Pharmacokinetics, -dynamics and dosing considerations in children

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ePTRI
European Paediatric Translational Research Infrastructure

Erasmus MC
Universitair Medisch Centrum Rotterdam

KATHOLIEKE UNIVERSITEIT
LEUVEN

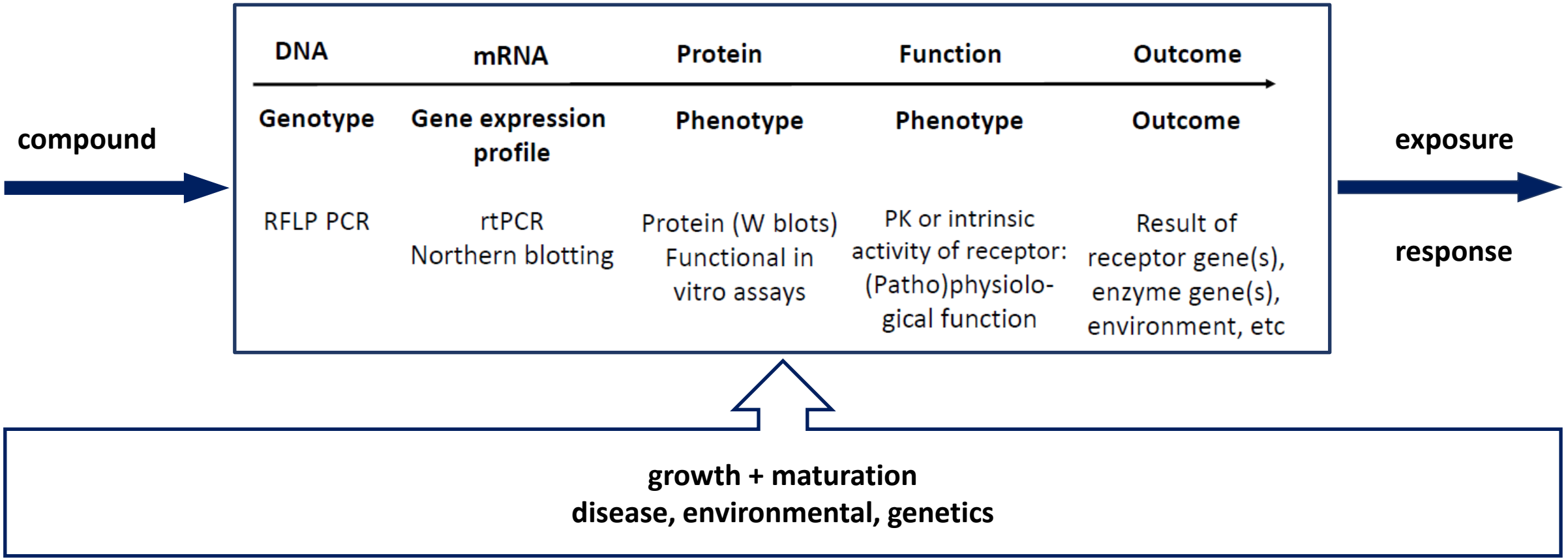
limited size, extensive variability

" Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but….it has its own independent range and horizon…"

Dr. Abraham Jacobi, 1889

a child is not (just) a small adult
a newborn is not (just) a small child
(a pregnant woman is not just a woman with a big belly)

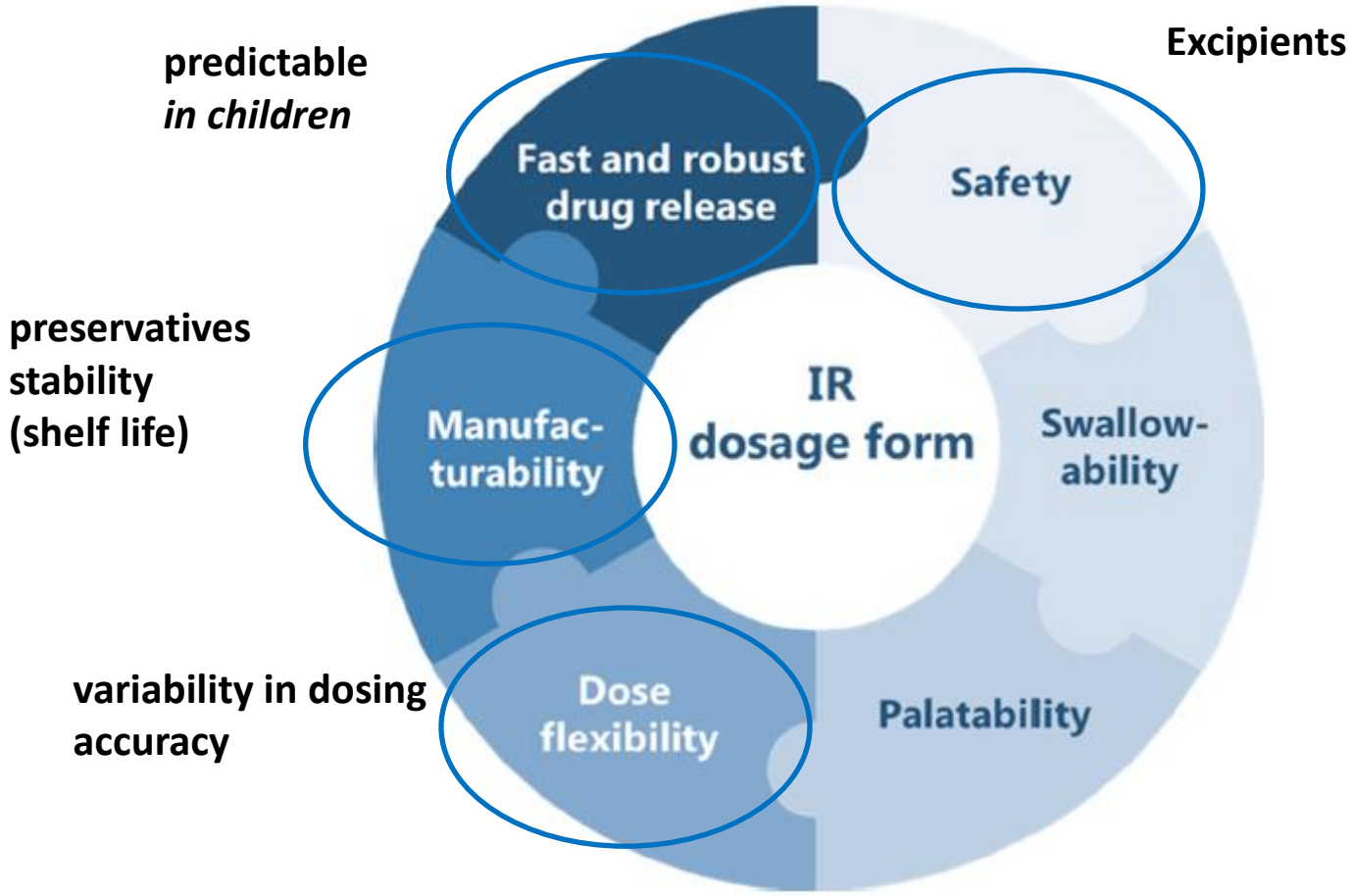
developmental pharmacokinetics and -dynamics



