Pattern genetici e Farmacoterapia

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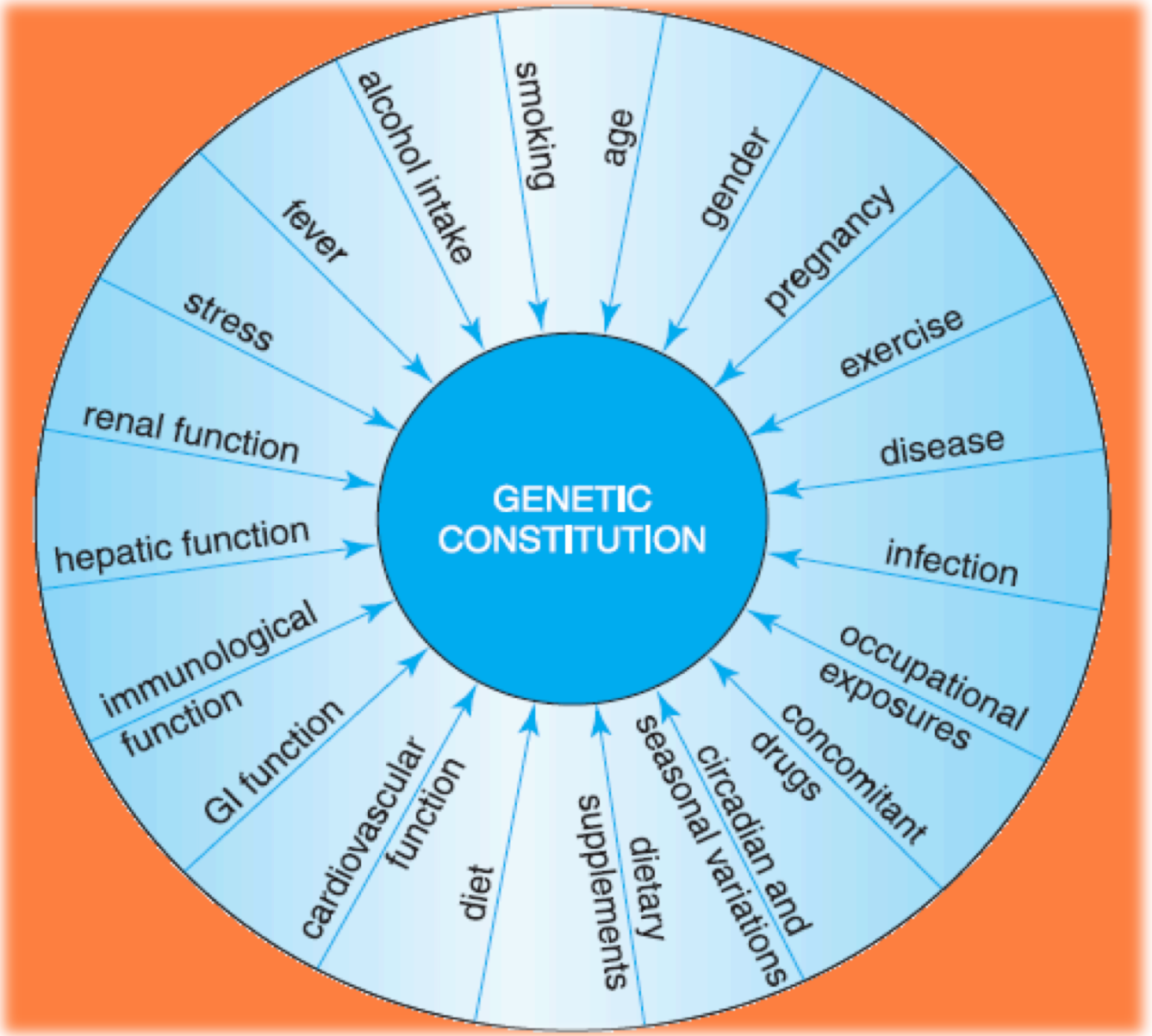
Differente efficacia dei farmaci

Stessa malattia,
Stessi sintomi,

Stesso farmaco
Stessa dose

Stesso paziente?

