Physiologically Based Pharmacokinetic (PBPK) Modelling in Vulnerable Populations

PBPK in young children: the importance of ontogeny

March 14th, 2019

Jean Dinh PharmD, PhD

Children's Mercy KANSAS CITY

UMKC School of Medicine

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2017-18

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

Disclosures

- Consultant for ReveraGen BioPharma

Highlights

- Target population: children
- Specific population issues prime for PBPK as a tool: ontogeny
- Why PBPK may out-perform other pharmacometric tools:
  - Minimize ethical and technical concerns with conducting intense pharmacokinetic studies in children, particularly young children.
  - Incorporation of ontogeny functions.
  - Can adjust physiological parameters to model specific pediatric population of interest.

Precision Medicine

Precision Diagnosis

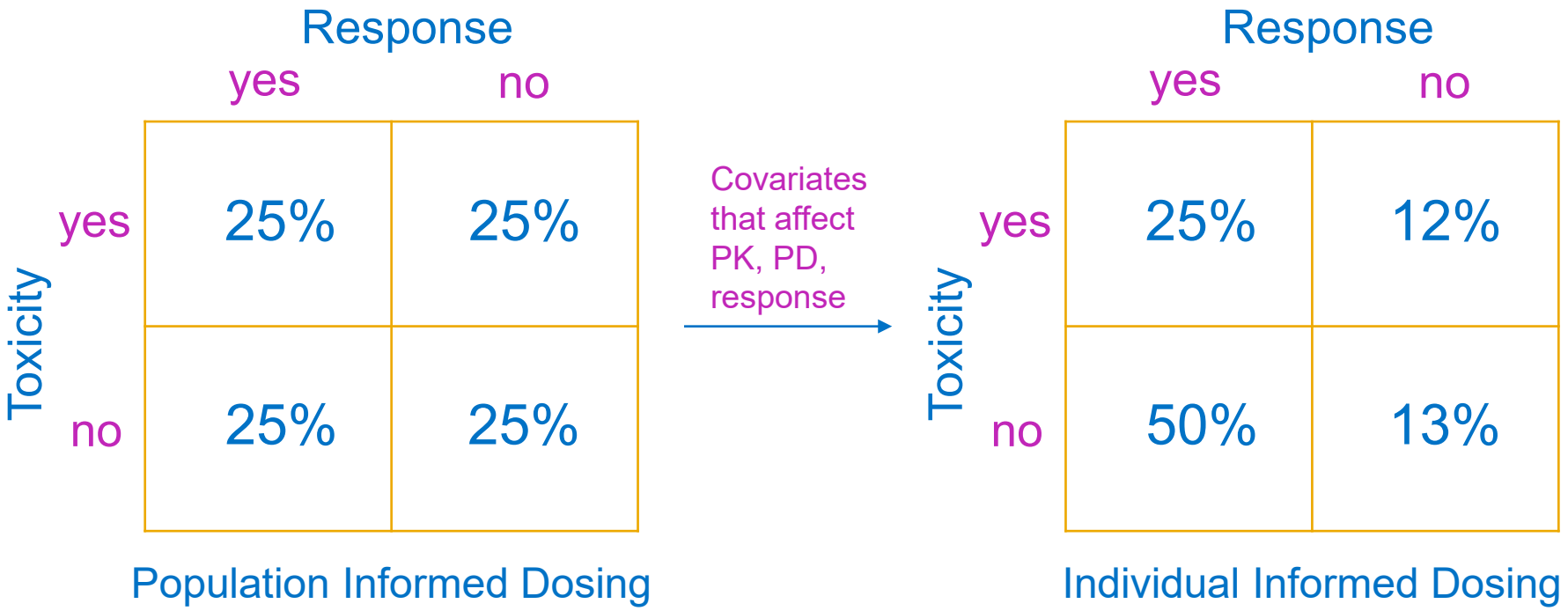
- Understanding mechanism of pathophysiology
- Determine the biological processes that are dysregulated
- Biomarkers of disease progression

Precision Therapeutics

- Determine the “right” medication
- Determine the “right” dose
- Anticipate efficacy and possible adverse events