TAILORED

DRIVEN

developmental ‘formulations/medical devices’



Freerks et al. Eur J Pharm Biopharm 2020

why this matters: off label, off target…

Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study

Esse N Menson, A Sarah Walker, Mike Sharland, Carole Wells, Gareth Tudor-Williams, F Andrew I Riordan, E G Hermione Lyall, Diana M Gibb, for the collaborative HIV paediatric study steering committee

differences (mg) between recommended dose (300 mg/m^2) and the previous used dosing regimes

2-7 years (*14 mg/kg*), mean difference + 30 mg
8-12 years (*8 mg/kg*), mean difference - 80 mg

an illustration: chronic systemic corticosteroid use

Weight gain

Mood changes

Growth stunting (specific for children)

Cushingoid appearance

Risk of bone fracture

Adrenal suppression

Delayed puberty (specific for children)

Sleep disturbances

Immune suppression

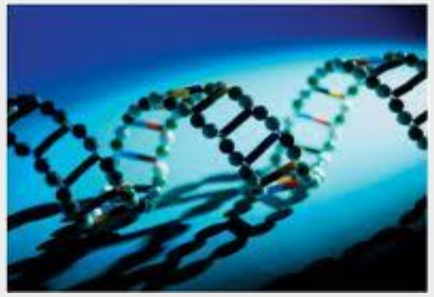
Cerebral palsy, cognitive impairment (specific for preterm in neonatal life)

