers in the table include but are not limited to germ-line or somatic gene variants, functional deficiencies, expression changes, and chromosomal abnormalities; selected protein biomarkers that are used to select patients for treatment are also included.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

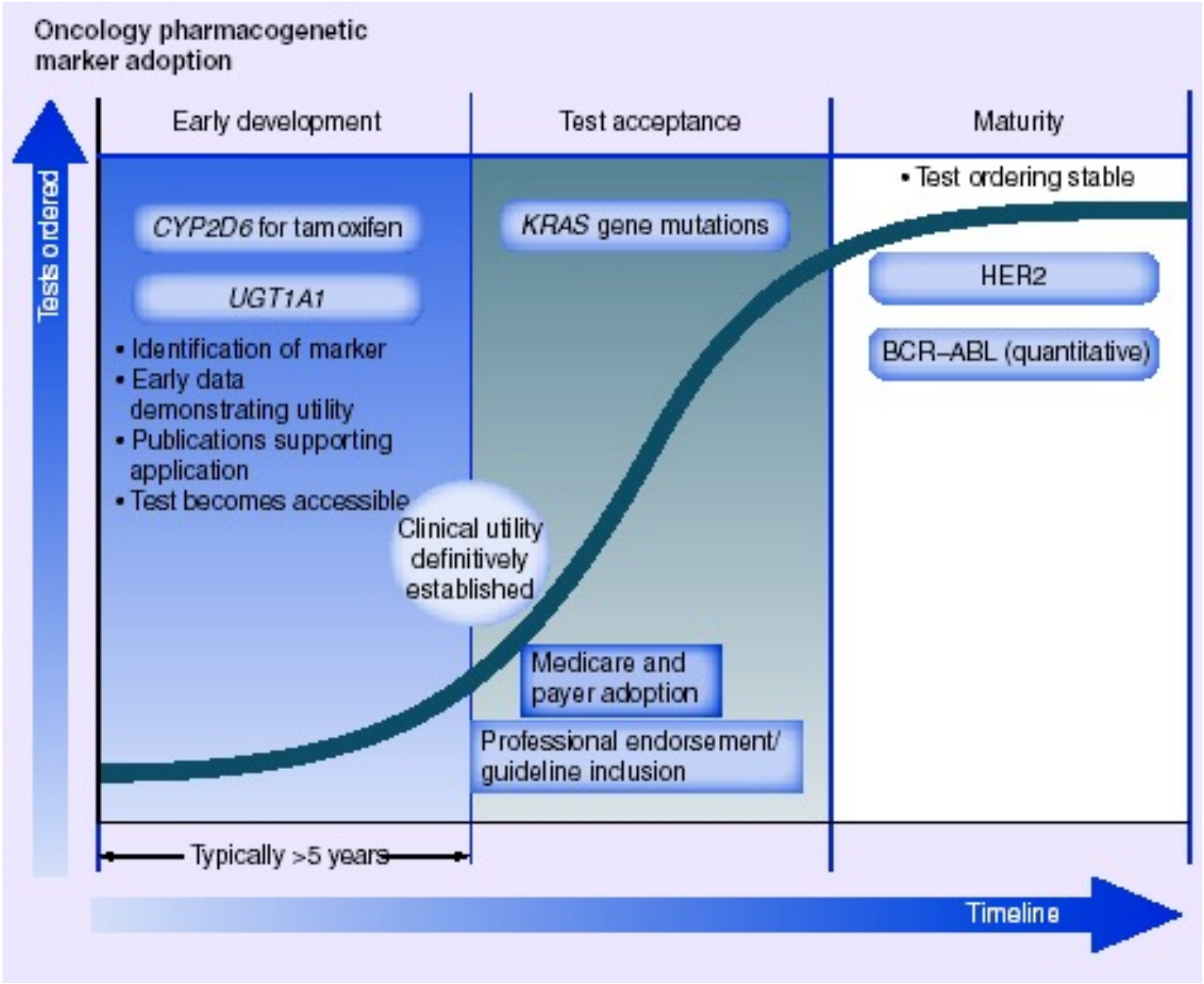
Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomic Biomarkers in Drug Labeling

