Pharmacogenomics

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The Promise of Personalised Medicine

Outline of the talk:

Pharmacogenomics:

- Definition
- Polymorphism
- SNP
- Consequences of Polymorphism
- Therapeutic importance
- Bio-informatics

Present Scenario in drug therapy

- **Optimal therapy for major illness:** Still elusive
- **Schizophrenia:** 30 % do not respond
- **Hypertension:** 27 % adequately controlled
- **ADR:** 1 lakh patients die every year in USA
- **Cost of drug development :** $ 500 – 700 million for each drug …… 80% fails in clinical trial

This can be improved by

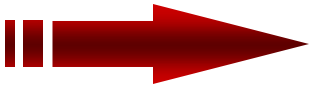
Giving the right drug

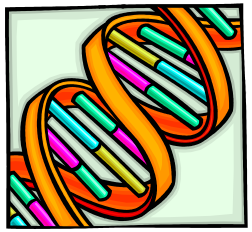
- In the Right Dose
- To the Right Patient
- At the Right Time

Patient specific selection of medication and their dosage

A NEW TOOL TO ACHIEVE THIS OBJECTIVE IS .....

PHARMACOGENOMICS





Right Drug **Right Gene**

Individualized medicine

Pharmacogenetics: **Study of the effect of variation in a single gene**

Pharmacogenomics: **Study of the effect of variation in multiple genes**

DNA sequence of all human beings is 99.9% identical

- Our DNAs differ by 0.1%.
- Does it make a difference ? Yes

0.1% difference translates into 3 million separate “spelling” differences in a genome of 3 billion bases

What is Genetic Polymorphism?

Genetic polymorphism is any mutant or variant gene that occurs with a frequency of more than 1% in the normal population