covariates of drug metabolism

herbal medicine

disease

drugs

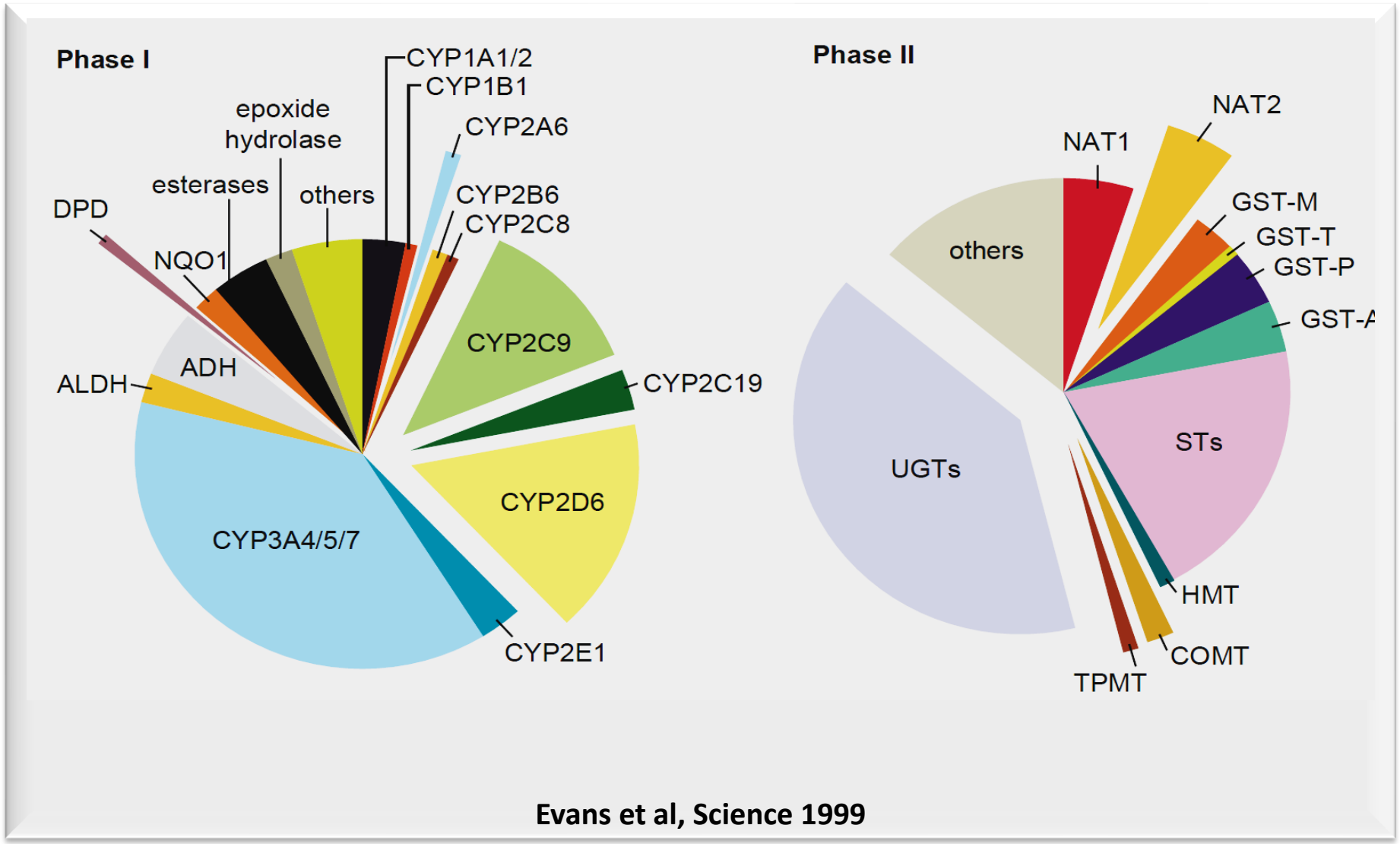


genetics

age

nutrition

covariates of drug metabolism



Evans et al, Science 1999

covariates of renal elimination: GFR + renal tubular activity

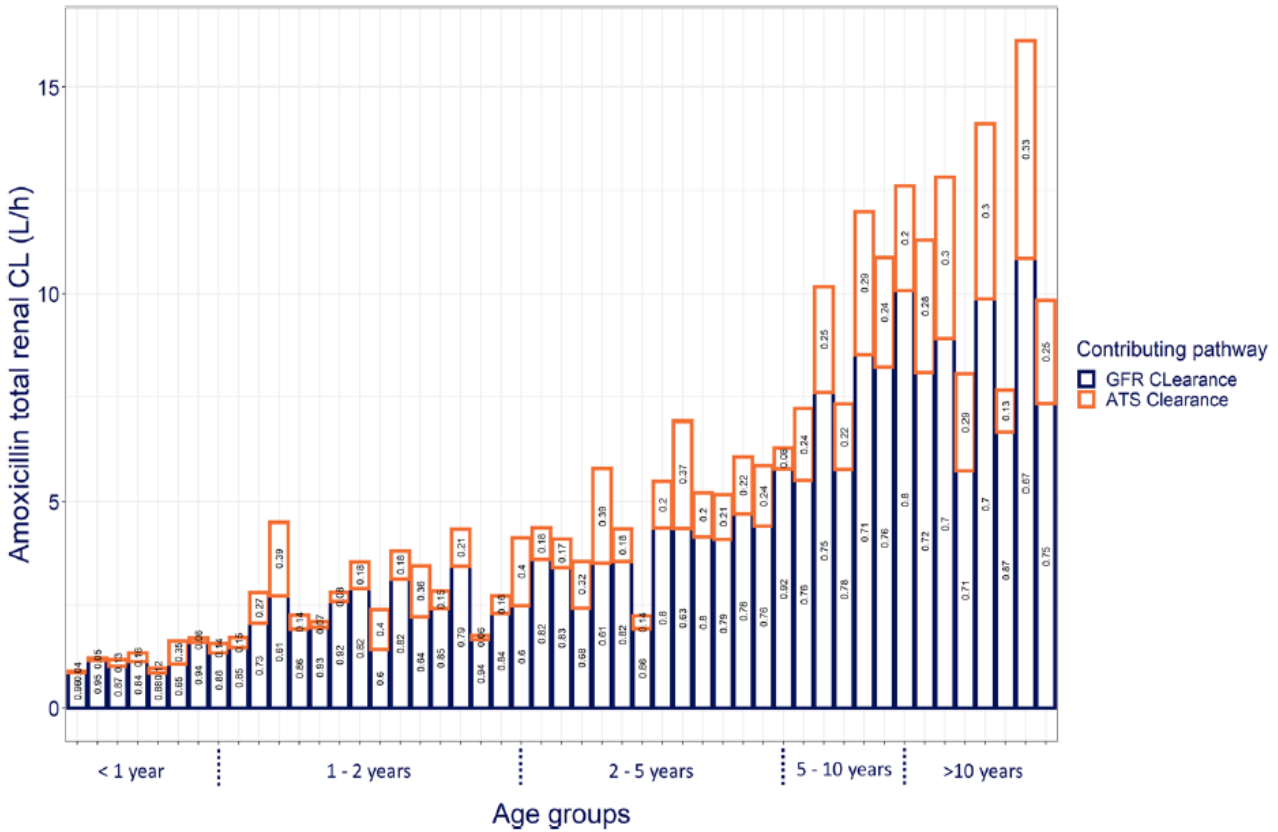
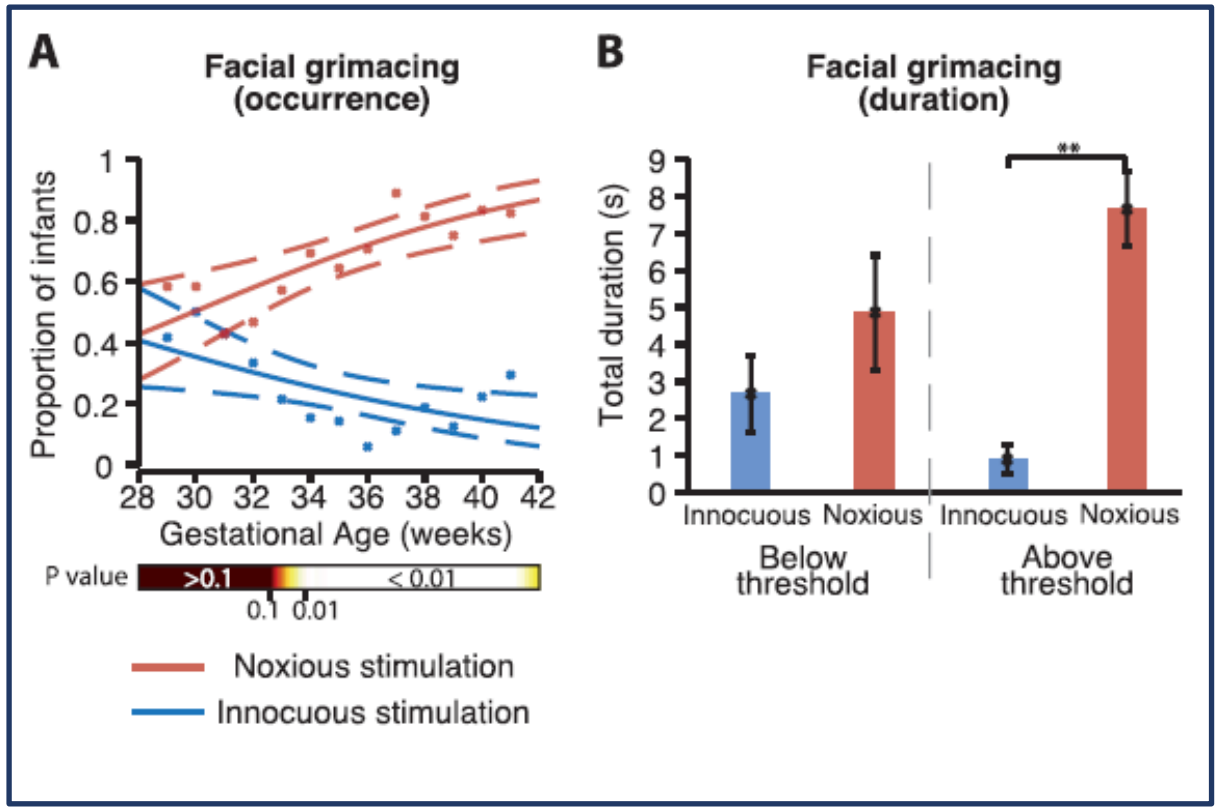


