Pharmacogenetics of Antiretroviral Therapy in Paediatrics

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Children's National™

Ageing with HIV
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Elizabeth Glaser Pediatric AIDS Foundation

Some important milestones in the history of pharmacogenomics

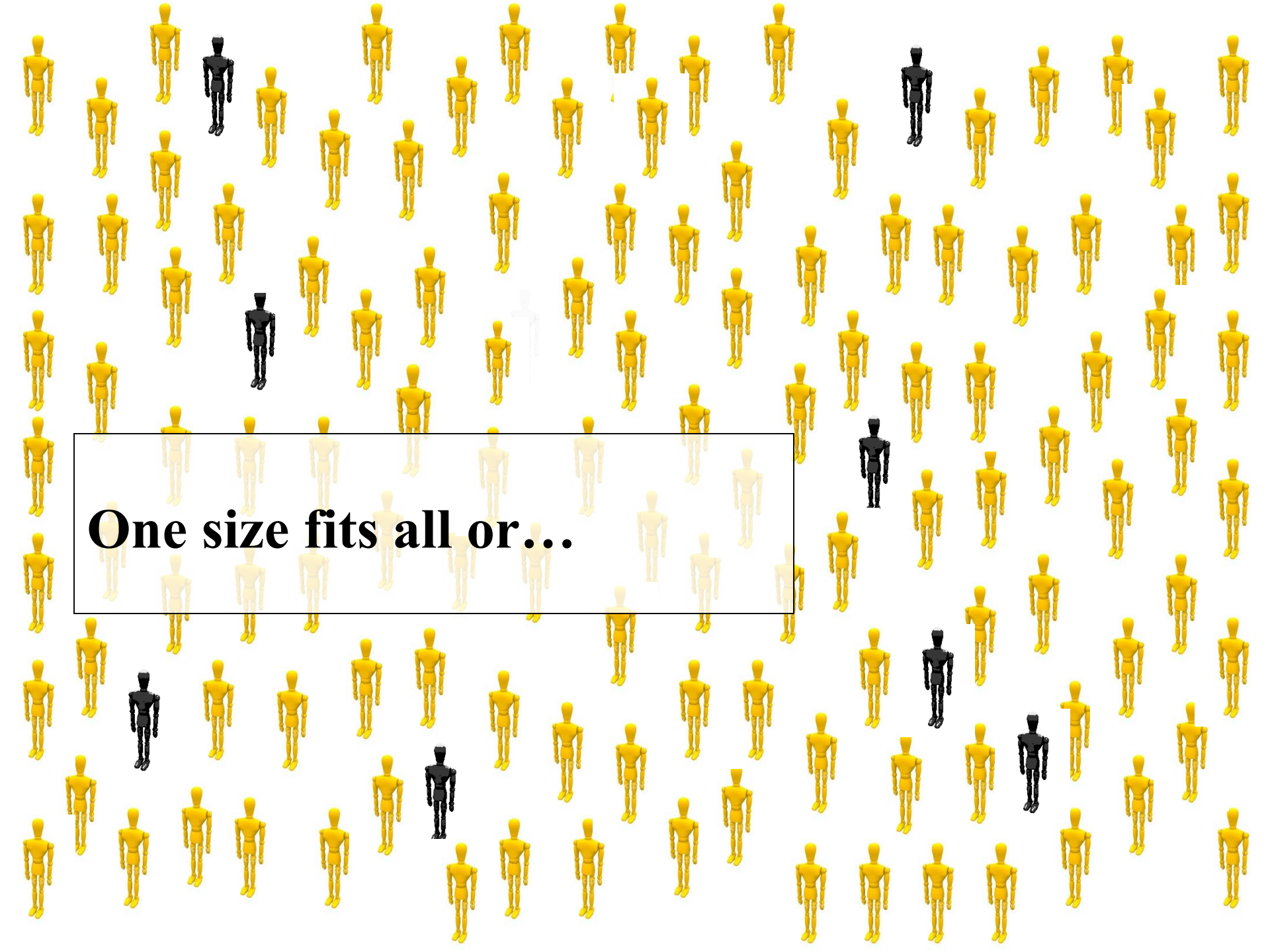
1866 Mendel Lays down the principles of heredity
1909 Garrod Publication of 'Inborn Errors of Metabolism'
1932 Snyder Characterization of the *phenylthiourea-non-taster* as an autosomal recessive trait
1954 Hughes *et al.* Relates isoniazid neuropathy to metabolism –n-acetyltransferase
1956 Carson *et al.* Discovery of glucose G-6 PD deficiency
1957 Kalow Characterizes acetylcholinesterase deficiency
1957 Motulsky Inherited differences in drug metabolism
1957 Vogel Coins the term 'pharmakogenetik'
1960 Price Evans Characterization of acetylators polymorphisms
1962 Kalow The first textbook on pharmacogenetics
1979 Eichelbaum*et al.* Describes sparteine metabolism polymorphism
1982 Eichelbaum *et al.* Recognition of link between sparteine and debrisoquine metabolism
1984 Wedlund *et al.* Description of the cytochrome CYP2C19 polymorphism
1988 Gonzalez Explanation for the debrisoquine phenotype
1997 Yates *et al.* Polymerase chain reaction (PCR) based methods used to detect thiopurine

PHARMACOGENETICS

Inherited genetic differences in drug metabolic pathways which can affect individual responses to drugs including therapeutic and adverse effects

PHARMACOGENOMICS

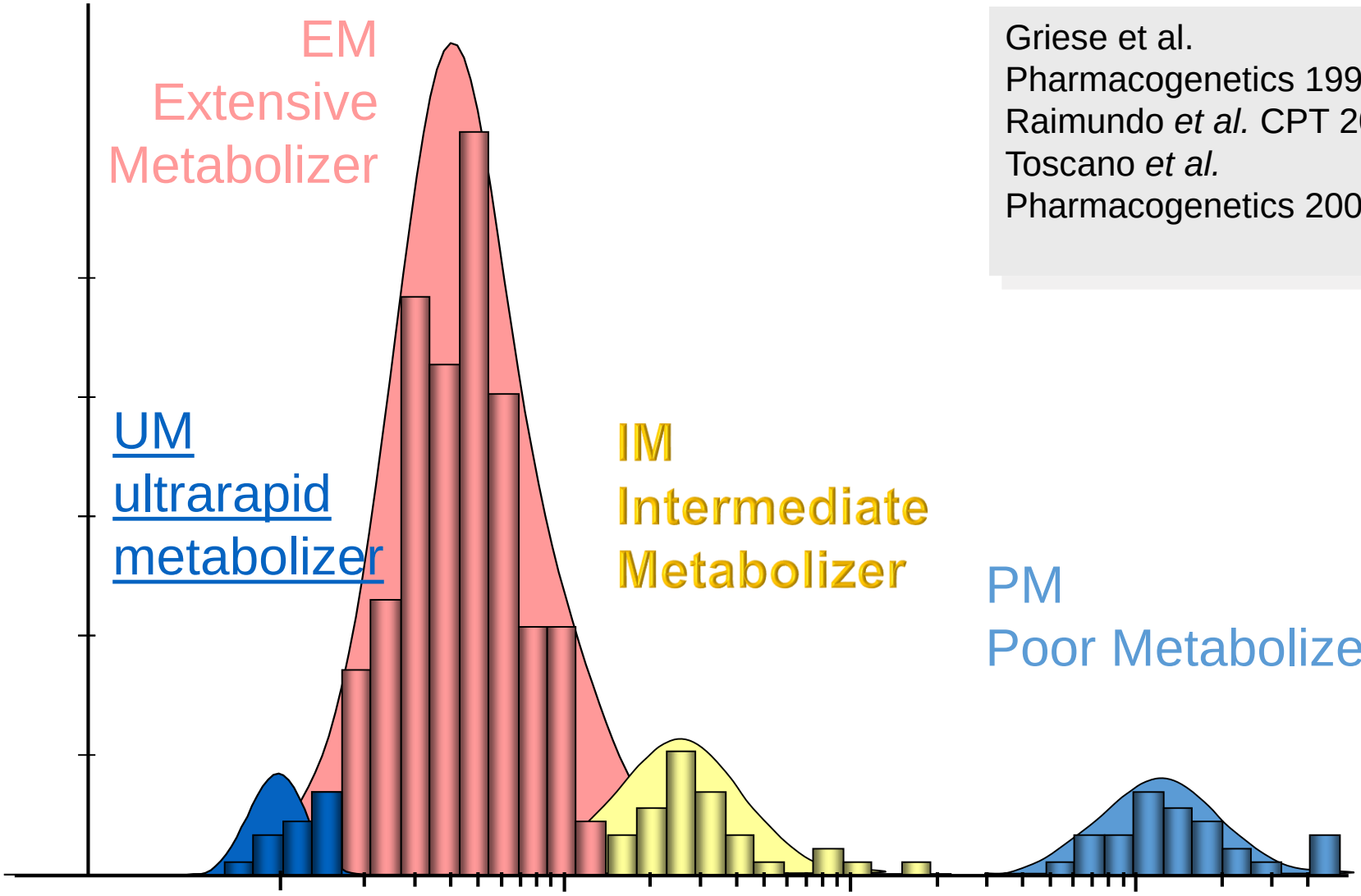
Study of the role of genetics in drug response