POLYMORPHISMS

SNP

- Missense
- Nonsense
- Silent
- Frameshift
- Splice site

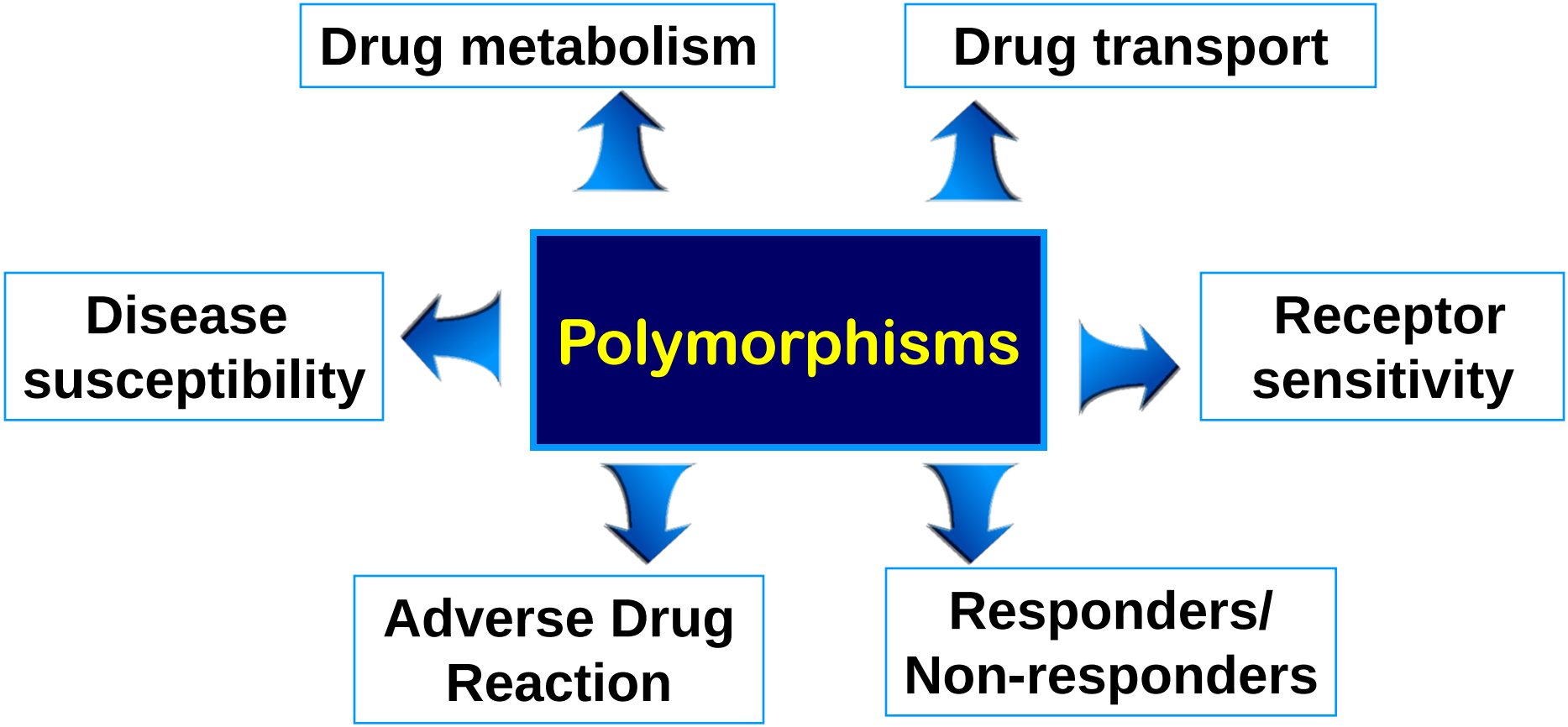
INSERTIONS

- Missense
- Nonsense
- Frameshift

DELETIONS

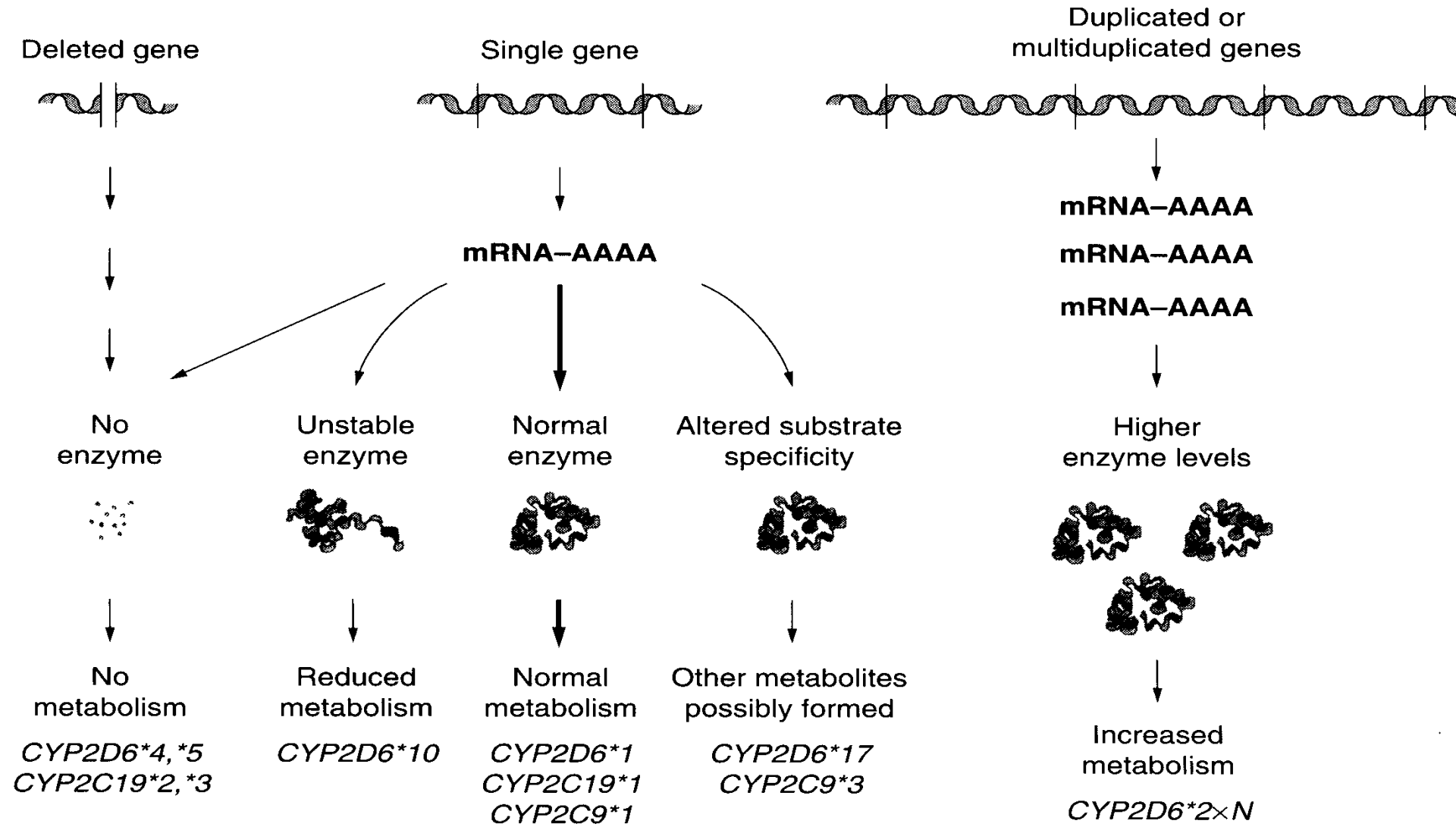
- Missense
- Nonsense
- Frameshift

Consequences of polymorphisms



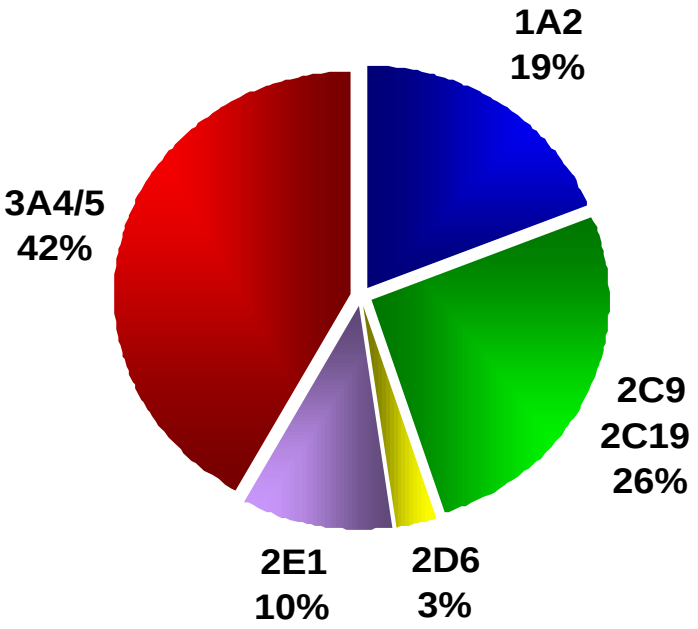
DRUG METABOLISM

Molecular mechanisms that can alter drug metabolism

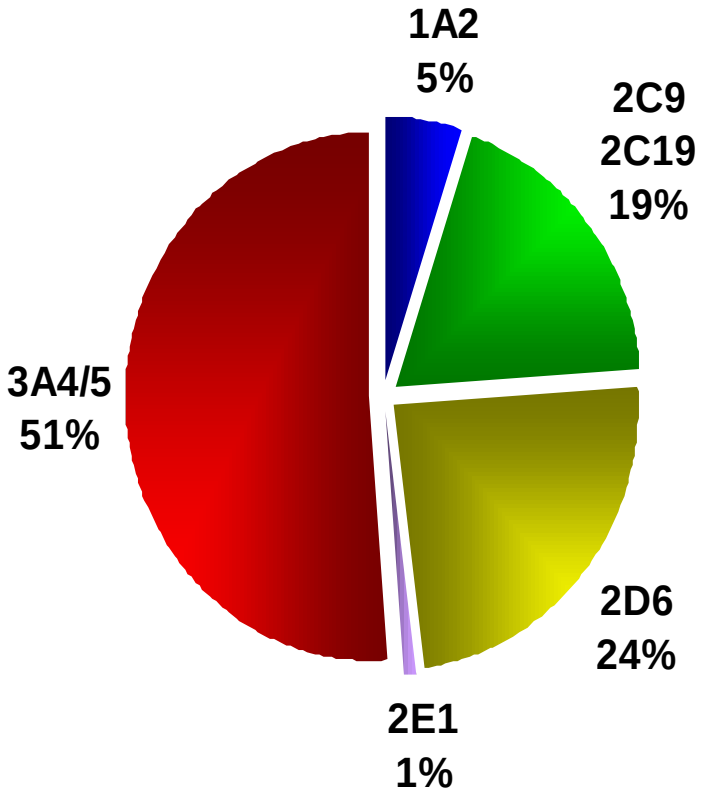


Primary CYP Enzymes in Drug Metabolism

% of total enzyme



% of drugs metabolised



Phase - I enzymes known to have polymorphism

- **CYP2C9:** Phenytoin, warfarin, NSAIDs etc
- **CYP2C19:** Omeprazole, proguanil, diazepam
- **CYP2D6:** More than 60 drugs
- **CYP2E1:** Ethanol
- **CYP1A6:** Nicotine

Mutant alleles of Phase I enzymes

CYP 450 gene	Mutant Alleles	Substrates
CYP2C9*1	*2, *3, *4, *5, *6	Warfarin, losartan phenytoin, tolbutamide