Different Effects

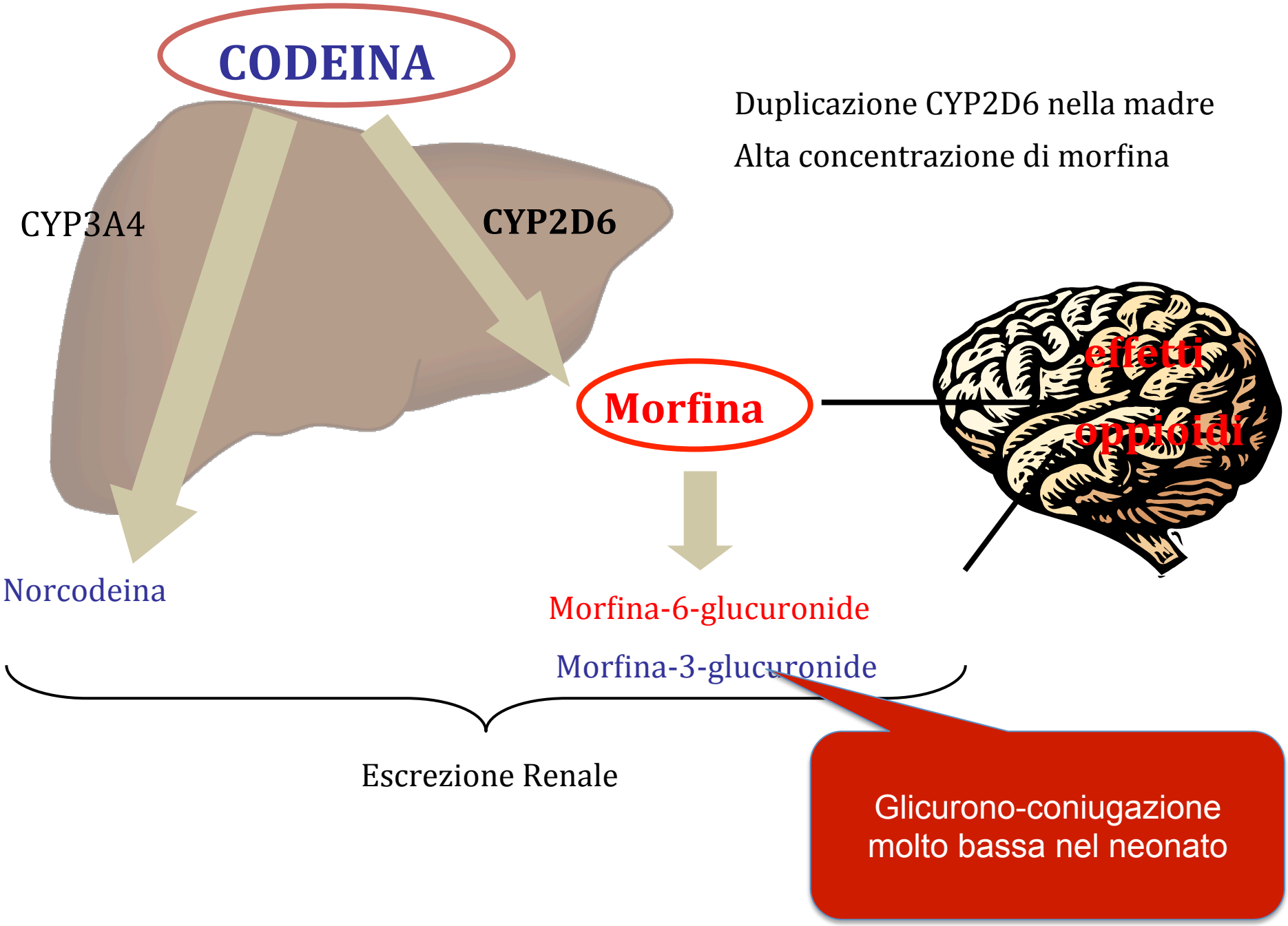


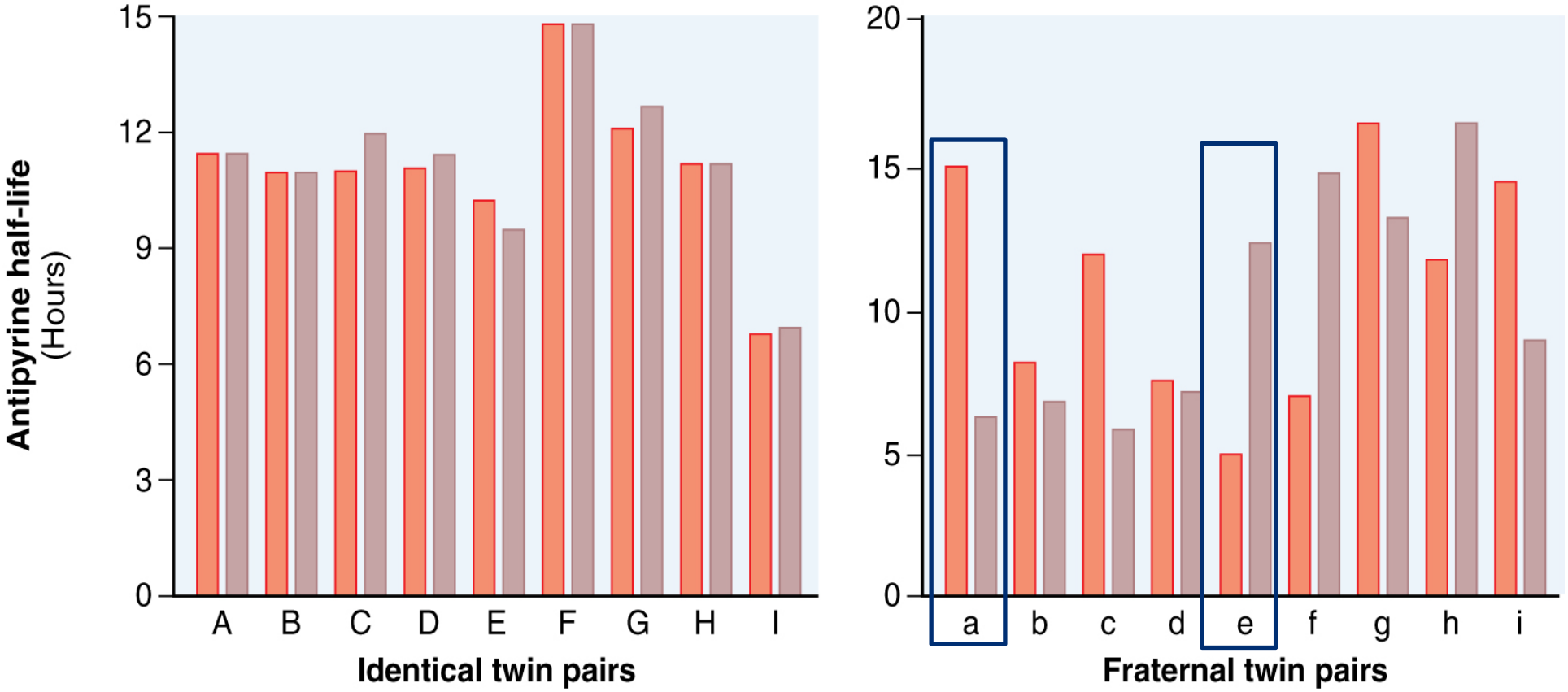
Exogenous & Endogenous factors contribute to variation in drug response