One size fits all or…

CYP2D6 Pharmacogenetics

"Functional" overdose

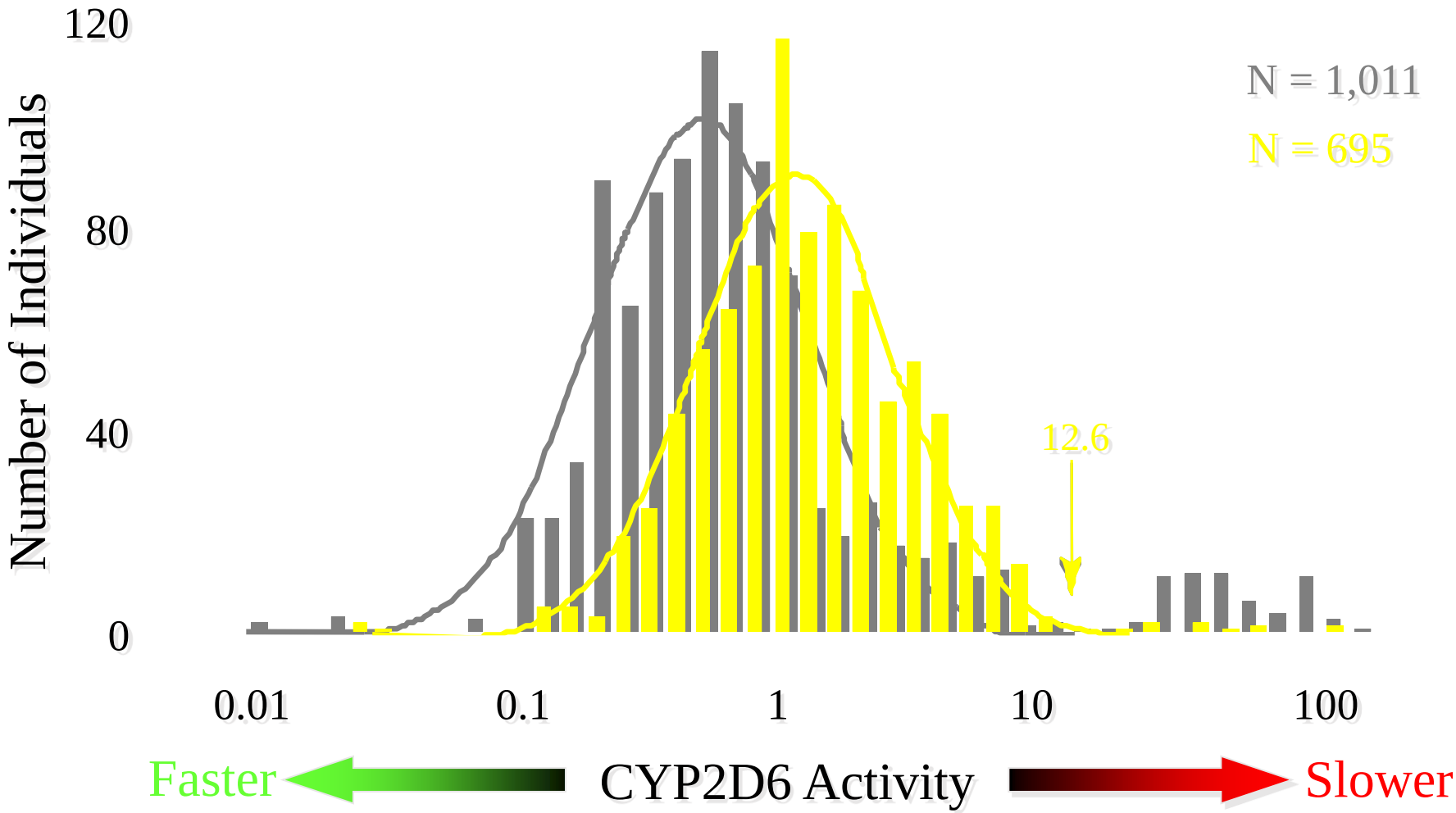
Unravelling CYP2D6 Pharmacogenetics



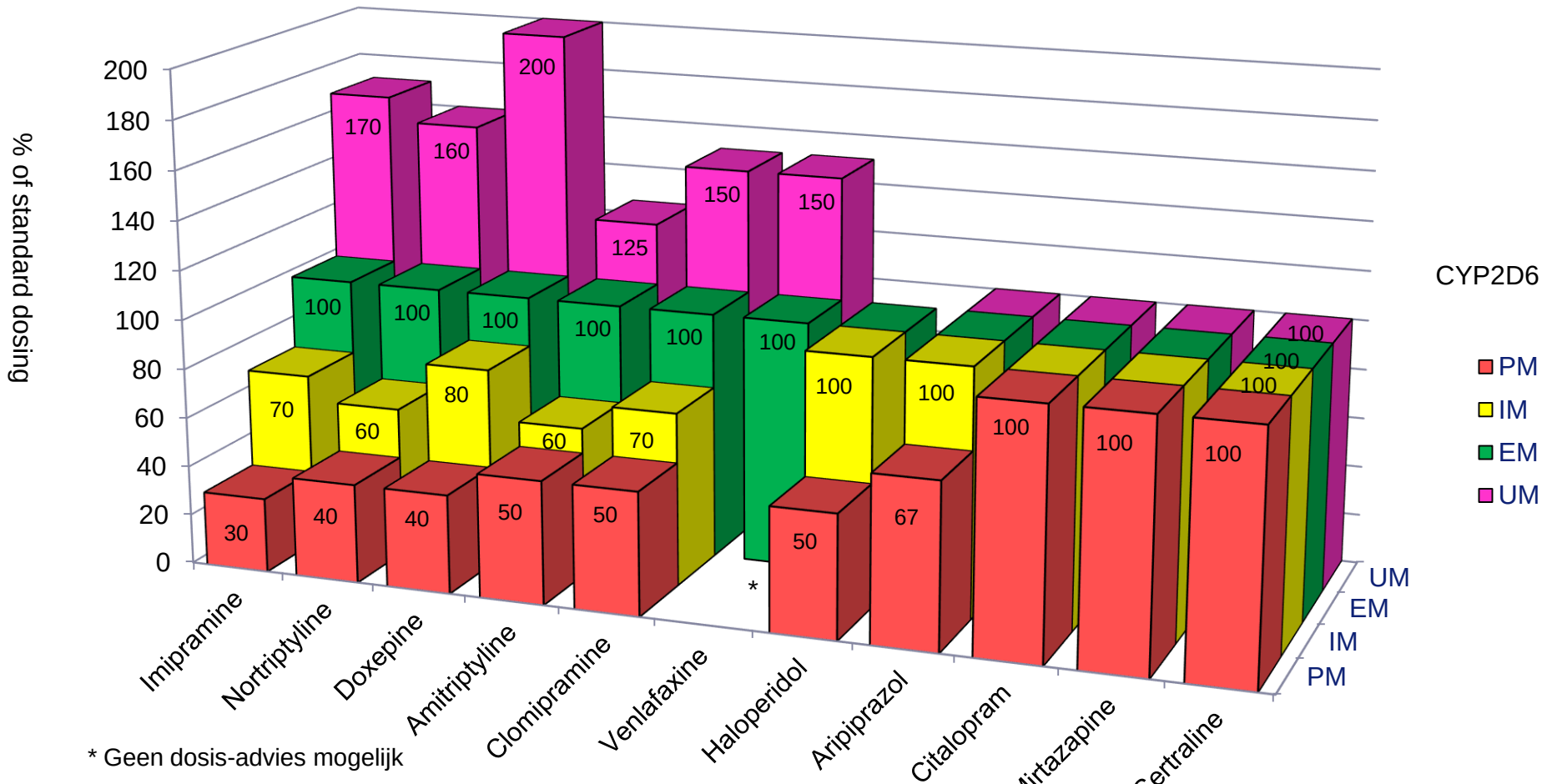
Griese et al. Pharmacogenetics 1998, Raimundo *et al.* CPT 2004, Toscano *et al.* Pharmacogenetics 2006

CYP2D6 Activity: Chinese

Bertilsson *et al.* Clin. Pharmacol. Ther. 51:388-97, 1992



Dosing advices for CYP2D6 substrates



* Geen dosis-advies mogelijk

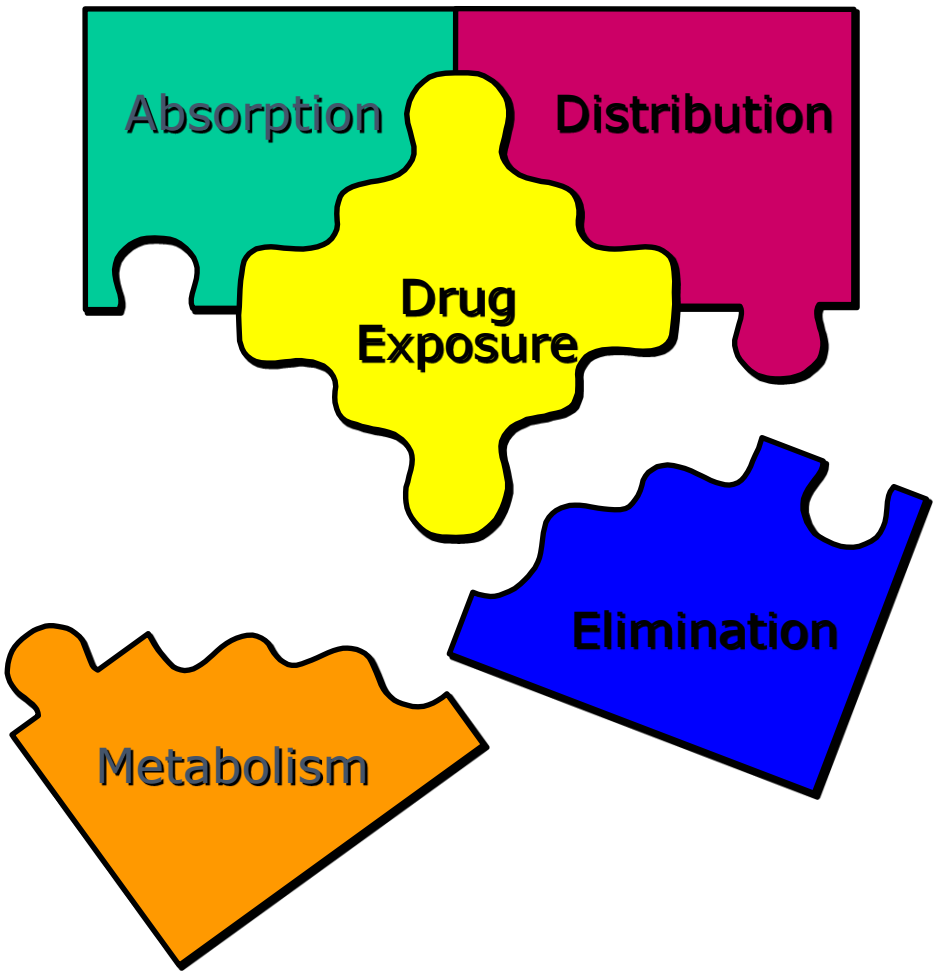
Adviezen KNMP-Kennisbank (1-10-2013) op basis van genotype.
Wijziging dosering alleen in overleg met voorschrijver of apotheek. Zie ook: www.erasmusmc.nl/farmacogenetica.
Contact: r.vanschaik@erasmusmc.nl (010-7033119), b.koch@erasmusmc.nl of t.vangelder@erasmusmc.nl