Children's Mercy KANSAS CITY

Precision Therapeutics: Making better decisions for the child, based on the child's data



Precision Therapeutics Strategy: Stratification with Biomarkers

Demographic Information

- Age (Ontogeny!)
- Weight
- Gender
- Ethnicity

High-Throughput Information

- Genomics
- Transcriptomics
- Proteomics
- Metabolomics

Children's Mercy KANSAS CITY

Ontogeny Definition

Ontogeny

The development, or course of development, of an individual organism

The development of individual to maturity: the development of an individual from a fertilized ovum to maturity

- Age in the case is a (crude) biomarker of complex biological processes.
  - Biomarker that correlates with activity/function of biological process that is critical to drug PBPK.

Considerations when studying/modelling a pediatric population

Clinical studies to characterize PK

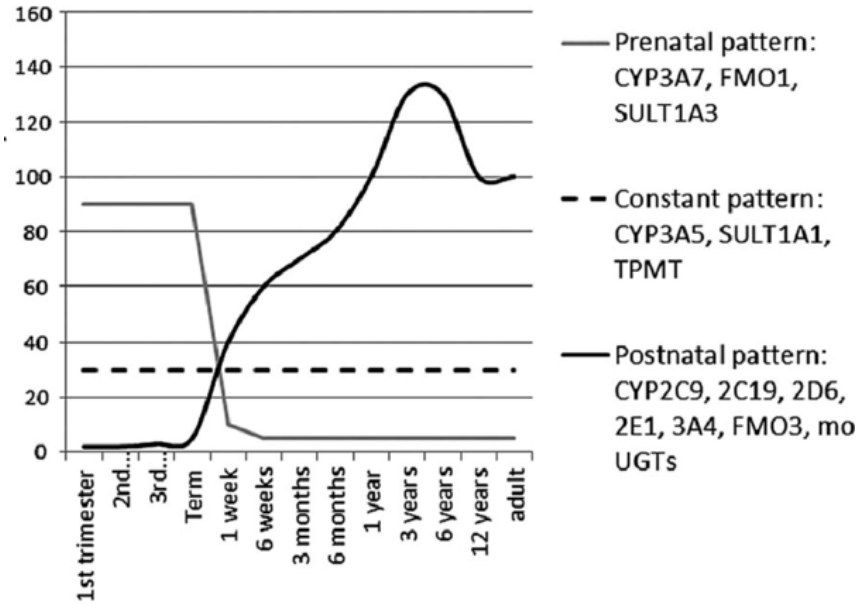
- Ethics (particularly young children)
- Highly heterogenous, increased noise (age range represents large change in physiological process of interest)
  - NICHD age group recommendation: term neonatal (Birth – 27 days); infancy (28 days – 12 months); toddler (13 months – 2 years); early childhood (2-5 years); middle childhood (6-11 years); early adolescence (12-18 years); late adolescence (19-21 years)

Modeling to anticipate PK

- Typically scaled down from adult
- Assumption:
  - Disease presentation, clinical targets, drug pharmacokinetics and pharmacodynamics are similar between adults and children.