CASO CLINICO

- Giorno 1 - bambino maschio sano nato a termine, madre assume 30 mg di codeina / 500 mg di paracetamolo per dolore
- Giorno 7 - difficoltà l'allattamento al seno e letargia
- Giorno 11 - bambino, stazionario permane letargia
- Giorno 12 - pelle grigiastra, allattamento difficoltoso
- Giorno 13 - neonato trovato morto
- concentrazione ematica di morfina postmortem = 70 ng/ mL (normale in neonati allattati al seno da madri che assumono codeina 0-2-2 ng/mL)
- analisi genotipo CYP2D6 – madre con duplicazione genica CYP2D6 * 2x2 - metabolizzatore ultra-rapido
- i neonati generalmente hanno ridotta capacità di metabolizzare ed eliminare la morfina

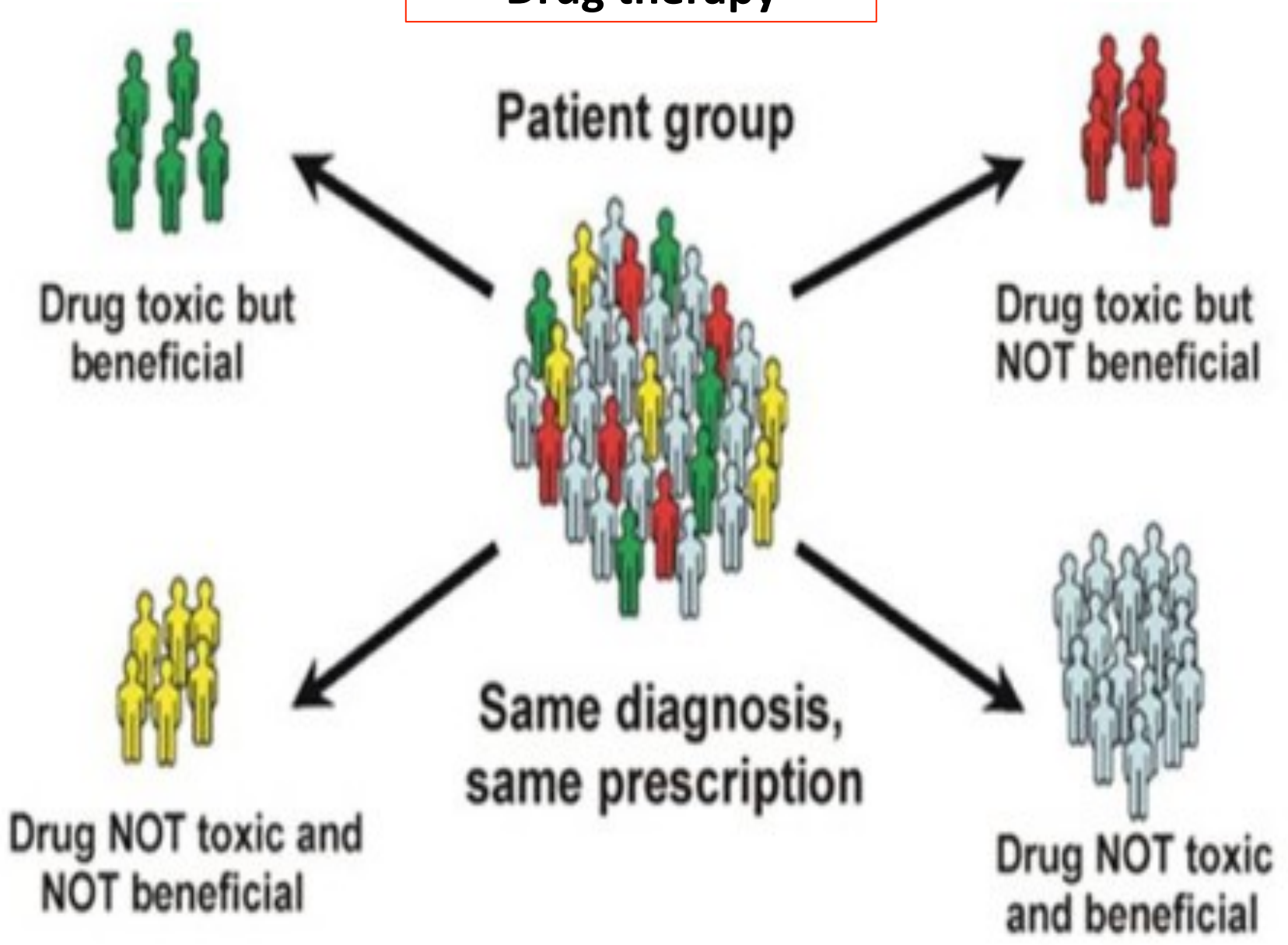
Lancet 368: 704, 2006


CODEINA
CYP3A4
CYP2D6
Duplicazione CYP2D6 nella madre
Alta concentrazione di morfina
Morfina
effetti oppioidi
Norcodeina
Morfina-6-glucuronide
Morfina-3-glucuronide
Escrezione Renale
Glicurono-coniugazione molto bassa nel neonato

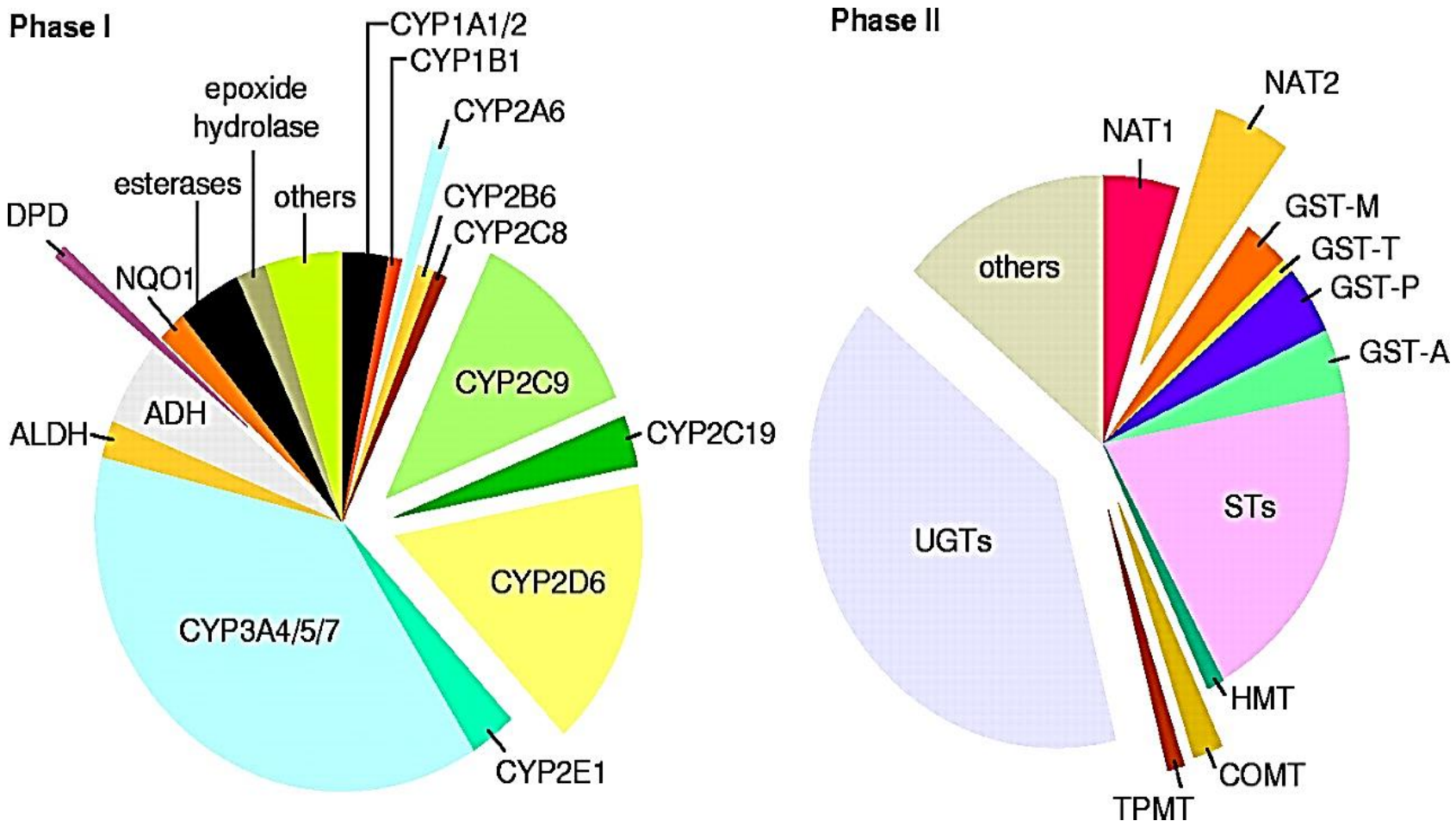


- ***<u>Pharmacogenetic contribution to pharmacokinetic parameters.</u>*** **$t_{1/2}$ of antipyrine is more concordant in identical in comparison to fraternal twin pairs. Bars show the $t_{1/2}$ of antipyrine in identical (monozygotic) and fraternal (dizygotic) twin pairs. (Redrawn from data in Vesell and Page, 1968.)**