HIV and Pharmacogenetics

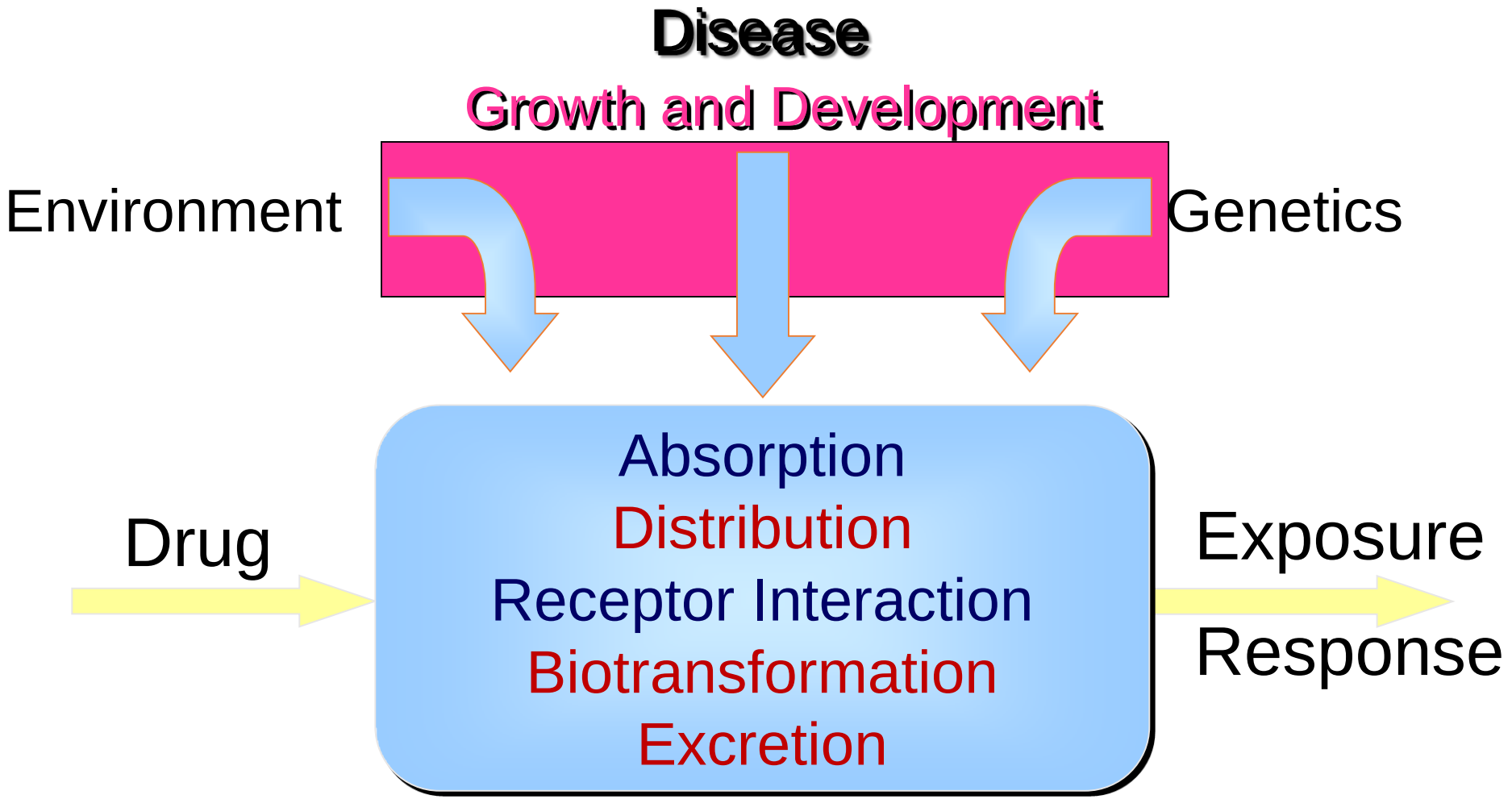
- Genetic polymorphisms may affect antiretroviral drugs (ARVs) disposition, efficacy and toxicity
- Many associations for ARVs drug metabolizing enzymes and transporters have been suggested
- HLA B*5701 in abacavir candidates is the only pharmacogenetic test used currently in clinical practice

Pharmacokinetics in Pharmacotherapy

ADME



Determinants of Drug Response in Children



Enzymes Involved in Dug Disposition

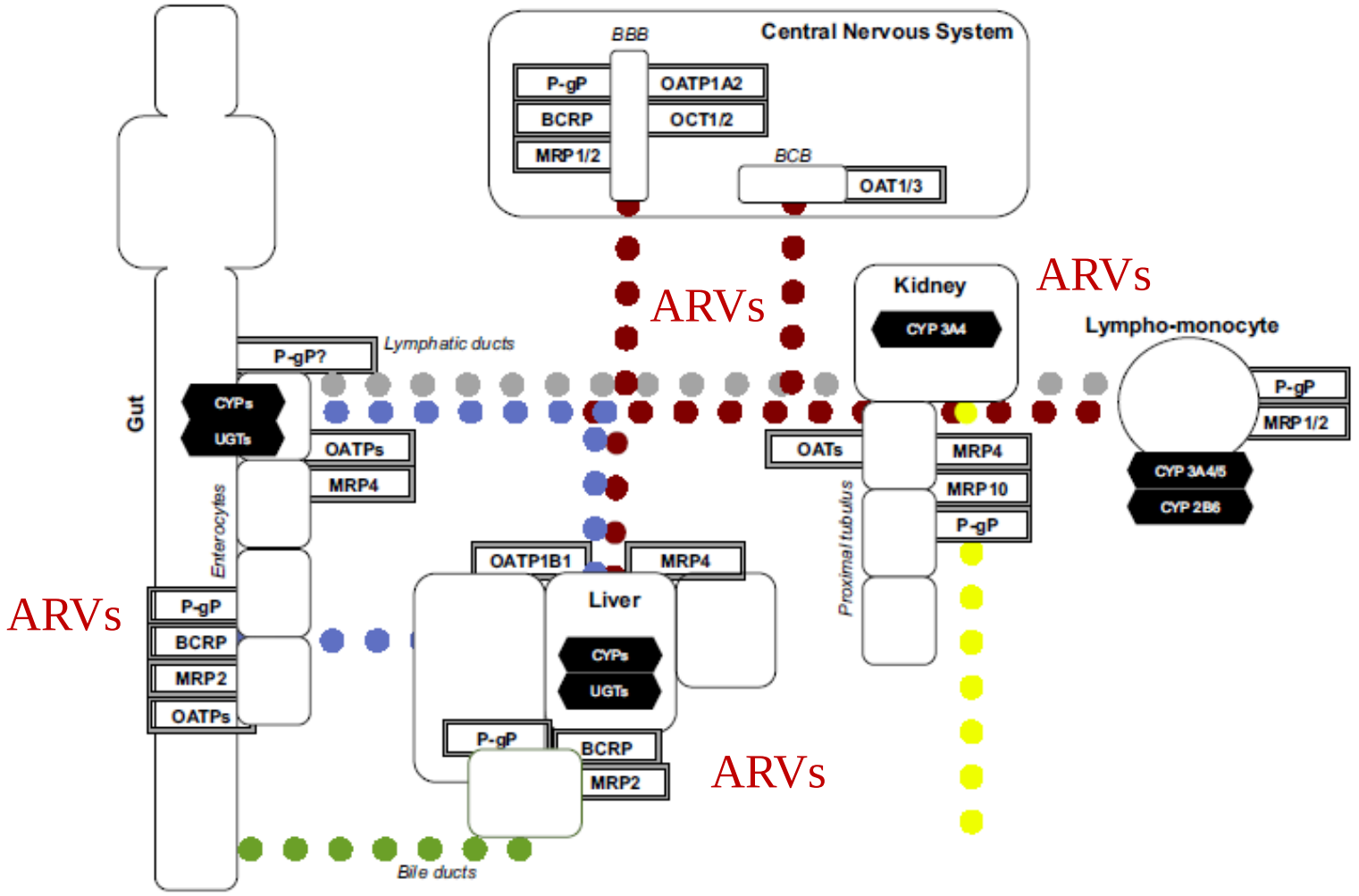
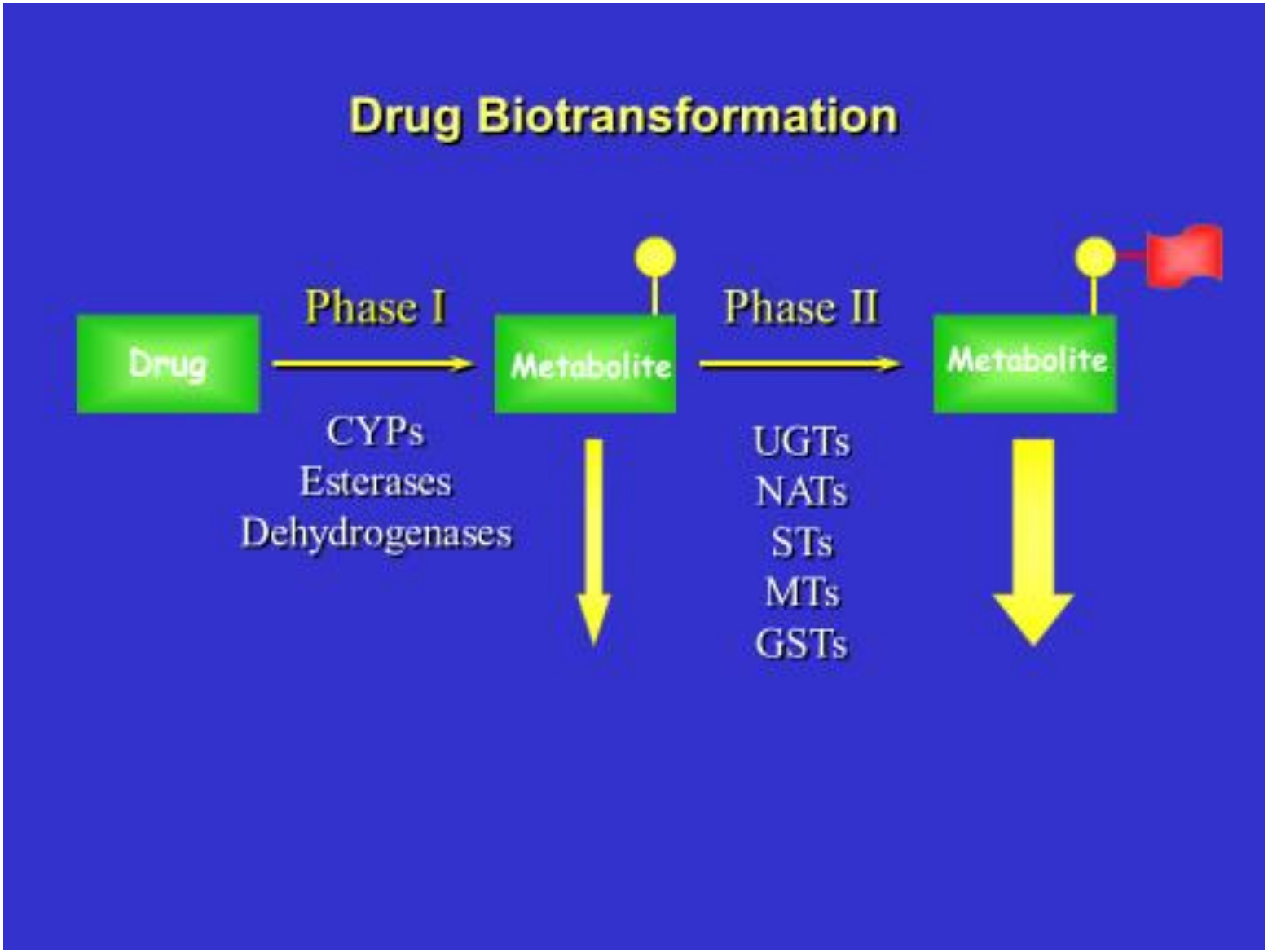