Red: Absent; **Blue**: Reduced; **Green**: Increased activity

Phase II enzymes known to have polymorphism

- **NAT2:** Isoniazid, hydralazine,
- **GST:** D-Penicillamine
- **TPMT:** Azathioprine, 6-MP
- **Pseudocholinesterase:** Succinyl choline
- **UGT1A1:** Irinotecan

Mutant alleles of Phase II enzymes

Gene	Mutant Alleles	Substrates
NAT2	*2, *3, *5, *6,*7, *10,*14	Isoniazid, hydralazine,

Red: Absent; Blue: Reduced;

Potential consequences of polymorphic drug metabolism

- Extended pharmacological effect
- Adverse drug reactions
- Drug toxicity
- Increased effective dose
- Lack of prodrug activation
- Metabolism by alternative, deleterious pathways
- Exacerbated drug-drug interactions

CYP2D6 – Implications for Poor metabolisers

- **Decreased elimination of parent compound.**
  Beta blockers: metoprolol, timolol
  Antidepressants: nortriptyline, clomipramine

- **Decreased prodrug activation:**
  Codeine, encainide

- **Decreased elimination of active metabolite**:
  imipramine

- **Decreased elimination of parent compound & active metabolite:**
  Amitriptyline & nortriptyline

CYP2D6 Vs Starting dose of nortriptyline

Normal CYP2D6 : 150 mg/day

***Mutant* CYP2D6 : *10-20* mg/day**

CYP2C9 Vs Phenytoin maintenance dose

Genotype	Mean dose (mg/d)
CYP2C9 *1/*1	314 mg/d
CYP2C9 *1/*2	193 mg/d
CYP2C9 *2/*3	150 mg/d

Why diazepam metabolism is slower in Asians compared to Caucasians?

Because Asians have high frequency of mutant alleles CYP2C19

Genotype	Allele	Diazepam $t_{1/2}$
EM	CYP2C19 *1/*1	20 hours
PM	CYP2C19 *2/*2	84 hours

CYP2C19 Vs Treatment of H.Pylori

Omeprazole 20 mg/day and amoxicillin 2gm/day

Genotype	Allele	Cure rate
Wild type	CYP2C19 *1/*1	29 %
Htz Mutant	CYP2C19 *1/*2	60 %
Hmz Mutant	CYP2C19 *2/*2	100 %