Fig. 2. Contribution of clearance through glomerular filtration (CL_{GF} – bottom blue boxes) and through active tubular secretion (CL_{ATS} – top orange boxes) to total renal clearance of amoxicillin (CL_R – sum of blue and orange boxes) for each pediatric patient of the studied population sorted and grouped by age. The numbers in each box show the relative contribution of CL_{GF} and CL_{ATS} to total CL_R for each individual

Cristea et al, AAPS J 2021

pharmacodynamics, effects

cns, pain assessment in neonates

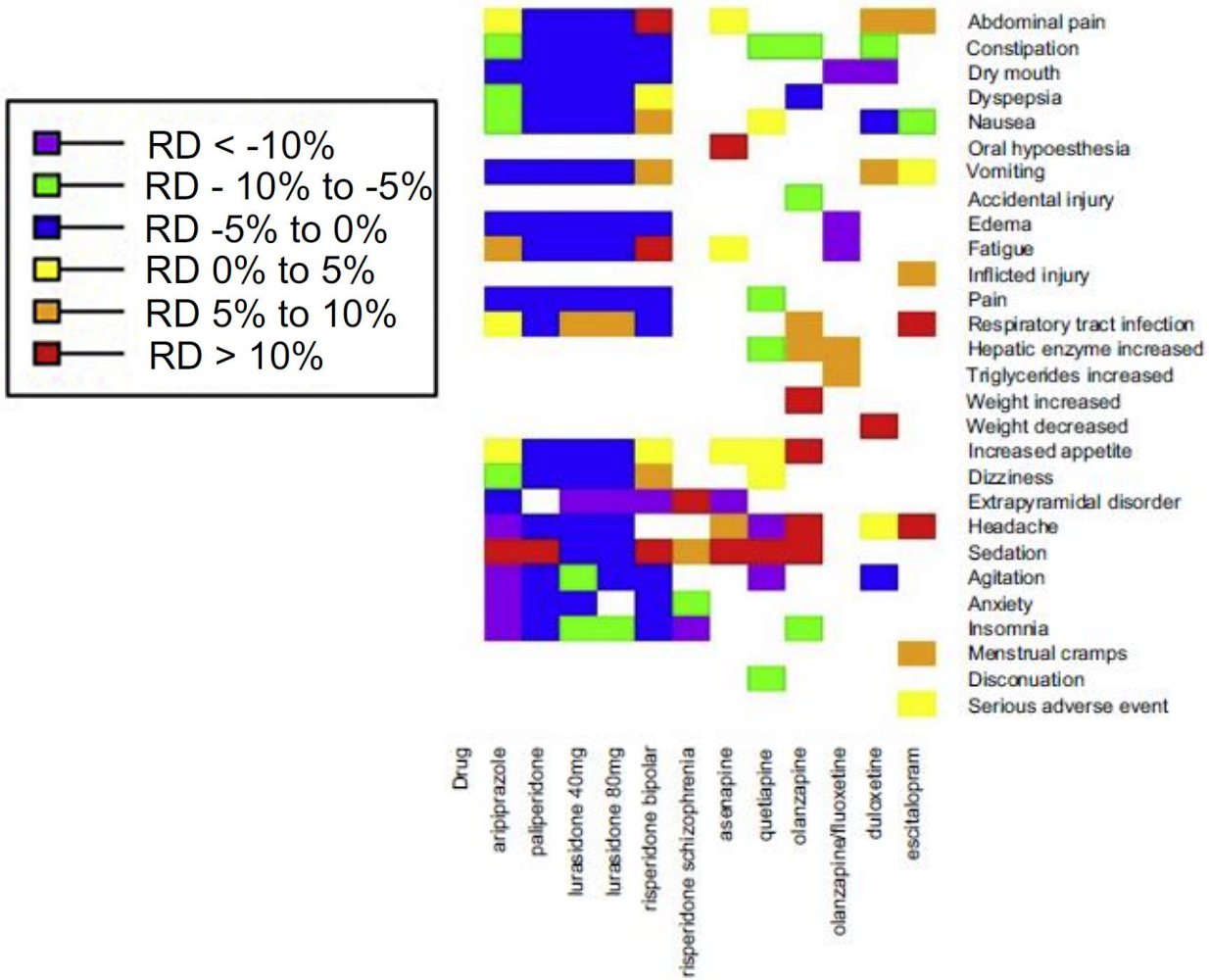


receptor **expression** and **activity**, maturational changes:
same concentration ≠ same effect ≠ clinical expression (pain)

Green et al. Pain 2019;160:493-500; Rakhade et al. Nat Rev Neurol 2009;5:380-389

pharmacodynamics, side effects

CNS (antidepressants, anti-psychotics), risk difference adverse event



Liu et al, J Pediatr 2019;208:236-242.e3

pharmacodynamics, safety/side effect

cardiac, developmental physiology (calcium flux, atrial myocytes)