Fig. 1 Schematic representation of enzymes involved in drug disposition. *Blue* and *red dots* represent venous and arterial circulations, respectively. *BBB* blood–brain barrier, *BCB* blood–cerebrospinal fluid barrier, *P-gp* P-glycoprotein, *OATP* organic anion transporter protein, *BCRP* breast cancer resistance protein, *OCT* organic cation transporter, *CYP* cytochrome P450 isoenzymes, *MRP* multi-drug resistant protein, *UGT* uridine diphosphate glucuronosyltransferases

A. Calcagno et al. Clin Pharmacokinet 2016

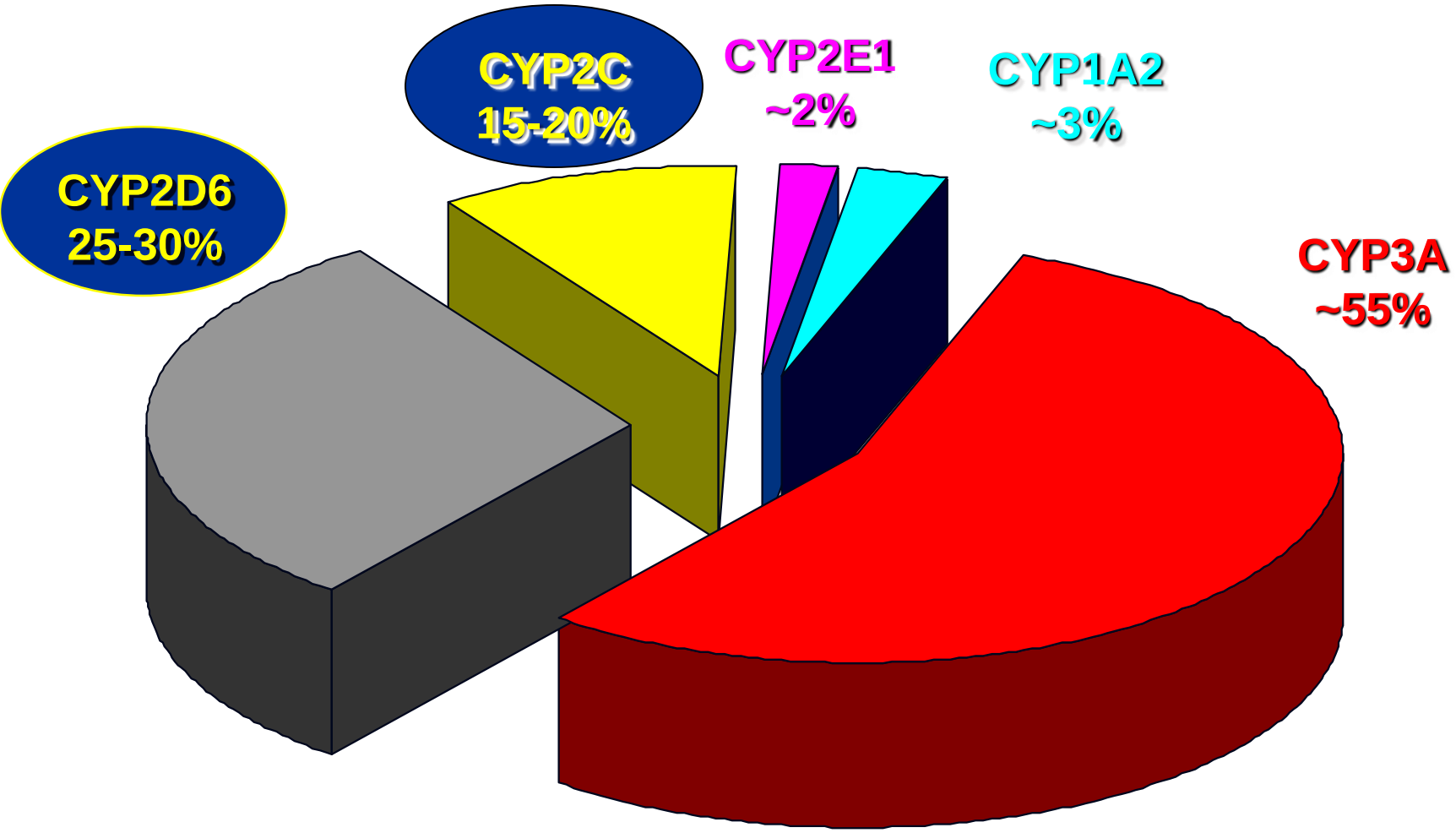

Drug Biotransformation
Drug
Phase I
CYPs
Esterases
Dehydrogenases
Metabolite
Phase II
UGTs
NATs
STs
MTs
GSTs
Metabolite

Most Important Association with ARVs

- Cytochrome P450 (CYP450)
- Multi-drug transporter (MDR) P-glycoprotein (Pgp)
- UDP-glucuronosyltransferase enzymes (UGT)

- PIs, NNRTIs and CCR5 inhibitor are mainly metabolized by CYP3A4 and, to a lesser extent, by CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6
- PIs, NNRTIs and CCR5 inhibitor are substrates to Pgp transport
- MRP ABCC2/ABCC10 affect tenofovir disoproxil fumarate-associated tubular impairment

Relative Contribution of CYP Isoforms to Drug Biotransformation



Most Important Association with ARVs

- **NRTIs** (abacavir and zidovudine), **PI (**atazanavir) and the Integrase Inhibitor (raltegravir) are primarily eliminated by glucuronidation by the UDP-glucuronosyltransferases (UGTs)
- Low expression of UGT leads to high ARVs plasma levels, and high UGT function can increase excretion and cause sub-therapeutic ARV plasma concentrations
- UGT1A1 expression has been linked to the atazanavir-associated hyperbilirubinemia, guidelines for prescreening published, but no plasma relationship is confirmed