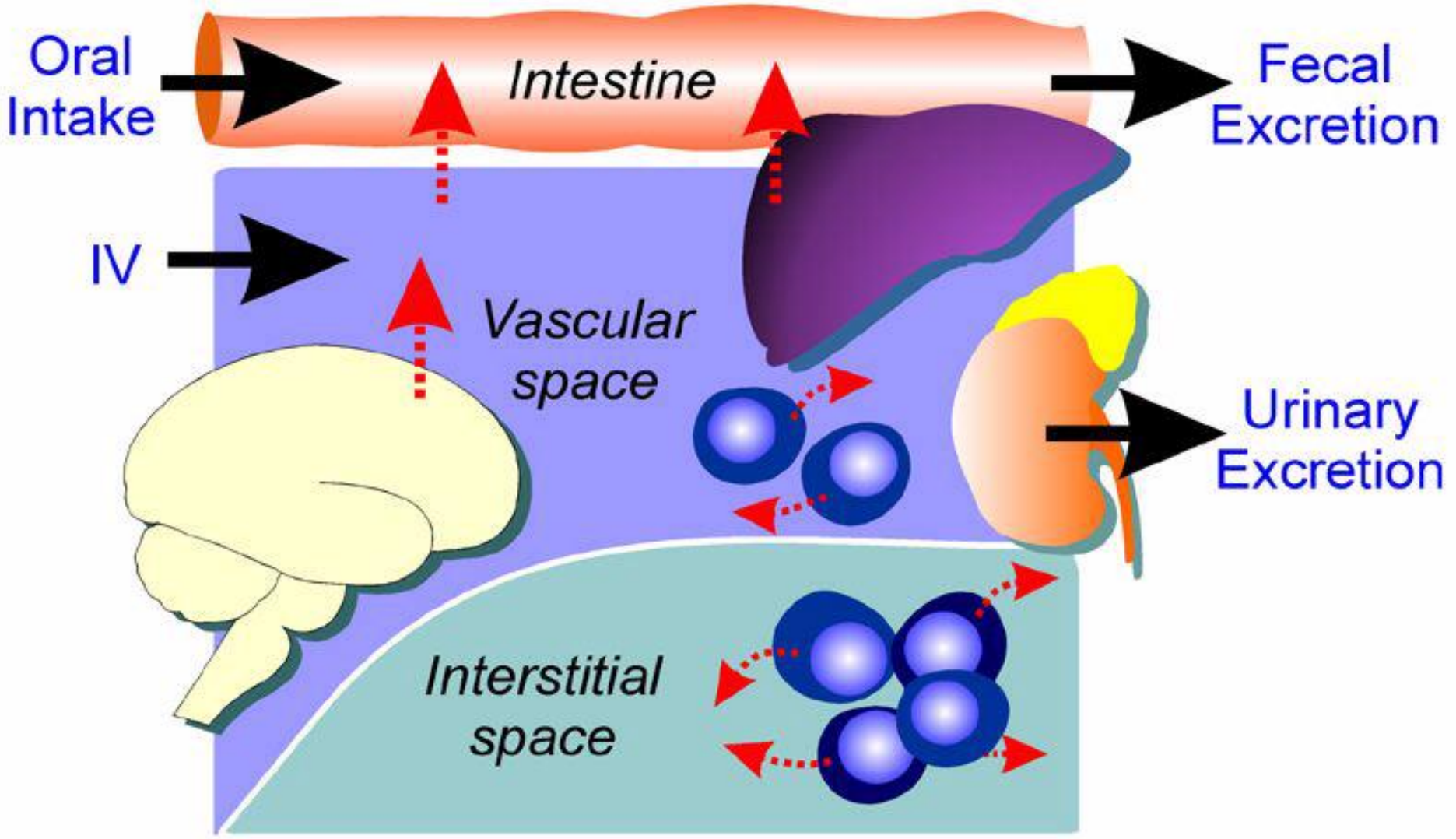
Due to higher concentration of omeprazole