Drug therapy



DRUG METABOLIZING ENZYMES



Phase I: biotransformation reactions: oxidation, hydroxylation, reduction, hydrolysis
Phase II: conjugation reactions—to increase their water solubility and elimination from the body. The reactions are glucuronidation, sulation,acetylation, glutathione conjugation

GENETIC VARIATION

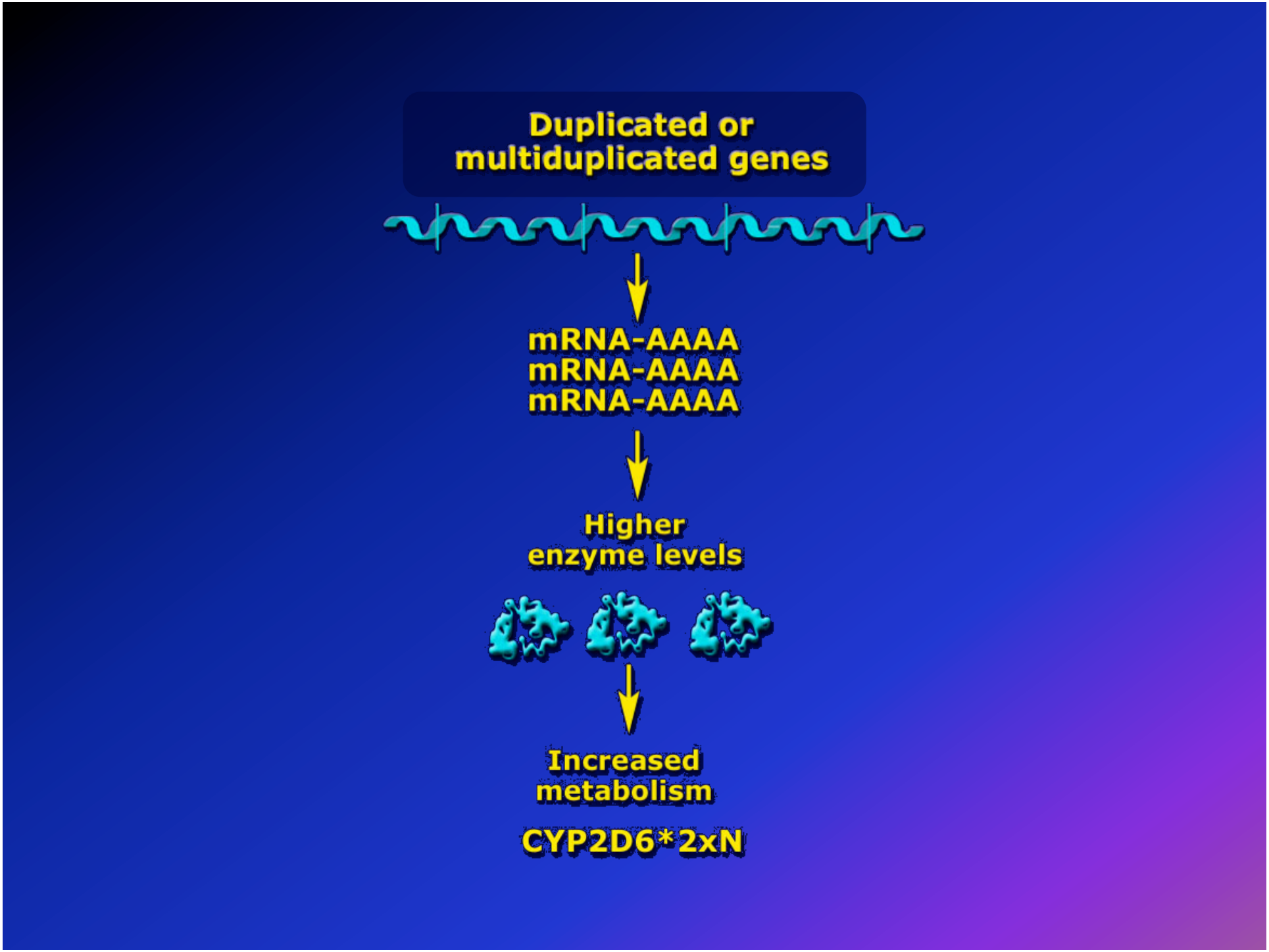
Types of Polymorphisms

- Single Nucleotide Polymorphism (SNP): GAATTTAAG