DEVELOPMENTAL DIFFERENCES IN HUMAN L-TYPE Ca^{2+} CURRENT

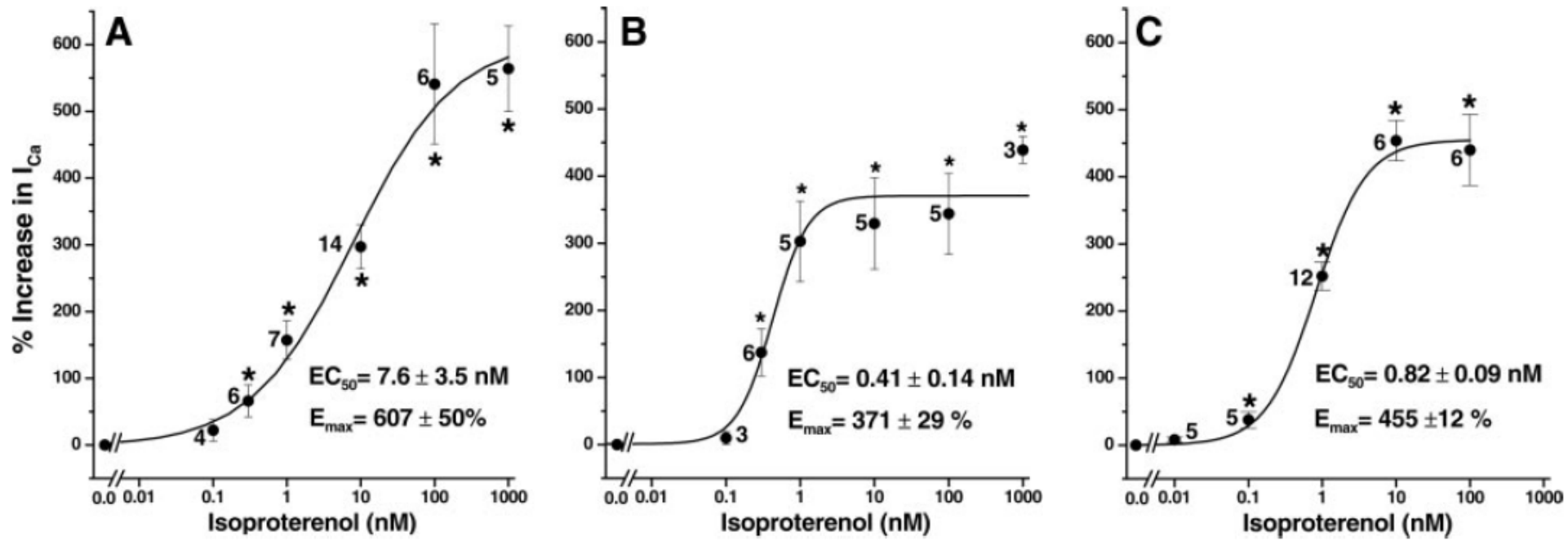
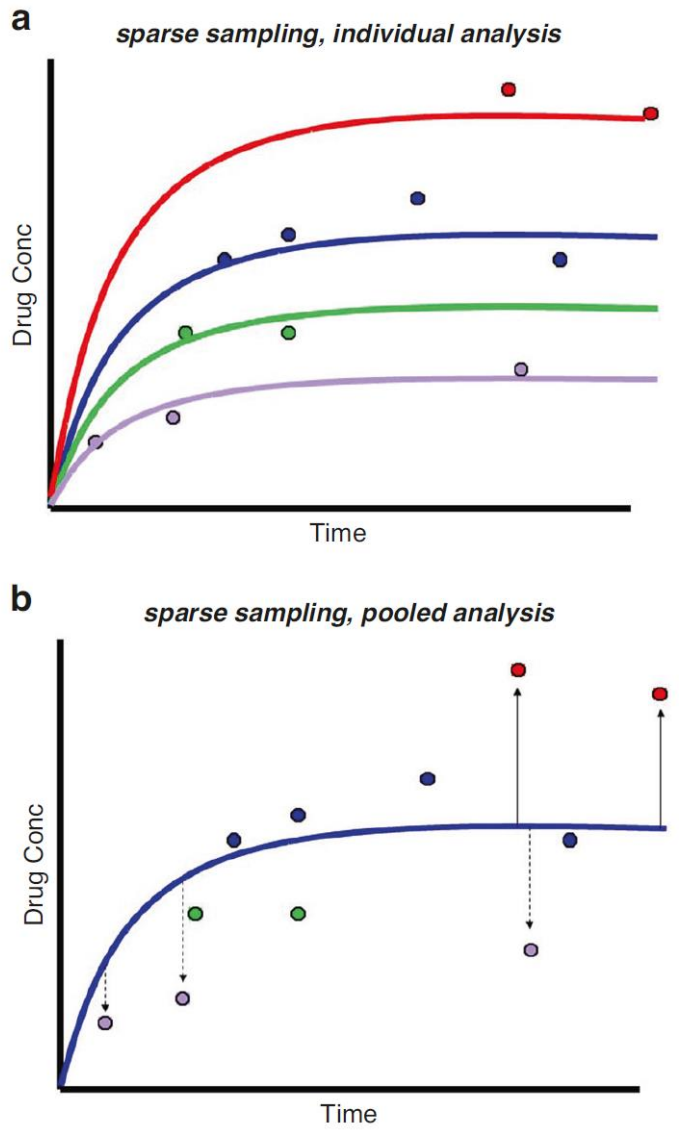


Fig. 3. Dose-response curves for percent change in I_{Ca} for INF, YAD, and AD atrial cells in response to Iso. Calculated values for EC_{50} (potency) and E_{max} (efficacy) are shown for INF (*A*), YAD (*B*), and AD (*C*) cells. *Significantly increased compared with control.