The Role of Ontogeny → Metabolism, Clearance, and PBPK

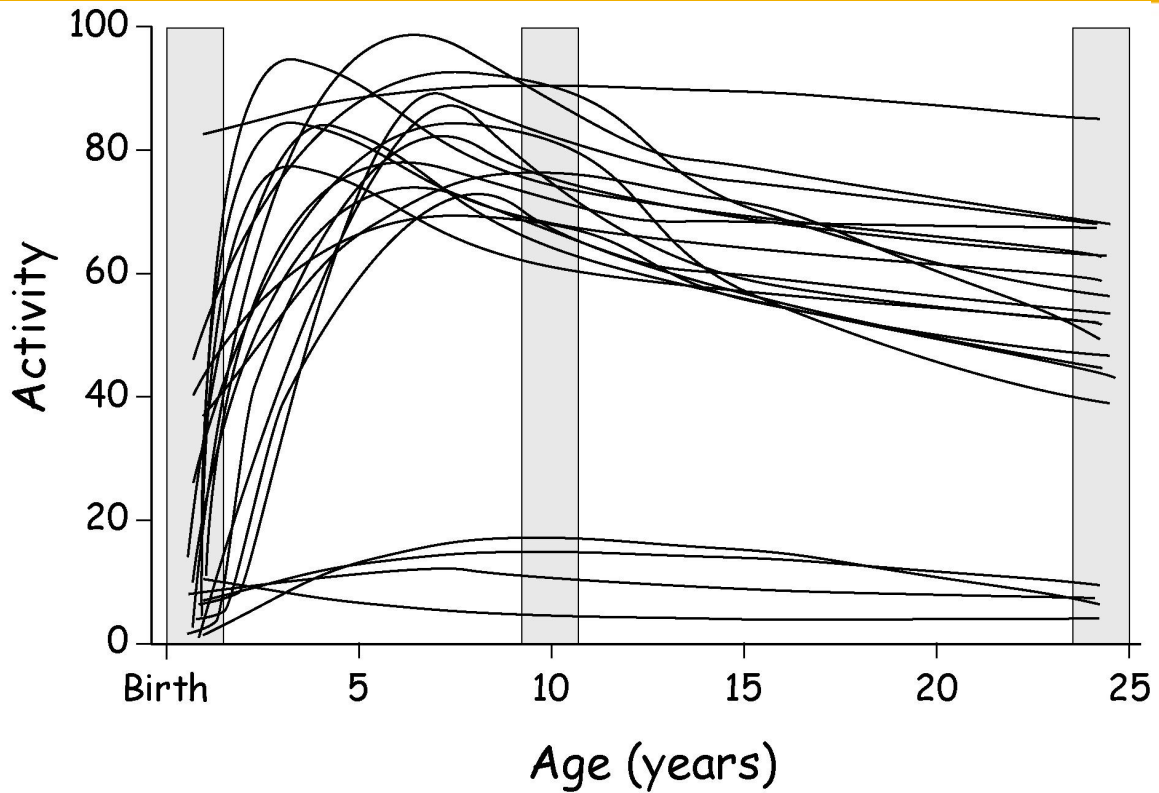
- Functional drug biotransformation capacity is acquired in gene-specific patterns ("developmental trajectories")
  - Group 1: Primarily fetal expression (CYP3A7; SULT1E1)
  - Group 2: SULT1A1, CYP2C19, CYP3A5, GSTA1
  - Group 3: CYP1A2, CYP2C9, CYP2D6, CYP3A4, UGTs
- Observed variability greatest in first 3 months of life



Children's Mercy KANSAS CITY

De Wildt et. al, (2014)