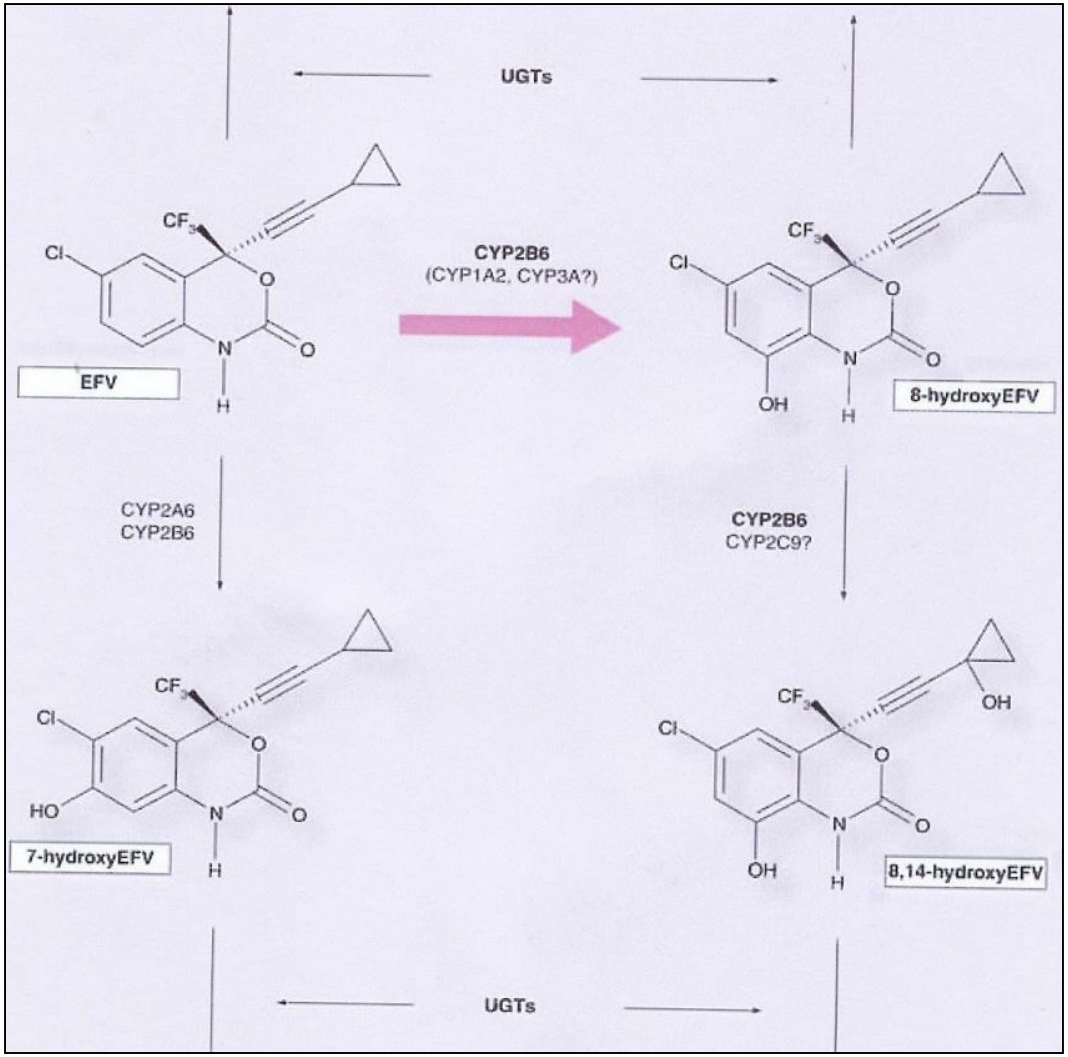
Tissue Expression and Potential Effects of Selected Enzymes Involved in the Disposition of ARVs

Enzyme	Gene	Highest tissue expression	Potential effect of decreased function/expression	ARVs with confirmed PK/PG association
CYP	*CYPs*	Ubiquitous with tissue-specific differences	Reduced metabolism with higher plasma concentrations, potential use of alternative metabolic pathways	*CYP2B6*: efavirenz, nevirapine
UGTs	*UGTs*	Ubiquitous, most isoforms in the liver and gut	Reduced metabolism and drug excretion, higher plasma concentrations	None
P-gp	*ABCB1*	Ubiquitous, on the surface of several cells	Increased intestinal absorption, higher intracellular concentrations, higher tissue distribution (including the central nervous system)	None
OATP1B1	*SLCO1B1*	Liver (hepatocyte membrane)	Reduced hepatic uptake, higher plasma and lower hepatic concentrations	None
PXR	*NR1I2*	Ubiquitous (intra-nuclear)	Mutated gene with gain of function and therefore higher expression of transporter and metabolizing enzymes; lower plasma concentrations	*NR1I2*: atazanavir

ARVs antiretrovirals, *PK/PG* pharmacokinetic/pharmacogenetic, *CYP* cytochrome P450 isoenzymes, *UGT* uridine diphosphate glucuronosyl-transferase, *P-gp* P-glycoprotein, *ABCB1* ATP-binding cassette subfamily b member 1 gene, *OATP* organic anion transporter protein, *SLCO1B1* solute carrier organic anion transporter family member 1B1, *PXR* pregnane X receptor, *NR* nuclear receptor subfamily genes

A. Calcagno et al. Clin Pharmacokinet 2016

Metabolism of Efavirenz

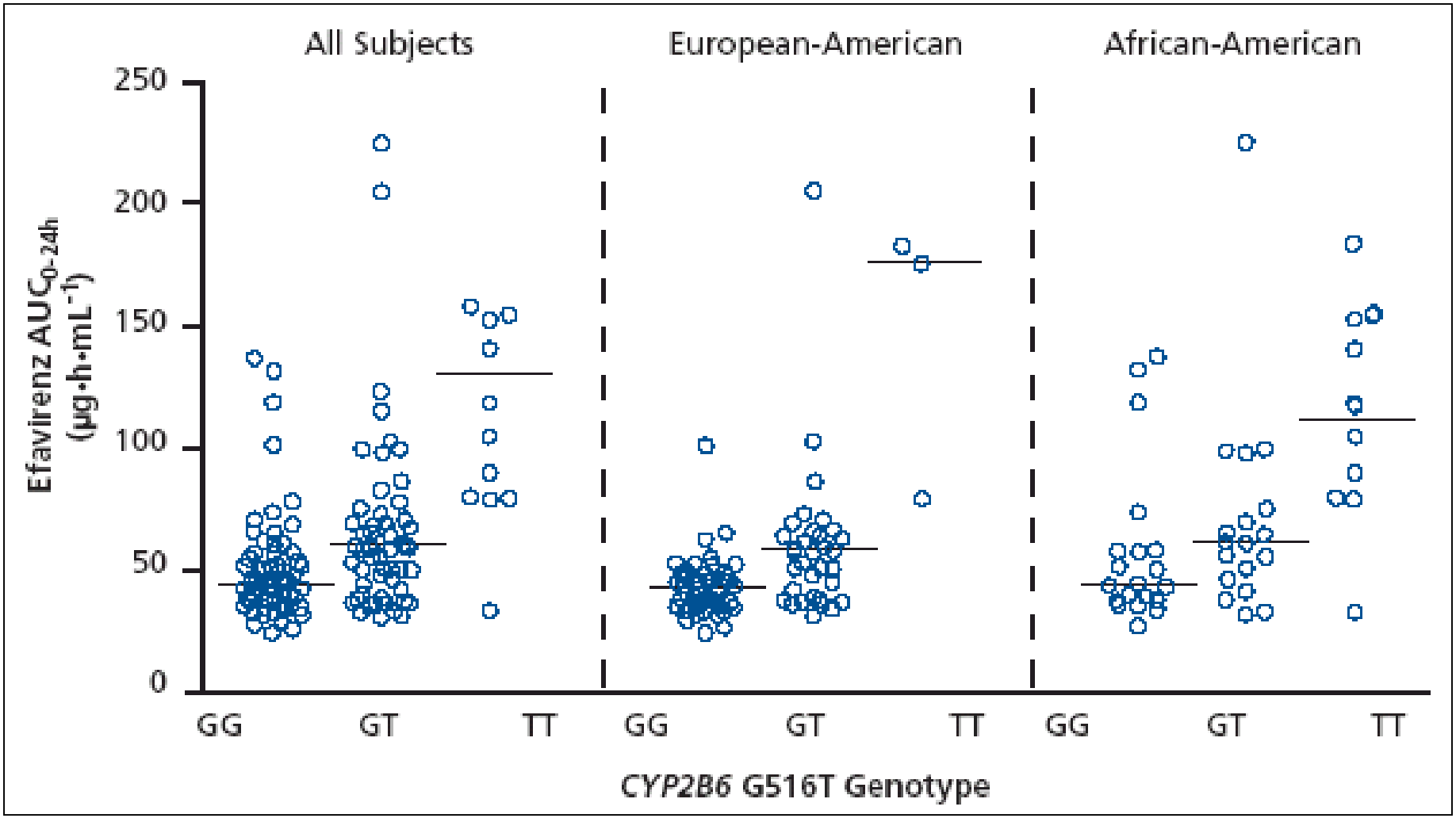


Desta Z, *Pharmacogenomics* 2007

Efavirenz and CYP2B6

- **CYP2B6 516GT** polymorphism most significant effect on Nevirapine and Efavirenz plasma concentrations
- Sub-therapeutic and toxic exposures (EFV, NVP) reported in children
- Neurotoxicity with Efavirenz has been linked to plasma exposures
- Based on the ethnicity – different expression in diverse populations with highest propotion of slow metabolizers (15%) among Blacks

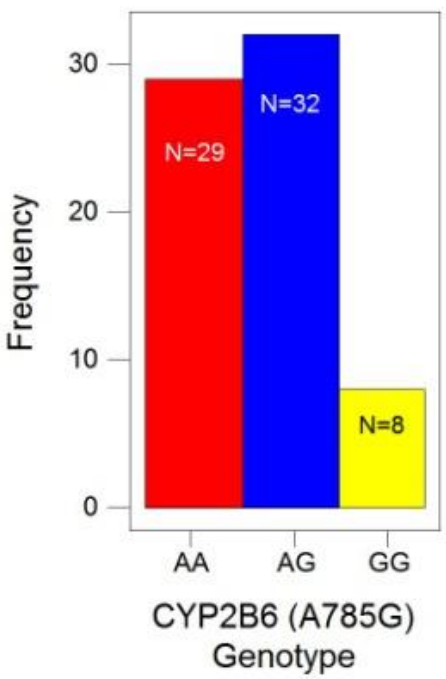
Efavirenz and CYP2B6

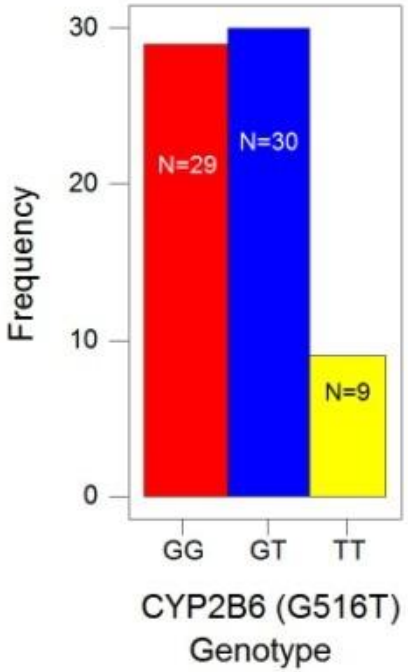


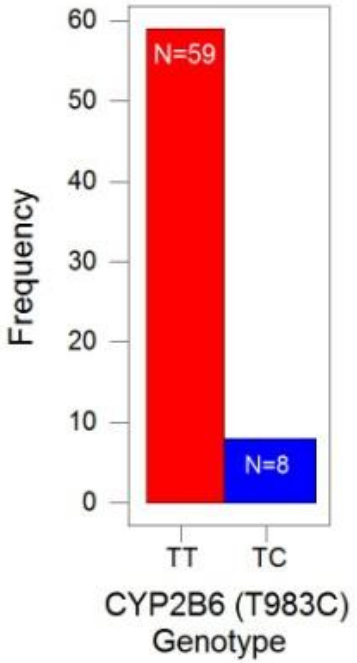
Haas et al, *AIDS*, 200418:2391-2400.