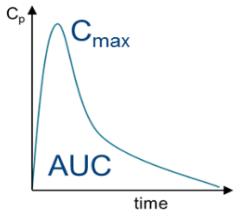
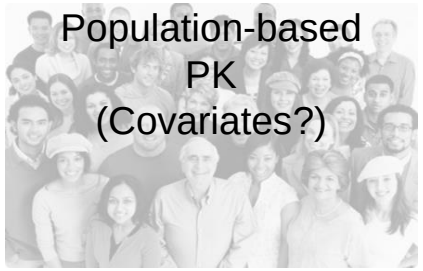
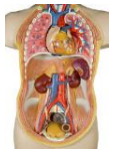
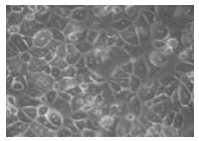
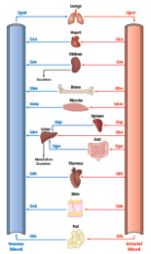
Tipparaju et al, Am J Physiol Heart Circ Physiol 2004;286:H1963-1969


THINK
POSITIVE

population PK as research tool

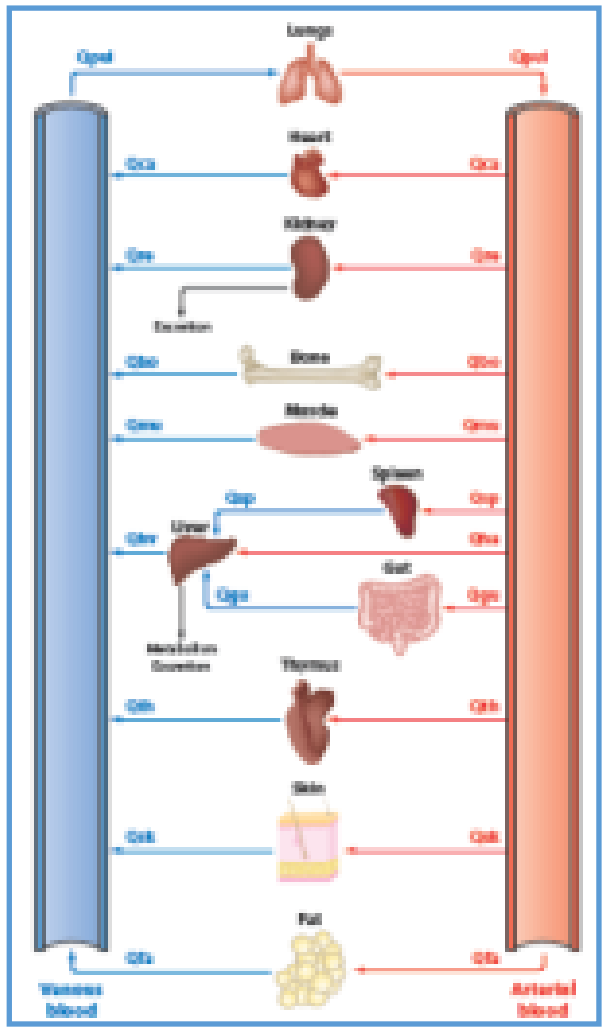


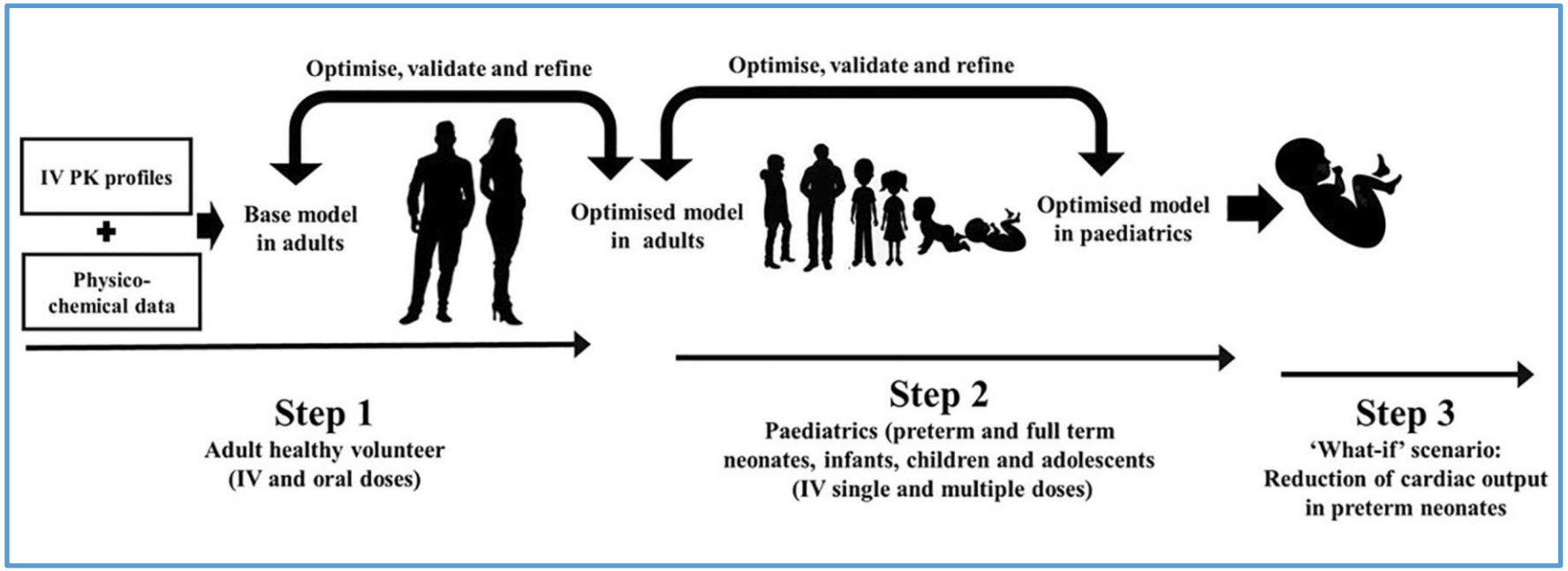
Li et al, Pediatr Research 2024 (online)