Variability in Group 3 Trajectories



Courtesy of JS Leeder

Caveats when Scaling Adult Models for Children

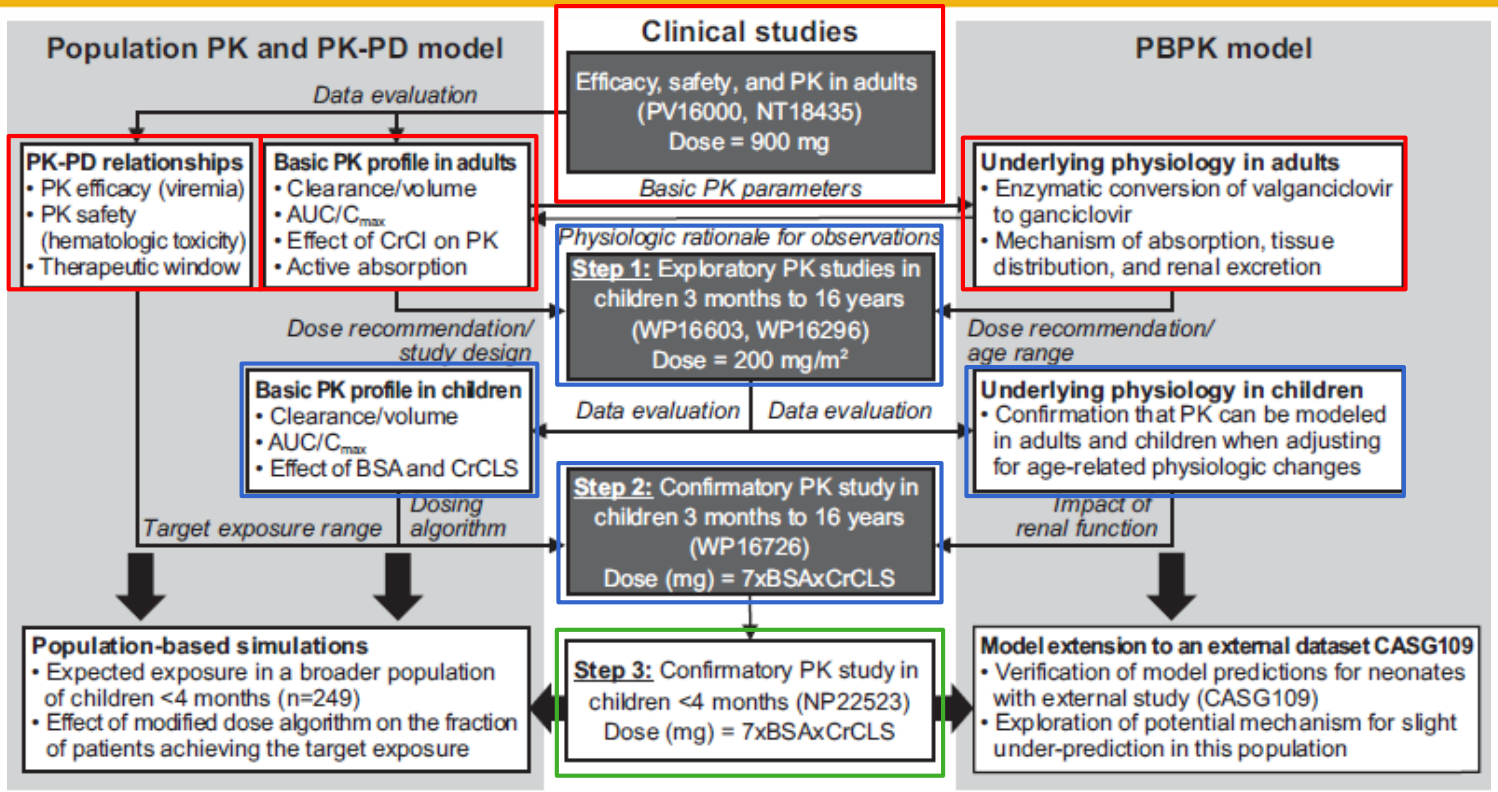
- Same pathways of clearance between adults and children (DMEs, transporters, etc.)
- Comprehensive data available for children about physiological, biochemical, and physiochemical processes (or good estimates).
- Drug does not impact trajectory of gene expression and/or protein content.

Valganciclovir: PopPK + PBPK

- Valganciclor (VGCV) is an oral prodrug of ganciclovir (GCV) → prevention and treatment of cytomegalovirus (CMV) infection.
- Goal: approval of dosing algorithm of children < 4 months old.
- Method: PopPK ("Top-Down") + PBPK ("Bottom-Up") = "Middle-out"
  - GCV PopPK → Covariates of importance to clearance were CrCl and ht (assoc with Vd).
  - PBPK adult VGCV model → esterase activity (conversion of VGCV → GCV); renal excretion of GCV; active transport processes (MRP4, OAT1, OCT1, MATE1, MATE2-K, PepT1)