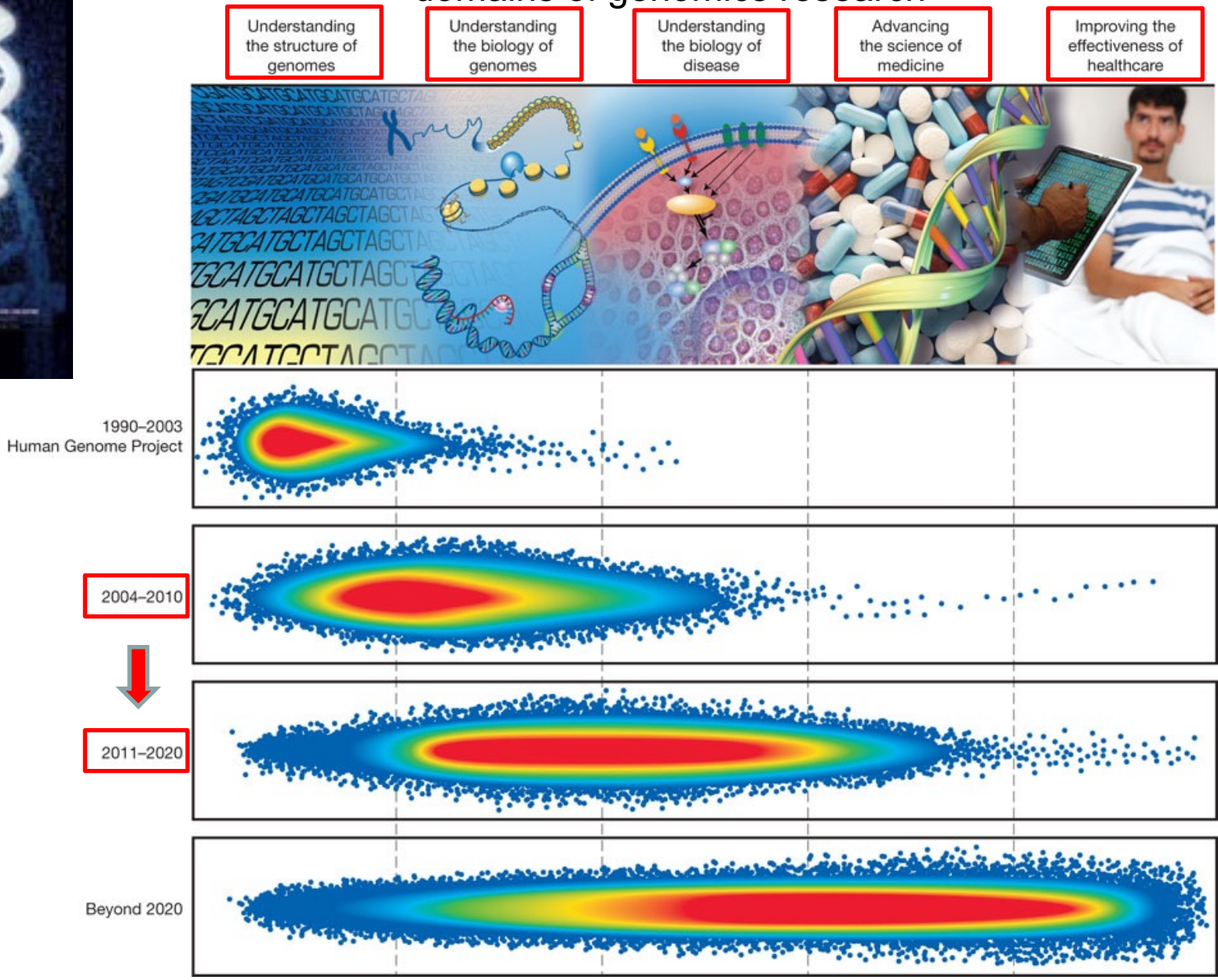
Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup‡	Labeling Sections
Azathioprine	Rheumatology	TPMT	TPMT intermediate or poor metabolizers	Clinical Pharmacology, Warnings, Precautions, Drug Interactions, Adverse Reactions, Dosage and Administration
Mercaptopurine	Oncology	TPMT	TPMT intermediate or poor metabolizers	Clinical Pharmacology, Warnings, Precautions, Adverse Reactions, Dosage and Administration
Warfarin (1)	Hematology	CYP2C9	CYP2C9 intermediate or poor metabolizers	Dosage and Administration, Drug Interactions, Clinical Pharmacology
Warfarin (2)	Hematology	VKORC1	VKORC1 rs9923231 A allele carriers	Dosage and Administration, Clinical Pharmacology

Application of a pharmacogenetic test adoption model to six oncology biomarkers

Personalized Medicine (2010) 7(4), 441–450



Schematic representation of accomplishments across five domains of genomics research



E D. Green *et al*. *Nature* **470**, 204-213 (2011) doi:10.1038/nature09764

CONCLUSIONS

The translation from bench to bedside of PGX tests to become a routine part of clinical practice will depend on:

the mandated incorporation of pharmacogenomics information in drug labeling (FDA and EMA) and the development of national and international guidelines.

Equally important is the integration of knowledge and common effort of clinicians, pharmacologists and clinical pathologists to reexamine pharmacological management programs.