	Data gathering	Modelling	Clinical implications
"TOP DOWN" Clinic to mechanistic (population-based)	Plasma Data 	Population-based PK (Covariates?) 	Confirming 
"BOTTOM UP" *In vitro* to *In vivo* (IVIVE)	 Demography Physiology Genetics *In vitro* data  	PBPK/IVIVE 	Learning 

how to integrate PK/PD, and safety

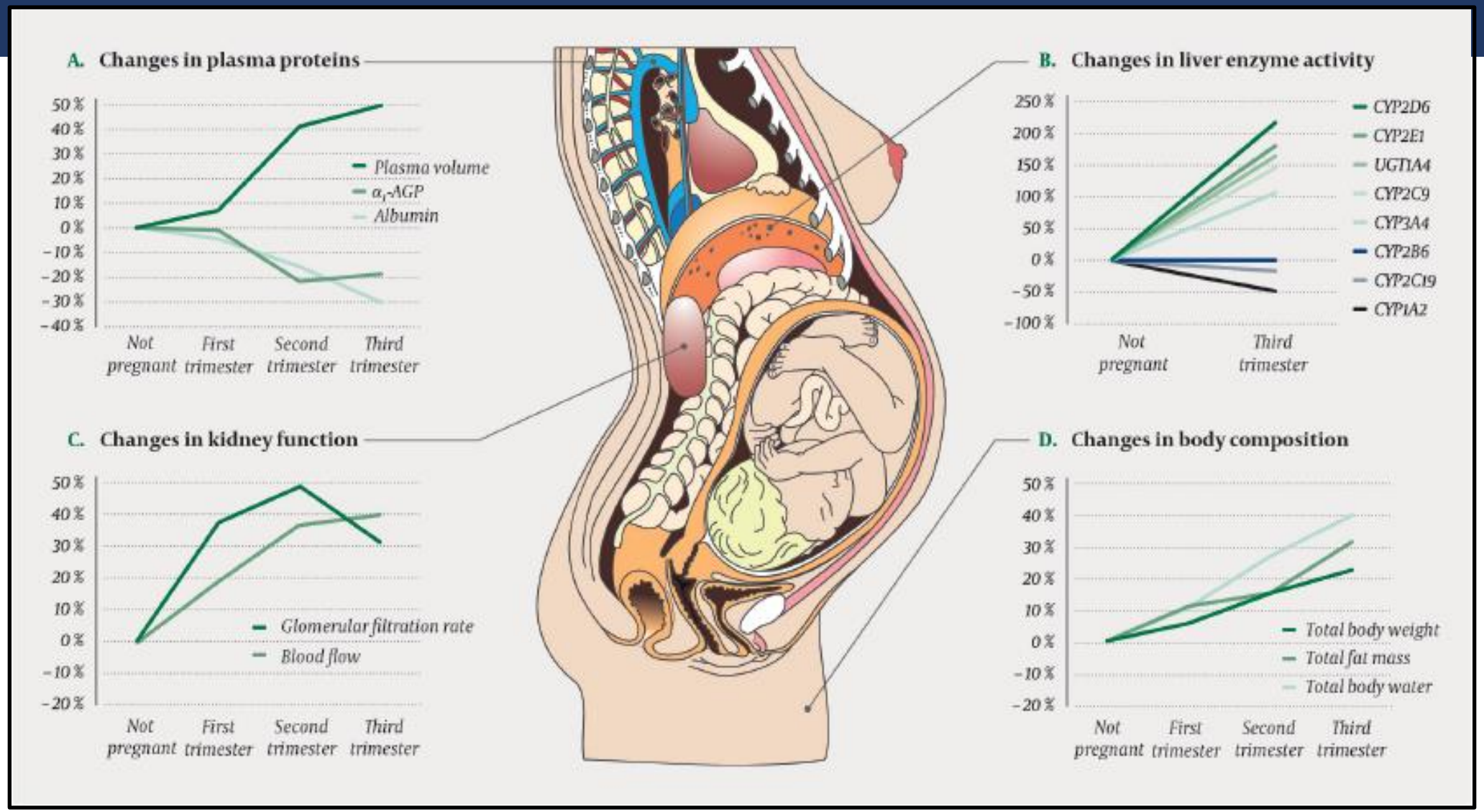
we can use what we already know, bottom up (‘*in silico*’, PBPK)





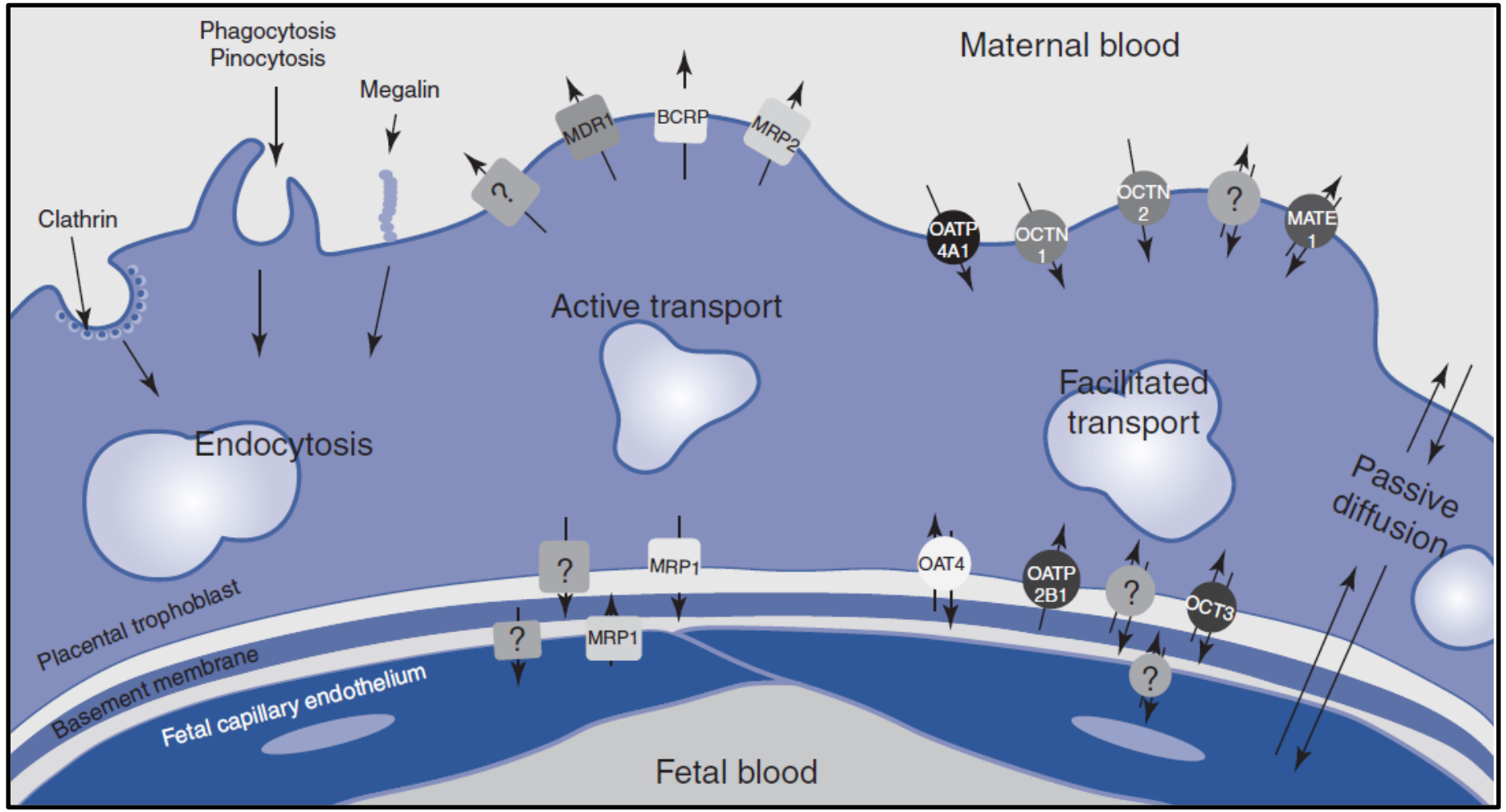
Olusola et al, Biopharm Drug Dispos 2021; Allegaert et al, Pharmaceutics 2022