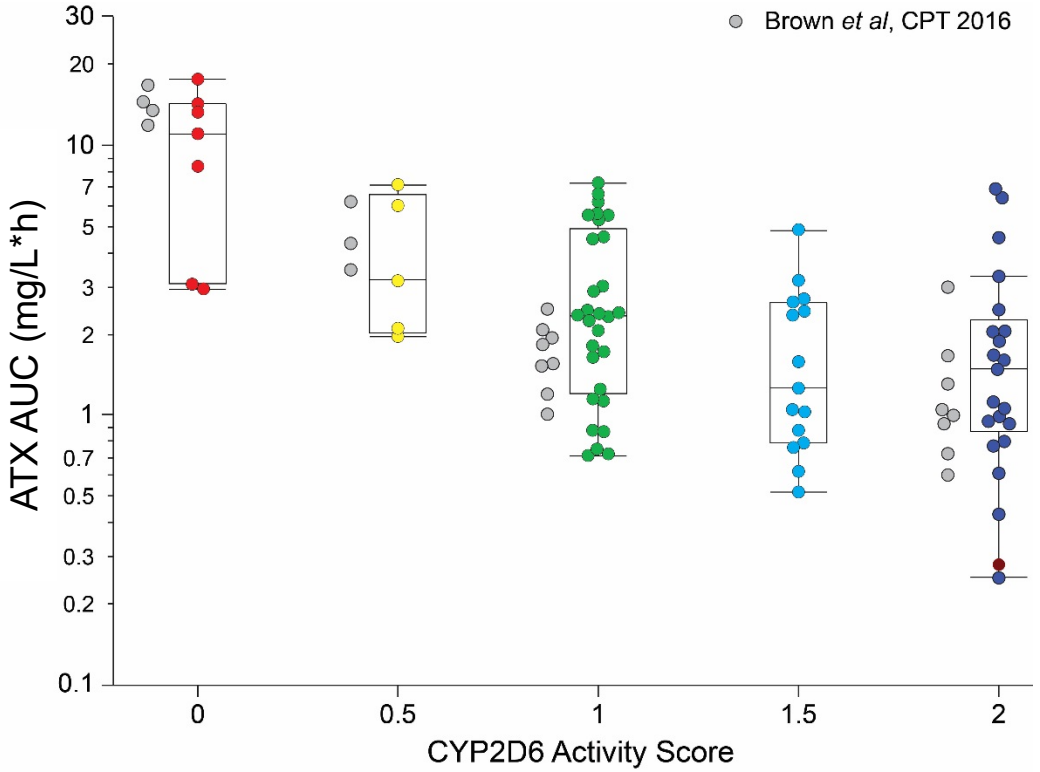
Jorga et al (2016)

VGCV–Dosing Algorithm Development



Jorga et al, (2016)

Virtual Child – Bottom-up PBPK



Atomoxetine Exposure Prediction

- Pediatric liver samples (n=78) genotyped for CYP2D6
- 0.5 mg/kg dose simulated
- *In vivo* within-genotype variability confirmed *in vitro*
- Activities of metabolic pathway determined by formation of 4OH-ATX, NDM and 2-OH pathways
- Inter-individual variability in competing pathways become important sources of variability in dose-exposure relationship for PMs and IMs

$$Cl_{int,u,ij} = \text{'Global'} Cl_{int,u} \; x \; f_{m,ij}$$

Scale contribution of enzymes by **abundance (CYP Protein conten)** and genotype.

$$\text{'Global'} Cl_{int,u,genotype} = \sum_{i=1}^{n} \left(\sum_{j=1}^{n} Cl_{int,u} \right)$$