  GAATTCAAG

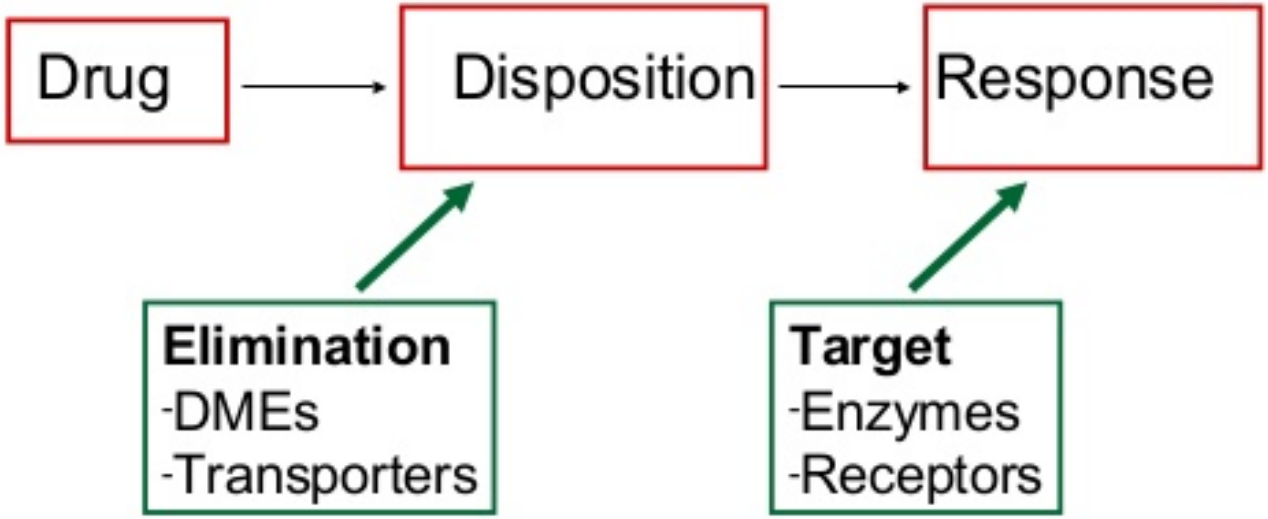
- Insertion/Deletion: GAAATTCCAAG

  GAAA[ ]CCAAG


Duplicated or
multiduplicated genes
mRNA-AAAA
mRNA-AAAA
mRNA-AAAA
Higher
enzyme levels
Increased
metabolism
CYP2D6*2xN

Pharmacogenetics

- **Definition**: how genes affect the way people respond to drug therapy.



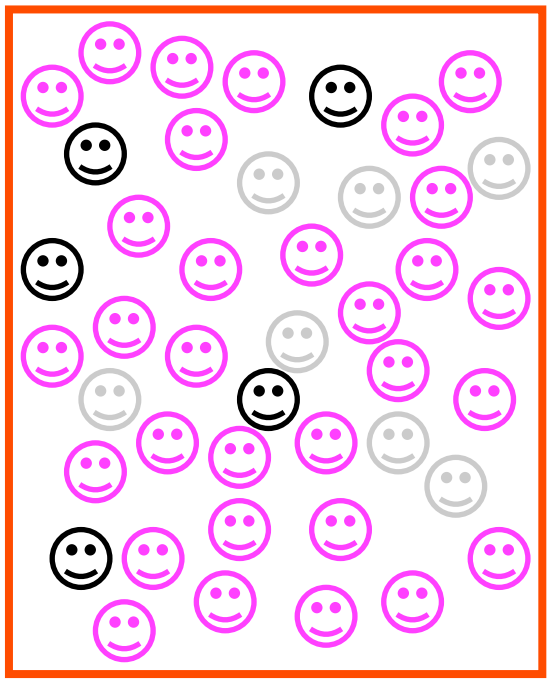
I pazienti rispondono in modo differente ai farmaci

"One size does not fit all …"