pregnancy related physiological changes



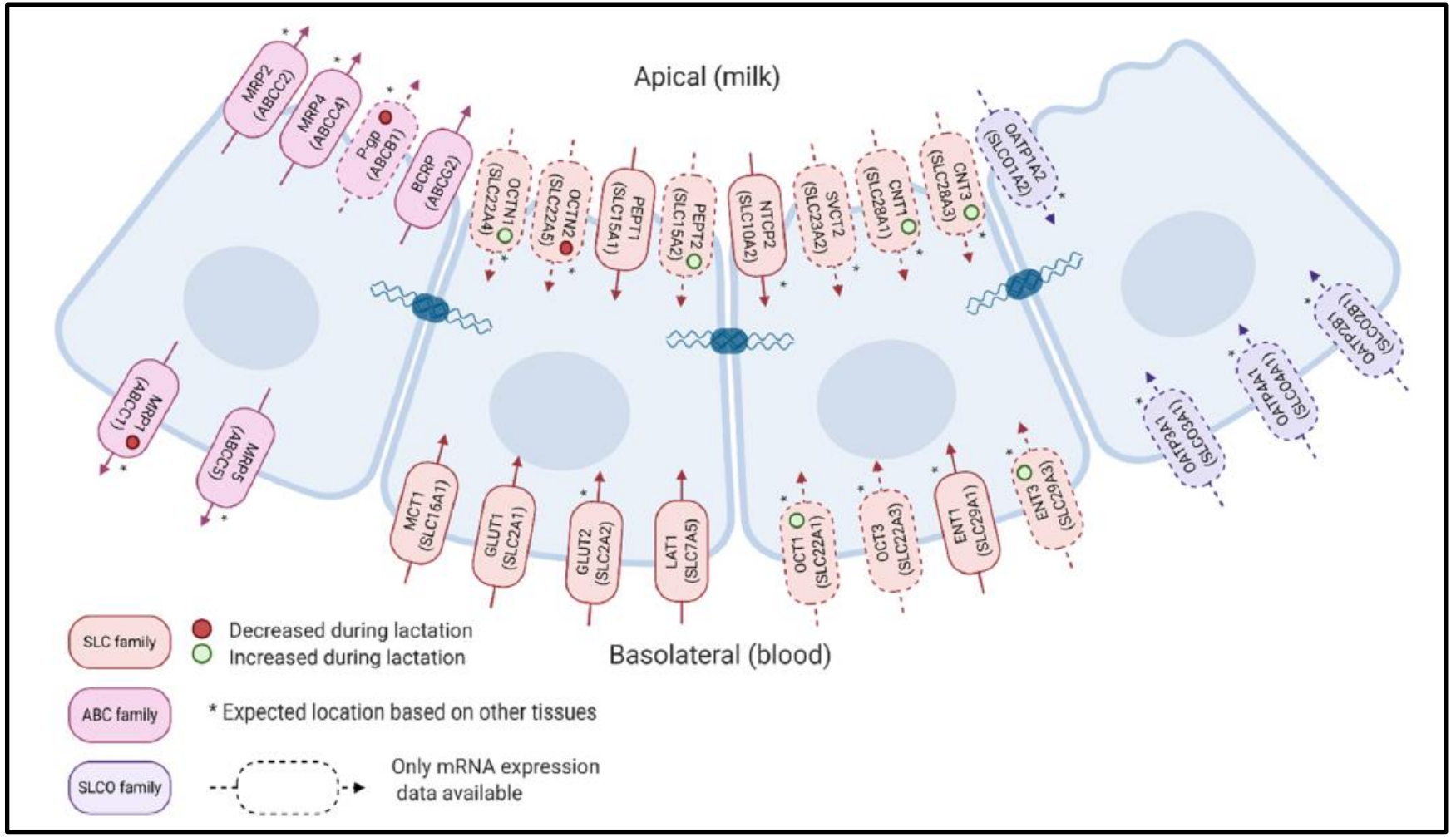
Westin, et al. Tidsskr Nor Legeforen 2018

placenta-related drug transfer: beyond passive diffusion



Kazma et al, chapter 9 Yaffe and Aranda's textbook Neonatal and Pediatric Pharmacology, 5th edition

lactation-related drug transfer



Nauwelaerts et al, Biomed Pharmacol 2021

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