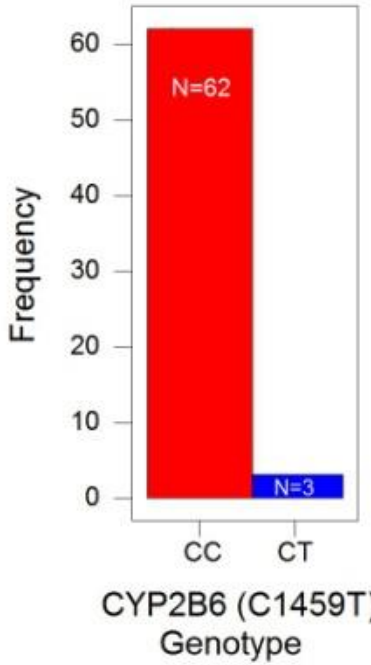
TT and GT slow metabolizers and **GG** fast

Prevalence of *CYP2B6* Polymorphisms in Pediatric and Adolescent Patients at CNMC





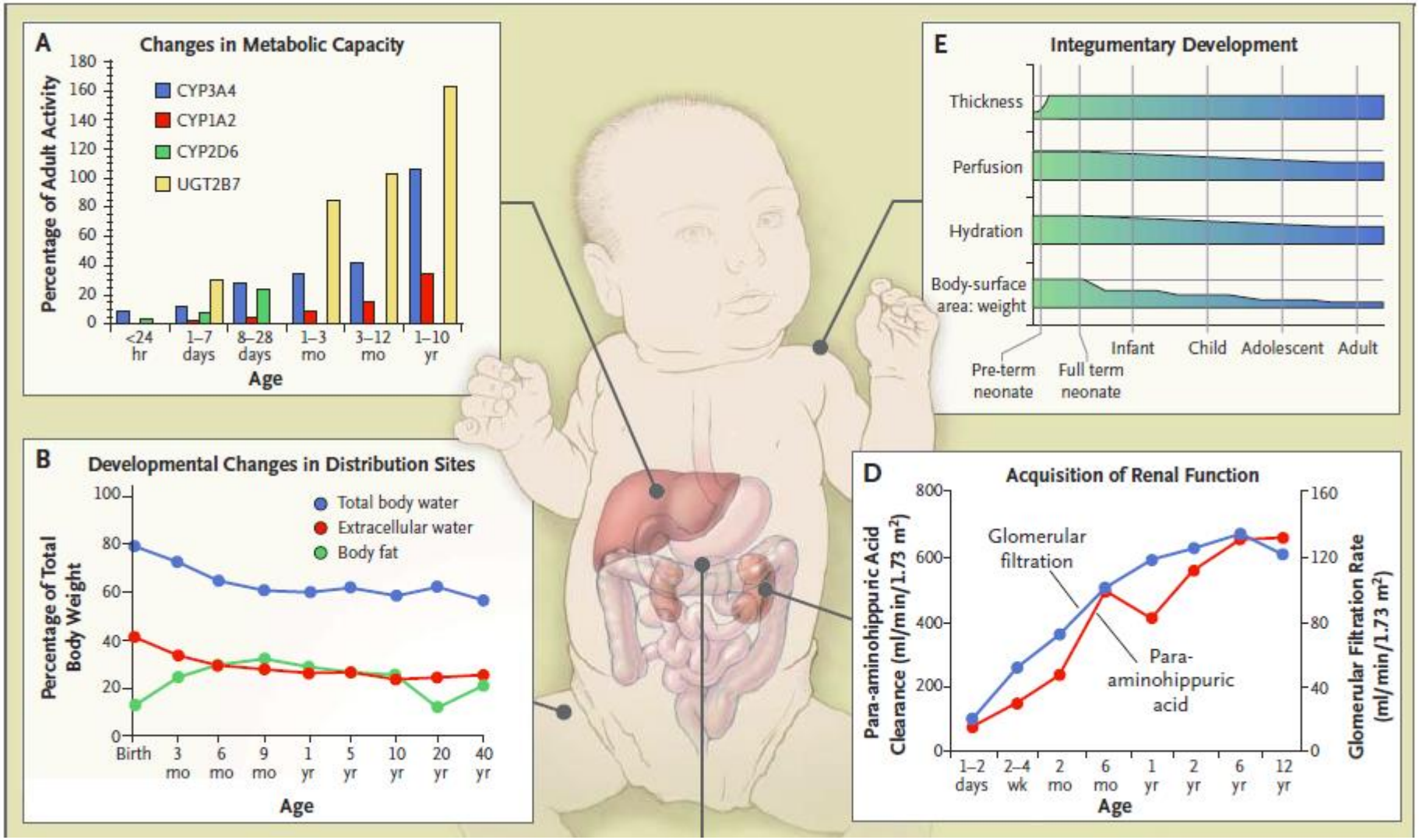




The Challenge of Pediatric Clinical Pharmacology

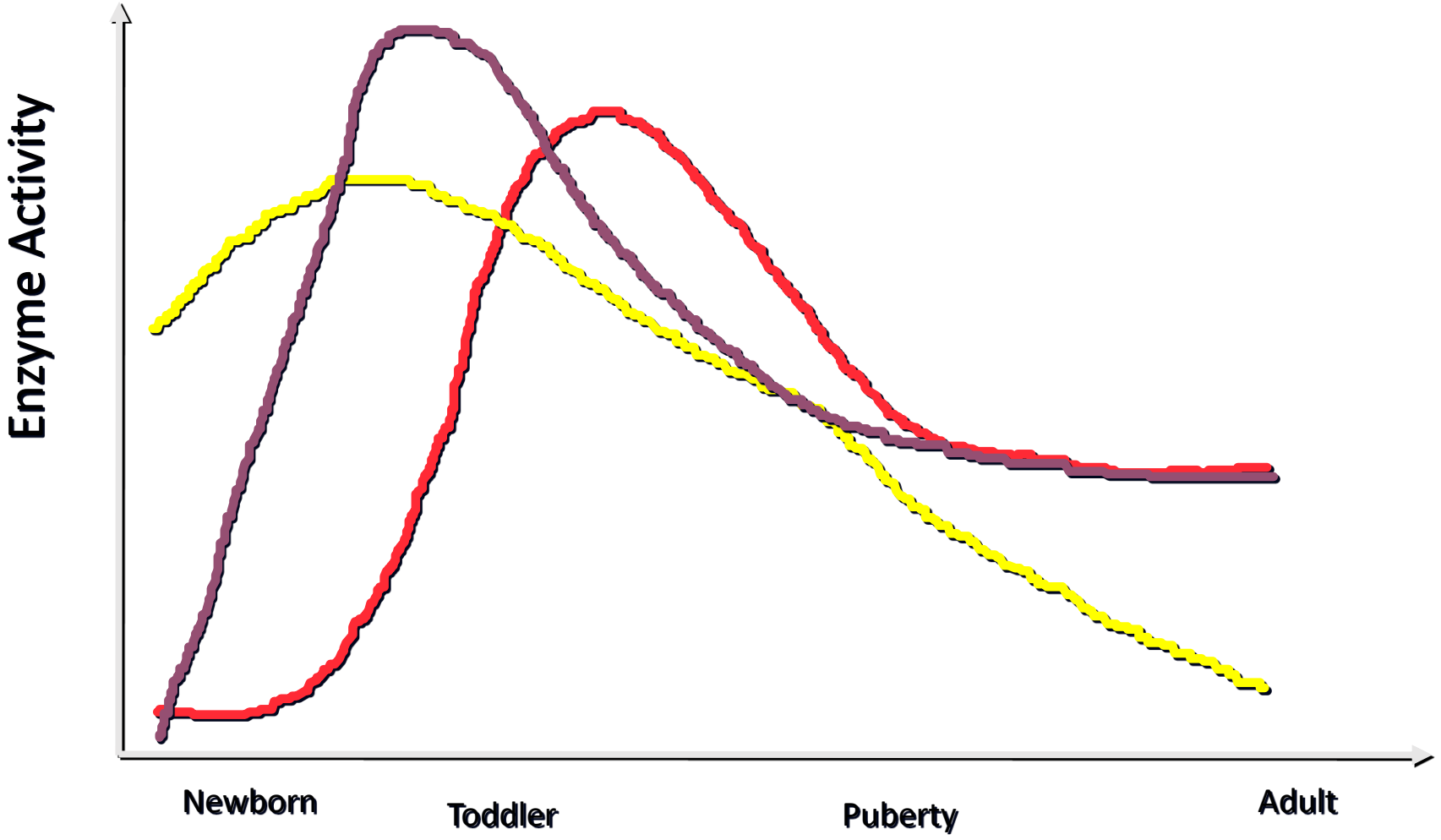
Ontogeny ⟷ *Pharmacogenetics*

Variability



G. Kearns NEJM 2003

Ontogeny of Drug Metabolism Pathways



G. Kearns NEJM 2003

Efavirenz and CYP2B6 in Children

- In children <3 years or with weigh <13 kg it is difficult to achieve target EFV concentrations
- The increase in oral clearance of efavirenz as a function of age (reaches 90% of mature value by 9 months of life)
- In children with CYP2B6 516 GG genotype, the oral clearance rate has been shown to be higher in children aged <5 years than in older children