Toxic responders

Non-responders

Responders



Patient population with same disease phenotype

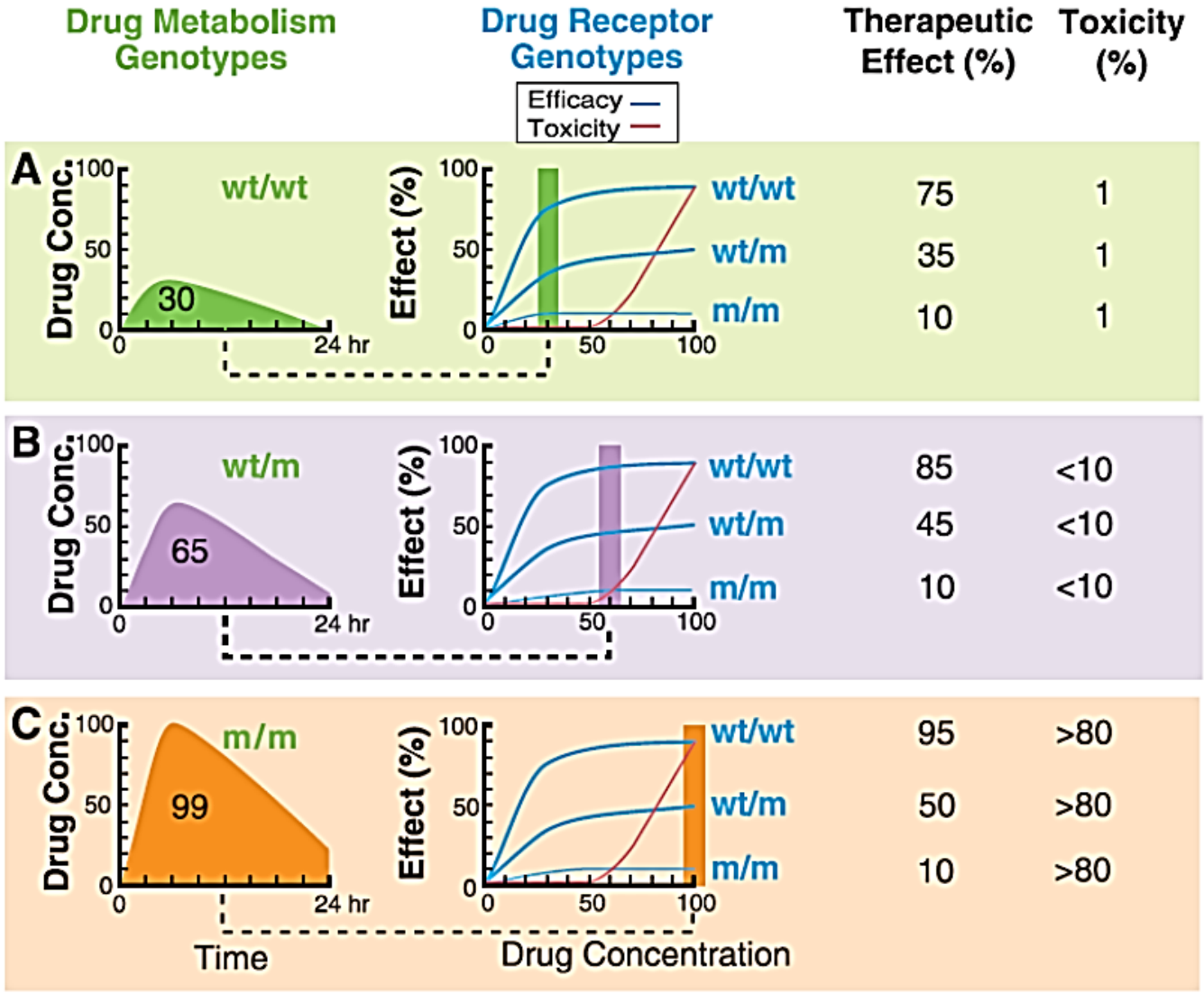
Genotyping

Patients with drug toxicity

Patients with non-response to drug therapy

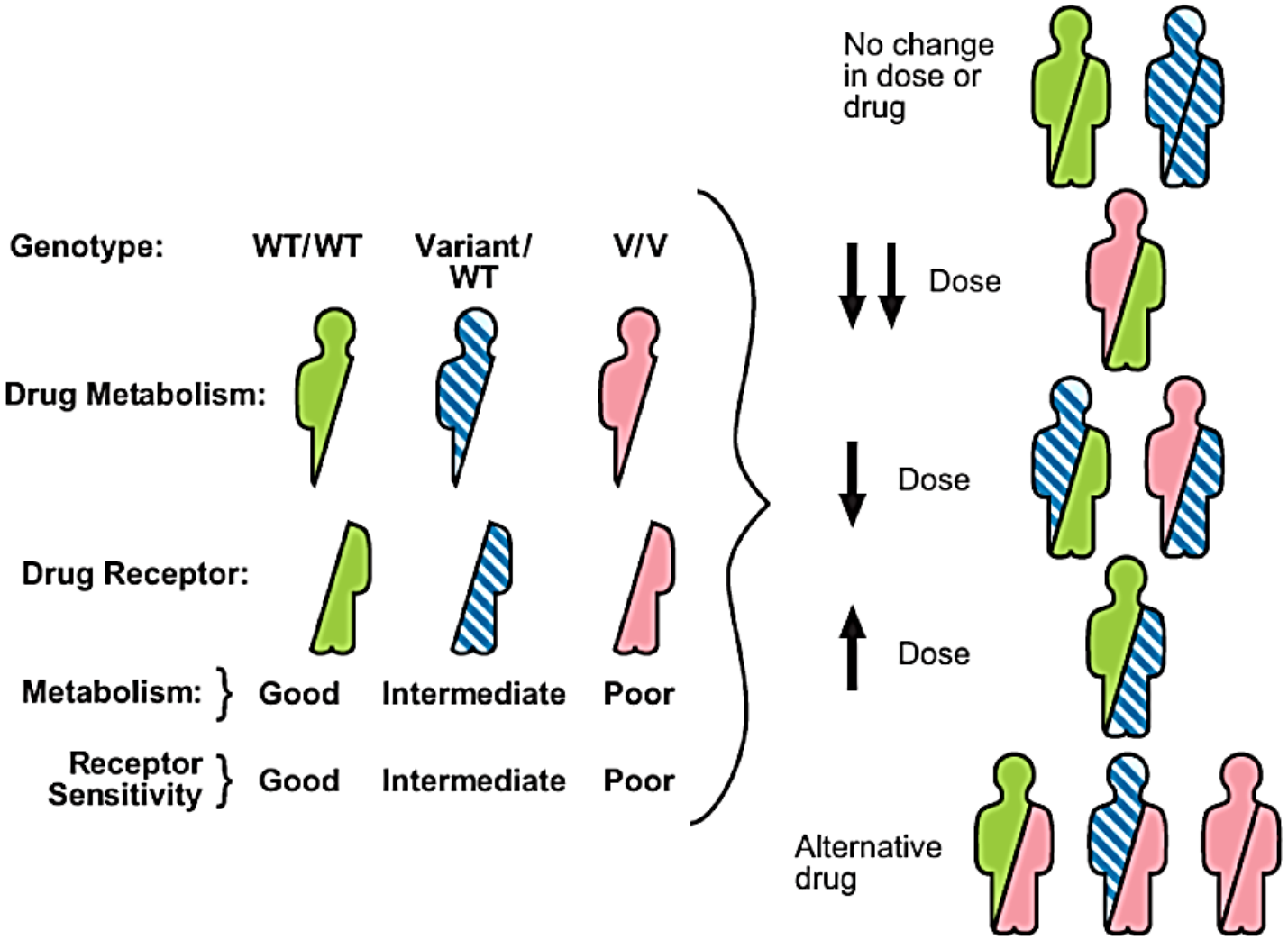
Patients with normal response to drug therapy