Scale by liver weight and **Microsomal Protein Per Gram Liver (MPPGL)**

$$Whole\ organ\ Cl_{int,genotype}$$

Factor in liver blood flow and hematocrit

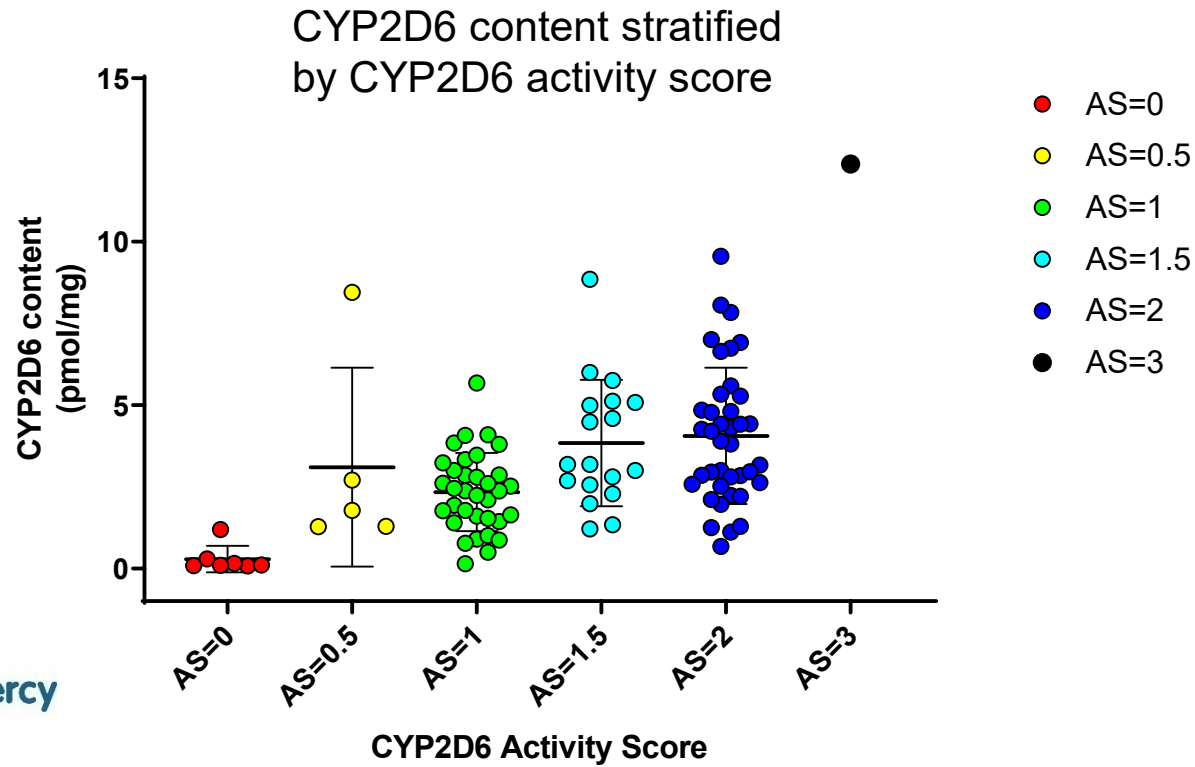
$$Cl_{H,genotype} = \frac{Q_H \; x \; fu_B \; x \; Cl_{int,u,genotype}}{Q_H \; + \; fu_B \; x \; Cl_{int,u,genotype}}$$

Determine oral clearance

$$Cl_{po,genotype} = \frac{Cl_{H,genotype} \; + \; Cl_r}{f_a \; x \; F_G x \; F_H}$$