Salem AH et al. *Antimicrob Agents Chemother 2014.*

Efavirenz and CYP2B6 in Children

- IMPAACT/PACTG 1070 study ongoing in children > 3 months and <3 years of age
- Showed HIV RNA <400 copies/mL in 61% by intent to treat analysis at 24 weeks
- Efavirenz doses higher than the FDA-recommended doses resulted in therapeutic efavirenz concentrations in a high proportion of study participants with GG/GT genotypes, but caused excessive exposure among children with TT genotype

Efavirenz and CYP2B6 in Children 3 months-3 years of age

3-4 fold difference in EFV dosing based on **CYP2B6 516GT** polymorphism

Weight (kg)	Efavienz Dose (mg)
3 kg - 4.99 kg	200 mg
5 kg - 6.99 kg	300 mg
7 kg -13.99 kg	400 mg
14 kg -16.99 kg	500 mg
≥17 kg	600 mg

IMPAACT 1070 dosing for CYP516 GG and GT

Weight (kg)	Efavirenz Dose (mg)
3 kg - 6.99 kg	50 mg
7 kg - 13.99 kg	100 mg
14 kg -16.99 kg	150 mg
≥17 kg	150 mg

IMPAACT 1070 dosing for CYP516 TT

Weight (kg)	Efavirenz Dose (mg)
3.5 kg to <5 kg	100 mg
5 kg to <7.5 kg	150 mg
7.5 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg

FDA Approved Dosing

Efavirenz and CYP2B6 in Children 3 months-3 years of Age

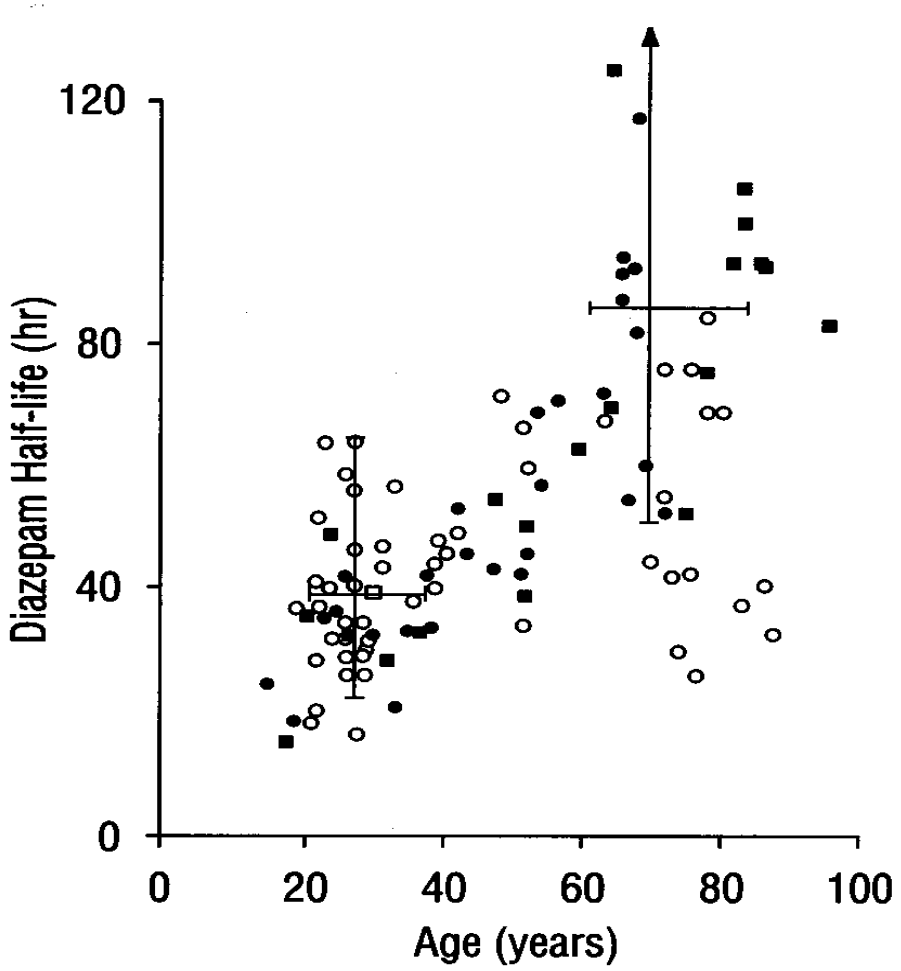
- Despite FDA approval, the US DHHS national treatment guidleines Panel recommends that efavirenz generally **not be used in children aged 3 months to <3 years**
- If efavirenz is used <3 years of age, Panel recommends determining CYP2B6 genotype (http://www.ncbi.nlm.nih.gov/gtr/labs)
- Patients to be classified as extensive CYP2B6 516 GG and GT genotypes versus slow CYP2B6 516 TT genotype metabolizers
- Efavirenz plasma concentrations should be measured 2 weeks post-initiation

ARVs for Adolescents

- Dosing of younger children is primarily weight-based
- Dosing ranges for adolescents are base don age:
  - Adolescents > 16 years old
  - Adolescents > 18 years old
  - Adolescents > 12 years old

    or weight
  - Adolescents (body weight ≥ 30; ≥35; ≥ 40)

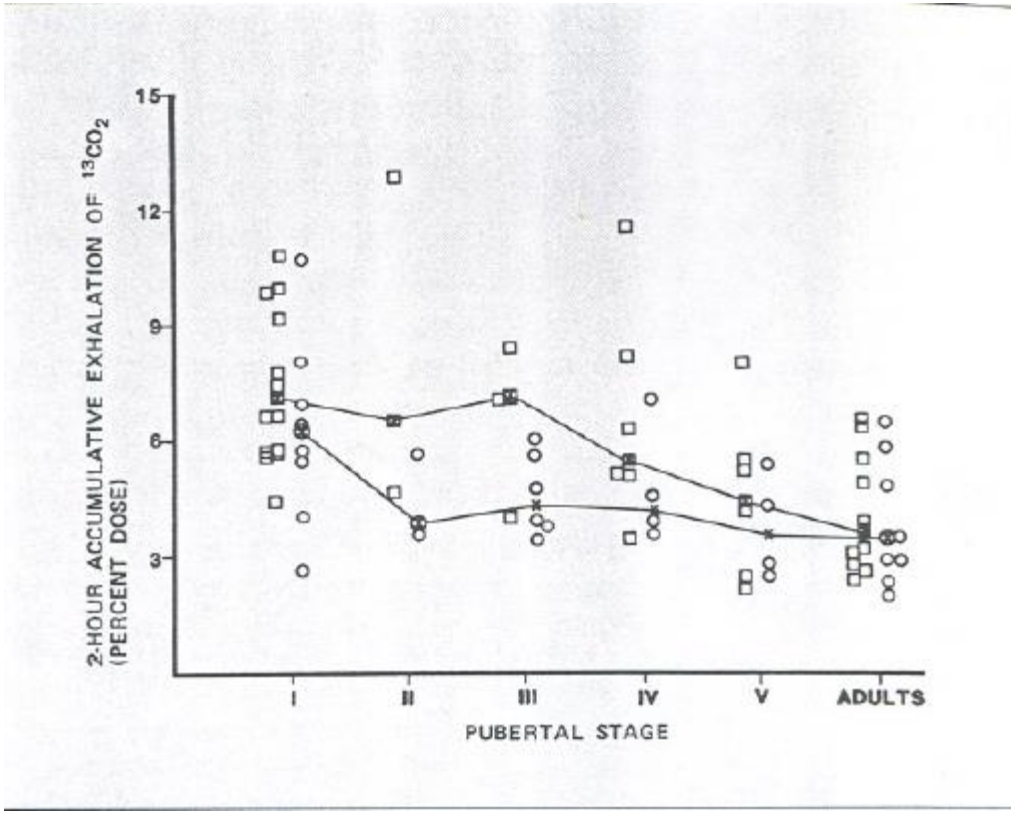
Metabolism in Young Adults may be Enhanced Compared to Elderly



Can Puberty Affect Drug Metabolism?

Changes in CYP 1A2 Activity During Adolescence

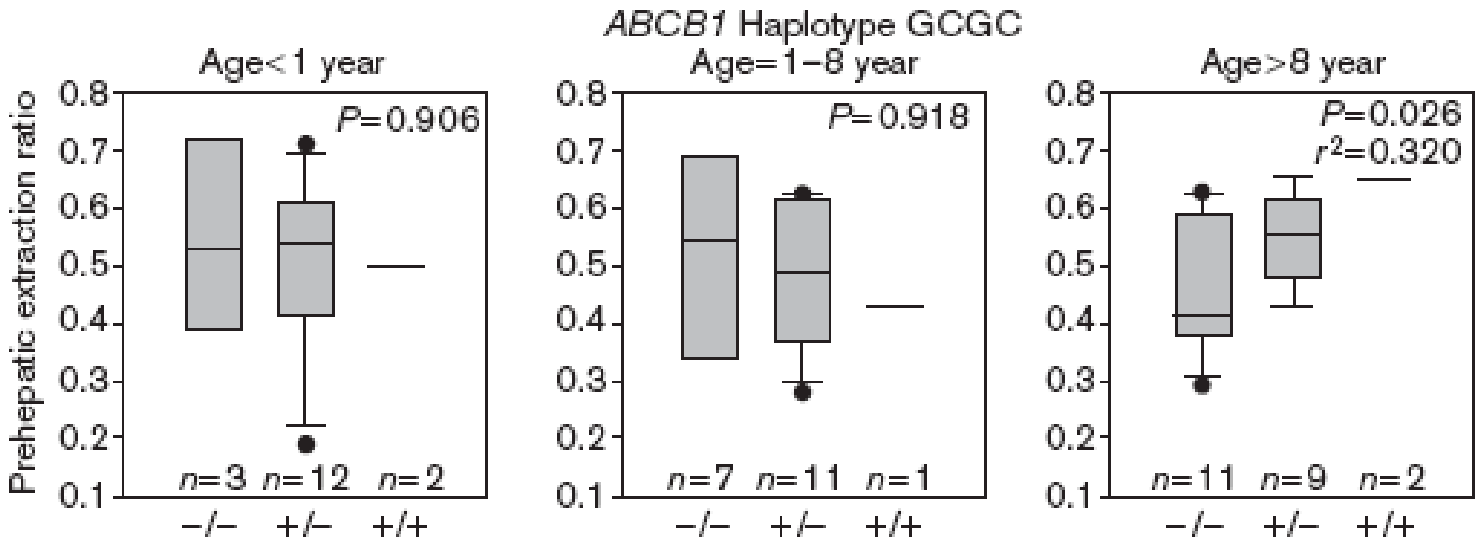
- Tanner stage dependent decrease in caffeine clearance
- Age dependent inducibility of the CYP1A2 pathway
- Gender dependent decrease in clearance in girls at an earlier Tanner stage as compared to clearances in boys



G Lambert Devo Pharmacol Ther 1986

Can Puberty Affect Drug Metabolism?