DRUG TRANSPORTERS

- **There are 7 different ABC transporters**
- **MDR1 is important among them.**

MDR1 **encodes a P-glycoprotein that mediates ATP-dependent efflux of drugs.**

Expressions of P-glycoprotein in different tissues



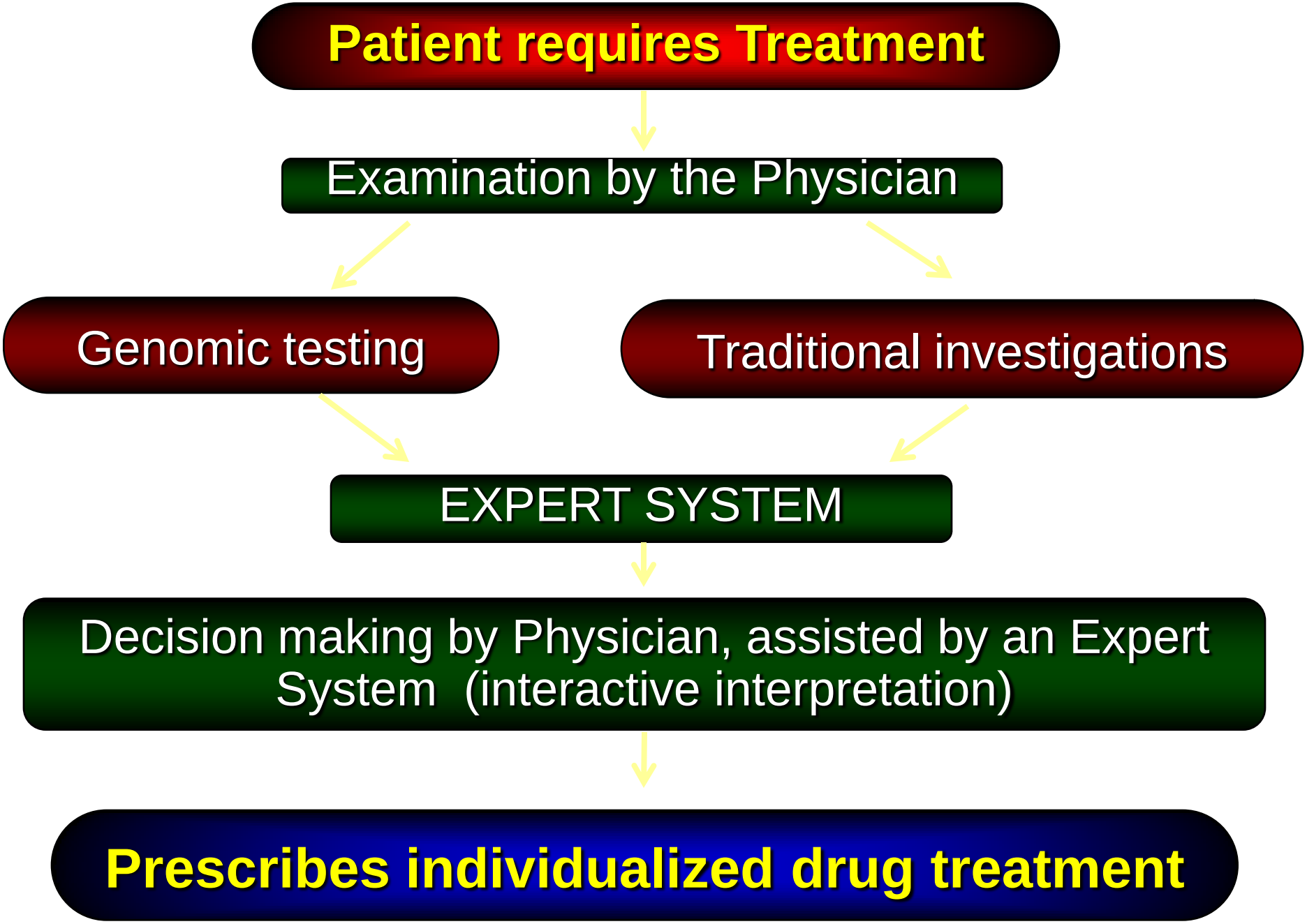
Substrates of P-glycoprotein

Category	Substrates of P-gp
Anti-cancer agents	Actinomycin D, Vincristine,etc
Cardiac drugs	Digoxin, Quinidine etc
HIV protease inhibitors	Ritonavir, Indinavir etc
Immunosuppressants	Cyclosporine A, tacrolimus etc
Antibiotics	Erythromycin,levofloxacin etc
Lipid lowering agents	Lovastatin, Atorvastatin etc

RECEPTOR SENSITIVITY

Receptor	Sensitivity/Effect
β_1 receptor gene	
$Arg^{389}Gly$	**Subjects with Gly ^{389} have reduced sensitivity to beta-blockers**
$Ser^{49}Gly$	**Subjects with Gly ^{49} have increased sensitivity to beta-blockers**
β_2 receptor gene	
$Arg^{16}Gly$	**Response to salbutamol is 5.3 fold lower in Gly^{16} asthmatics.**
$Gln^{27}Glu$	**Subjects with Glu^{27} have strong resistance to beta 2 agonists**

What next ?