Genetic Polymorphisms: Drug Concentration and Drug Effect



William E. Evans* and Mary V. Relling SCIENCE VOL 286 15 OCTOBER 1999

Treatment Modifications and Patient Genotypes



Pain Management

Common pain medications

Drug	Metabolic Route
Alfentanil	CYP3A4/CYP3A5
Carisoprodol**	CYP2C19
Celecoxib	CYP2C9
Codeine**	CYP2D6
Cyclobenzaprine	CYP1A2, CYP3A4/CYP3A5
Fentanyl	CYP3A4/CYP3A5
Hydrocodone**	CYP2D6
Hydromorphone	UGT2B7
Ibuprofen	CYP2C9
Lidocaine	CYP1A2
Methadone	CYP2C19, CYP2B6^{+}
Morphine	UGT2B7^{+} (OPRM1)
Naproxen	CYP2C9
Oxycodone**	CYP2D6, CYP3A4/5
Oxymorphone	UGT2B7^{+} (OPRM1)
Ropivicaine	CYP1A2
Tizanidine	CYP1A2
Tramadol**	CYP2D6
Zolmipitran	CYP1A2

**prodrug;

LIMITI della farmacogenetica

- Targeting complesso se coinvolgimento di più geni
- Difficile e richiede tempo per identificare variazioni di geni poco noti
- Interazione con altri farmaci e ambiente da determinare

Barriere della farmacogenetica

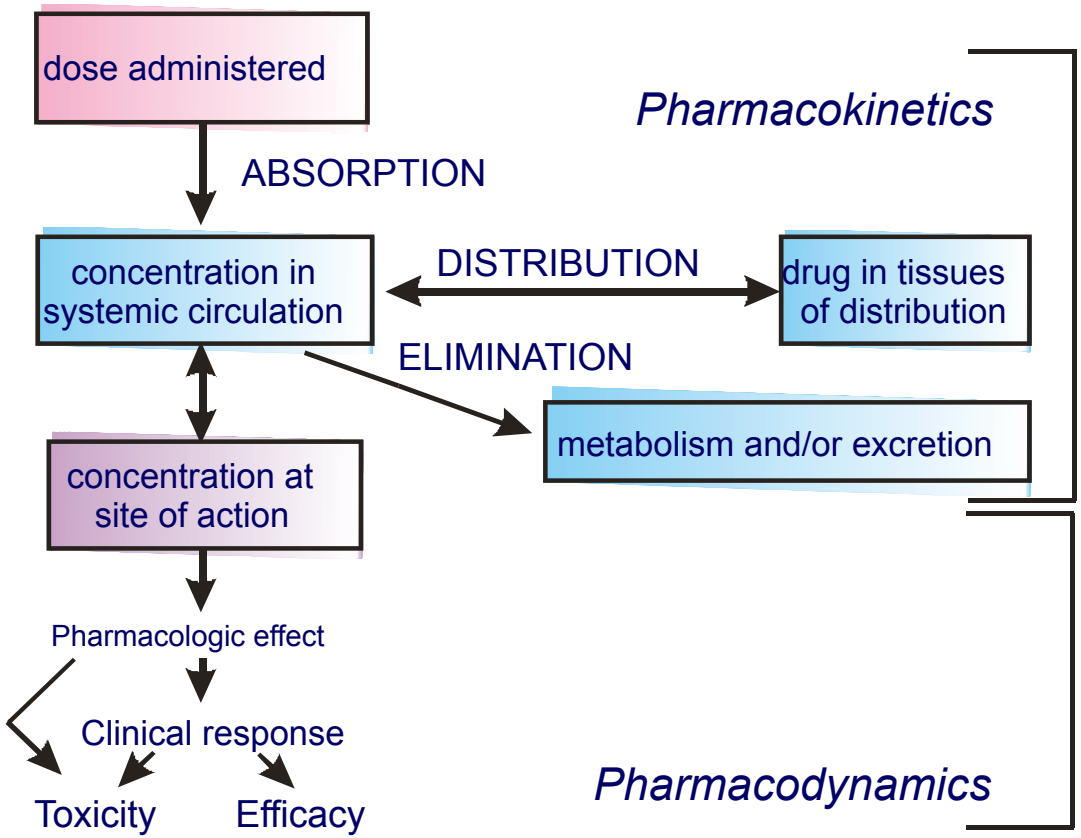
- Scarsità di laboratori di farmacogenetica
- Scarsa esperienza nei clinici
- Pochi farmacologi clinici con esperienza nell'adattamento della dose

Personalized medicine

- Grazie

Determinants of Drug Efficacy and Toxicity

A patient's response to a drug may depend on factors that can vary according to the alleles that an individual carries, including :



- **Pharmacokinetic factors**
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- **Pharmacodynamic factors**
  - Target proteins
  - Downstream messengers