Age-dependent changes in the effect of ABCB1 polymorphisms on the oral bioavailability of cyclosporine in pediatric renal transplant patients

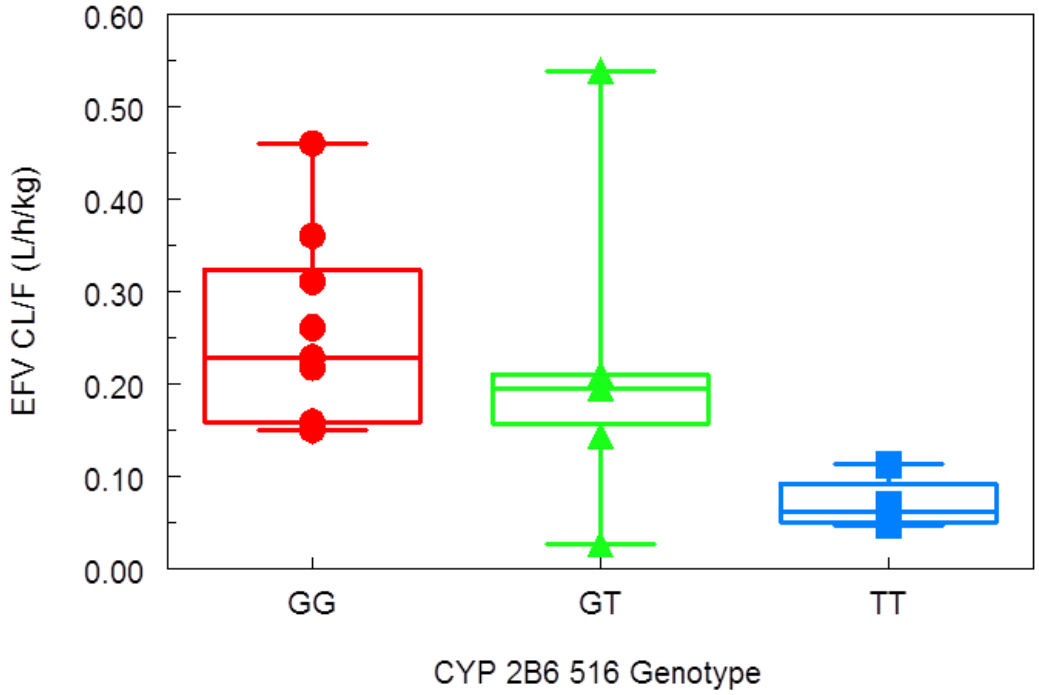


Fanta S, et al. Pharmacogenetics and Genomics 2007

Efavirenz in Adolescents

- 21 (9 African American, 11 African, 1 Hispanic)
- Pre-pubertal children with Tanner stage I-II (n=11; median age 11.7 years; 6 Females) and adolescent patients with Tanner stage III-IV (n=10; median age 15.2 years; 5 Females)
- The concentrations of EFV and its metabolites 8-hydroxy-EFV (E8F) and 8-hydroxy-EFV glucuronide (E8G), were measured at steady-state during a 24 hour PK study at time points 0, 1, 2, 4, 6, 8, 12 and 24 hours.

CYP2B6 genotype and CL/F of EFV



Efavirenz in Adolescents

- No significant differences were seen in E8F AUC, (E8F+E8G) AUC, E8F/EVF or (E8F+E8G)/ EFV ratios
- Median CNS toxicity score was 12.5 (1-23)
- There was no association between EFV AUC and CY2B6 genotype with CNS toxicity
- No differences in EFV AUC, CL/F and (E8F+E8G)/EFV were observed between children in Tanner Stages I-II and adolescents in Tanner stages III-IV.

Case Study – CYP2B6 and Efavirenz

- 13 year old AA boy (Tanner Stage III-IV) with perinatally acquired HIV, CDC category B3
- Past medical history includes lymphocytic interstitial pneumonitis, herpes zoster, and failure to thrive
- History of excellent compliance with ART and stable ART regimen with Stavudine (d4T), Efavirenz (EFV) and Amprenavir (APV) for >7 years
- Sustained (> 7years) undetectable HIV viral load (<400 copies/ml and later <48 copies/mL)

Case Study – CYP2B6 and Efavirenz

- Random ARV plasma concentrations during clinic visits – high concentrations of EFV (21,000 ng/mL) and low concentrations of APV (29 ng/mL)
- First 12 hours PK study – demonstrates high EFV AUC and negligent concentrations of APV (C_{max}=42ng/mL, $AUC_{0\text{-}12}$= 0.19 ng/L·h) with very high APV clearance (CL)=110.8 l/h/kg)
- The PK findings prompt the change in regimen to Lamivudine (3TC), ABC, TDF and EFV

Case Study – CYP2B6 and Efavirenz

- Prior to the release of the results of the first PK study the medical provider increases EFV dose based on the weight
- No clinical toxicity, no abnormal laboratory findings
- Change in EFV dose is discussed with the family
- Repeat PK study is conducted to confirm the high EFV exposure
- Following the second PK study family chooses to lower EFV dose to 200 mg

Pharmacokinetics of Efavirenz

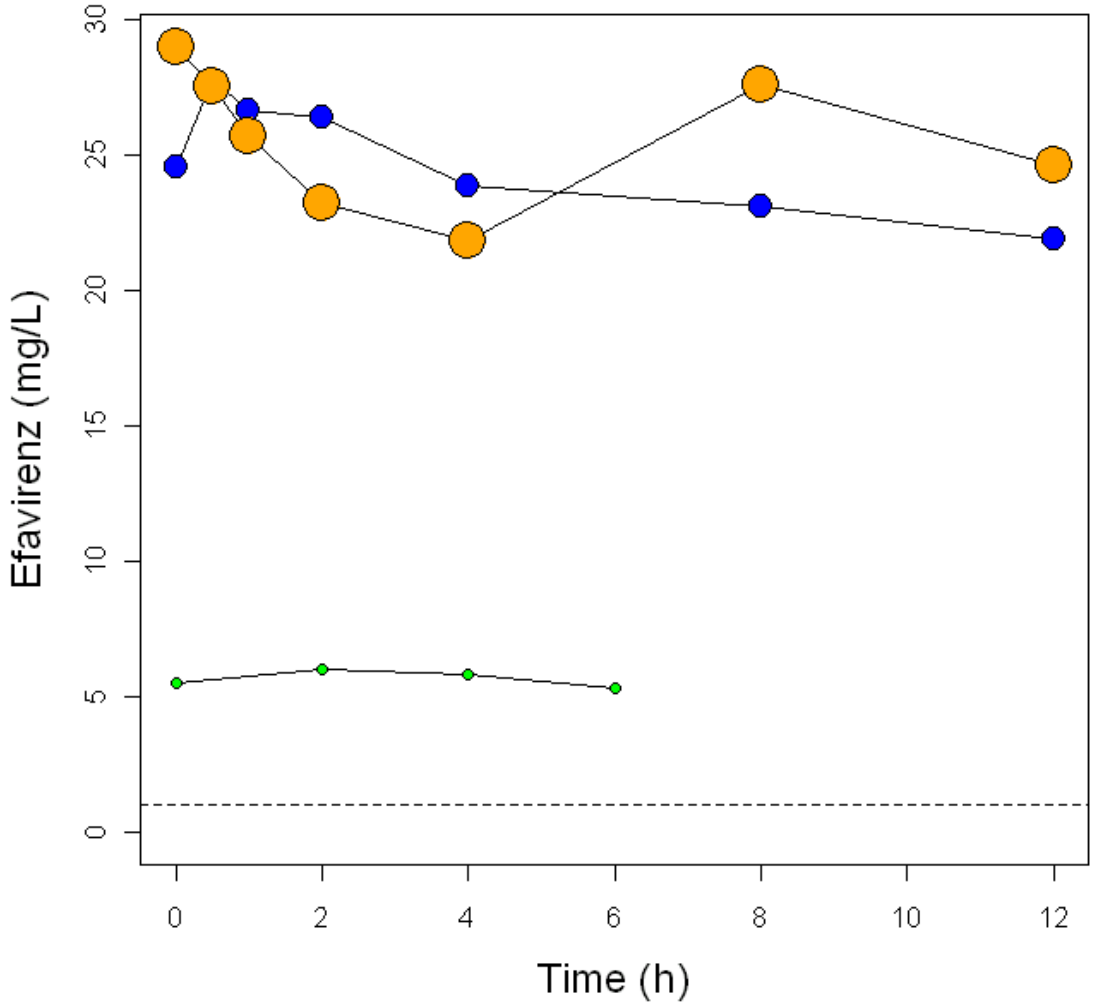
- 600 mg EFV dose

- 400 mg EFV dose

- 200 mg EFV dose

Genotype reveals CYP2B6 516TT mutation

HIV RNA viral load undetectable at >52 weeks on **200 mg EFV** with ABC/3TC/TDF



Conclusions

- Despite a large amount of data, pharmacogenetics have limited application in clinical practice
- The clinical application is limited to efavirenz dose reduction (CYP P450 2B6 variants) and to unboosted atazanavir (combination of polymorphisms in P-glycoprotein, OATP1B1 and pregnane X receptor (PXR))
- Studies on the clinical relevance and cost effectiveness of using phamracogenetics are missing
- A better understanding of the pharmacogenetic differences on the disposition of ARVs during infancy, childhood and puberty is needed

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