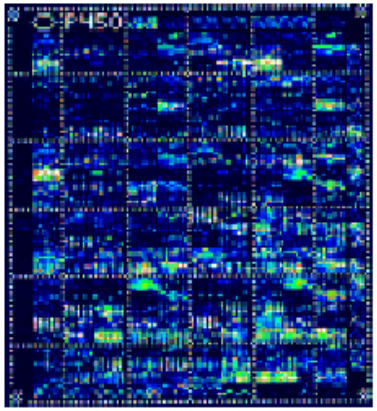

Patient requires Treatment
Examination by the Physician
Genomic testing
Traditional investigations
EXPERT SYSTEM
Decision making by Physician, assisted by an Expert System (interactive interpretation)
Prescribes individualized drug treatment

..And what many thought would not happen has already happened

Basel, 25 June 2003

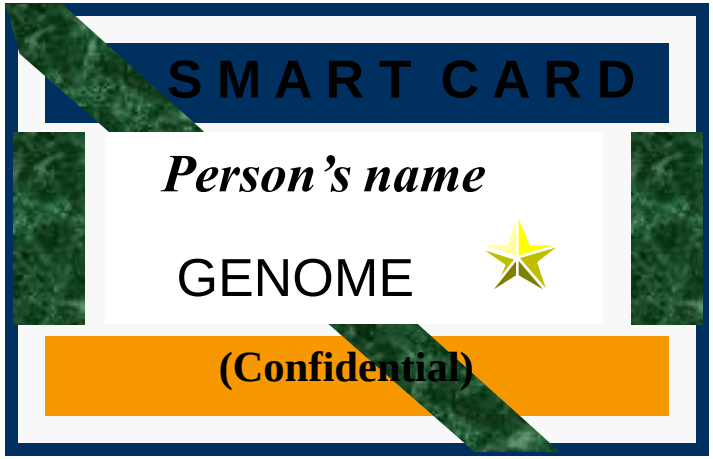
Roche Diagnostics Launches the AmpliChip CYP450 in the US, the World's First Pharmacogenomic Microarray for Clinical Applications