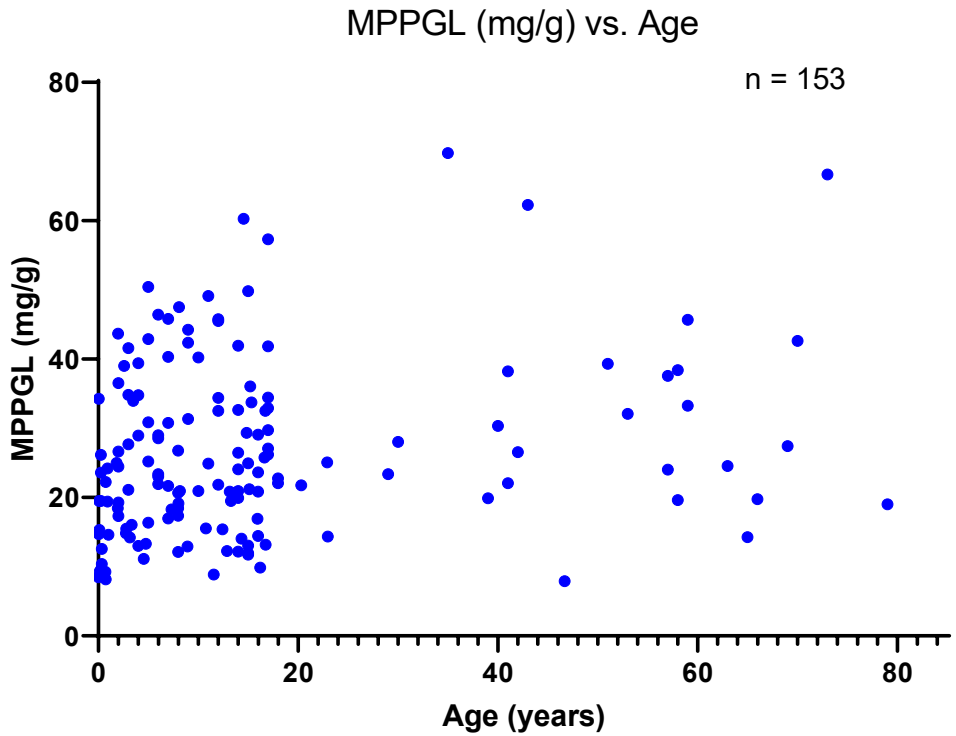
Children's Mercy KANSAS CITY

CYP2D6 Protein Content



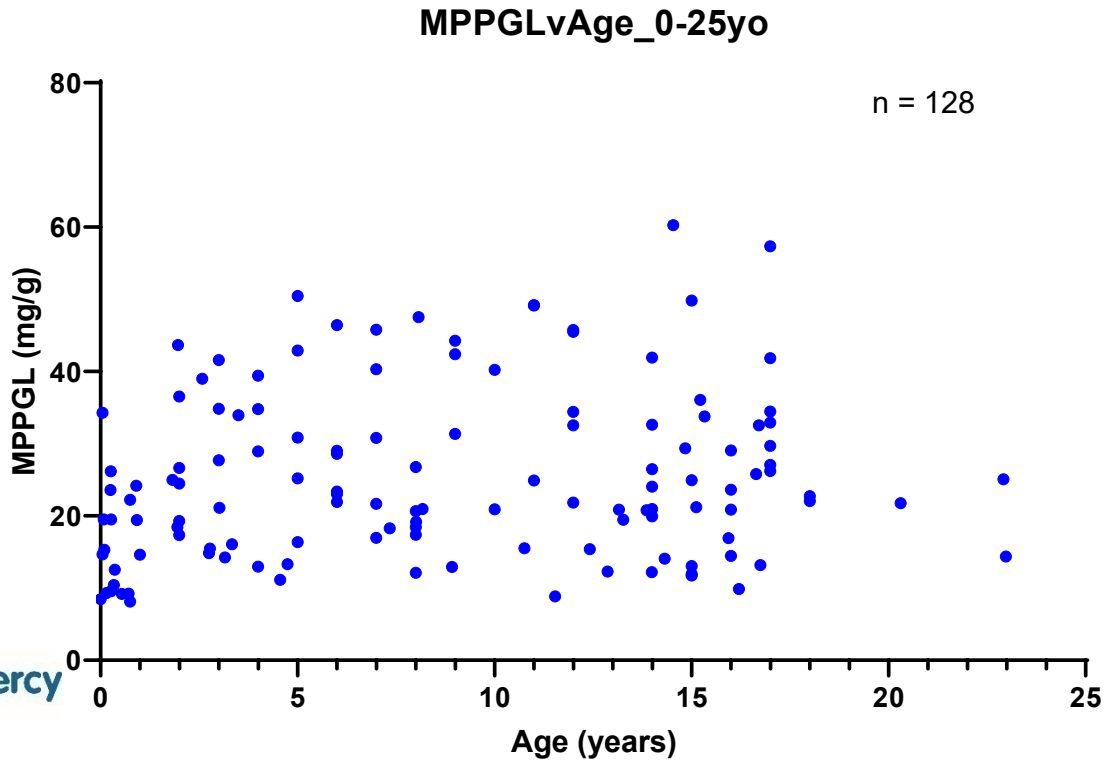
Children's Mercy KANSAS CITY

MPPGL Ontogeny



	Age	MPPGL
median	11.00	24.05
mean	15.93	26.56
min	0.00	7.93
max	79.00	69.77

MPPGL (0 – 25 yo)



Children's Mercy KANSAS CITY

Conclusions

- PBPK can be useful tools to extrapolate PK parameters for special populations, particularly in young children.
- A “middle-out” PBPK methodology is a useful approach for anticipating drug pharmacokinetics in younger population.
- Pediatric-derived bottom-up PBPK models may be utilized to develop pediatric specific PBPK models.