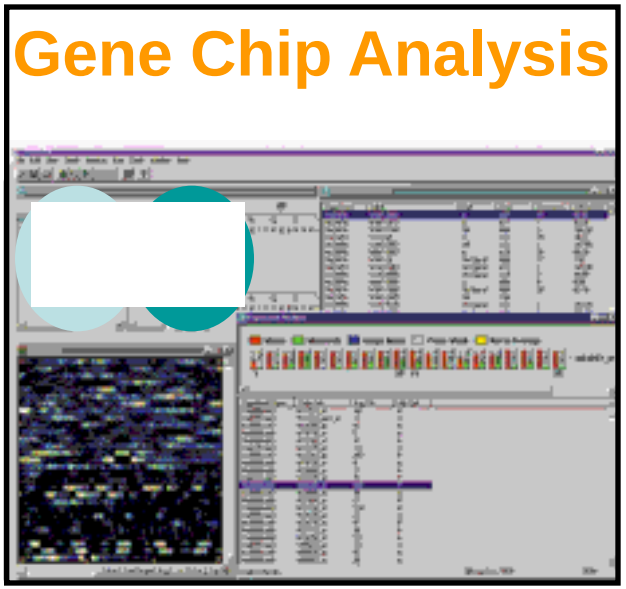
New diagnostic tool: the P450 chip



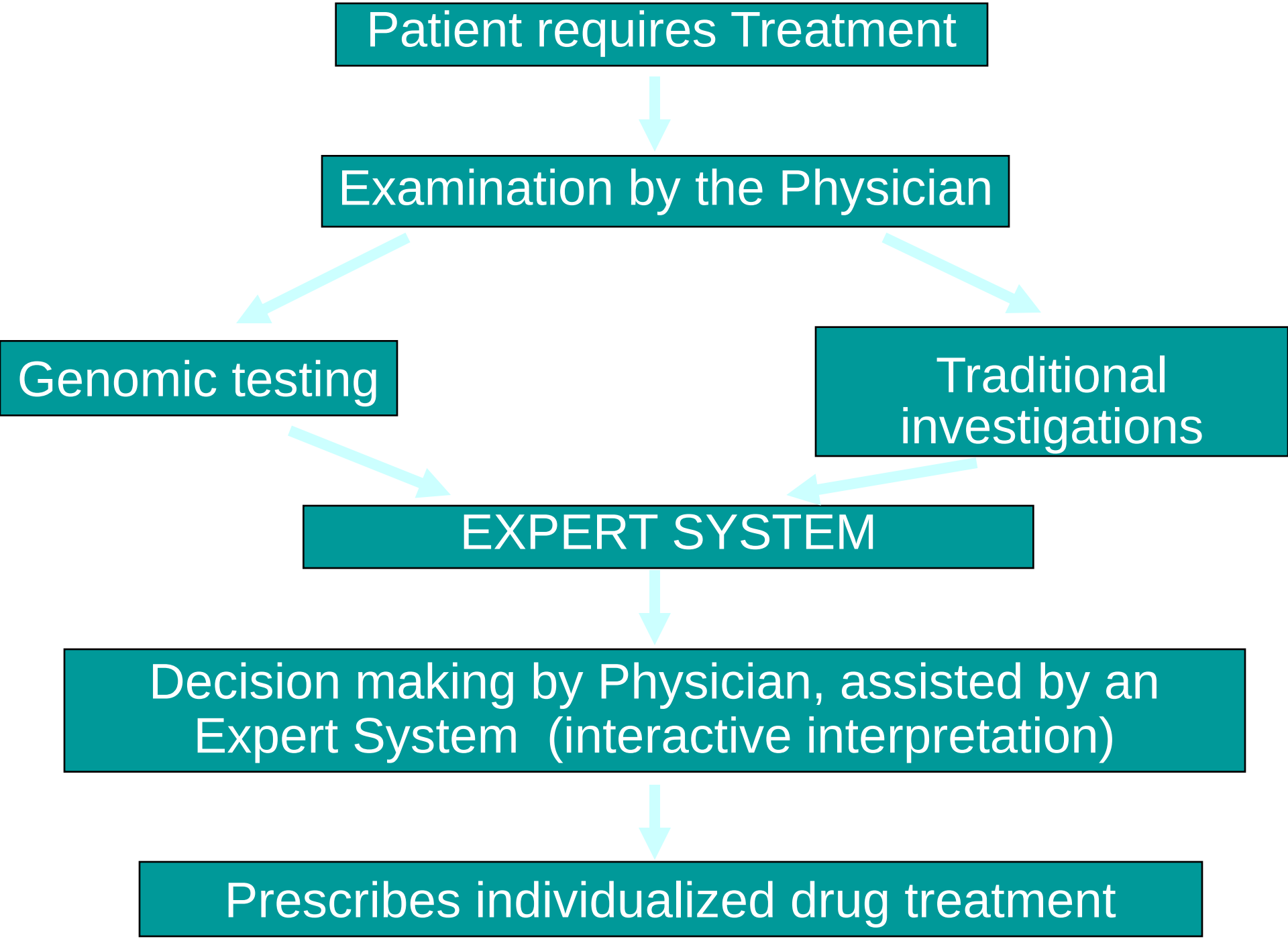
The 'AmpliChip CYP450' arrived on the market in 2003. The scientific basis of this chip is formed by pharmacogenomic data on the influence of the cytochrome P450 gene family on the efficacy and tolerability of drugs. The AmpliChip CYP450 is able to identify the most important variants of two important members of this group of genes.

Personalized Medication in the Future





In the future (? years), doctors will be able to select the best drug to treat your disease and the appropriate dose based on knowledge of your specific genetic makeup!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