Bayesian Population Pharmacokinetic Analysis in Children using Real World Data from Electronic Health Records and Remnant Specimens

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Berry Consultants
Statistical Innovation

Overview

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- Challenges
  - Sparse, missing, and erroneous EHR and specimen data
  - Increased computation time (larger sample sizes, more complex dosing/sampling)

Overview

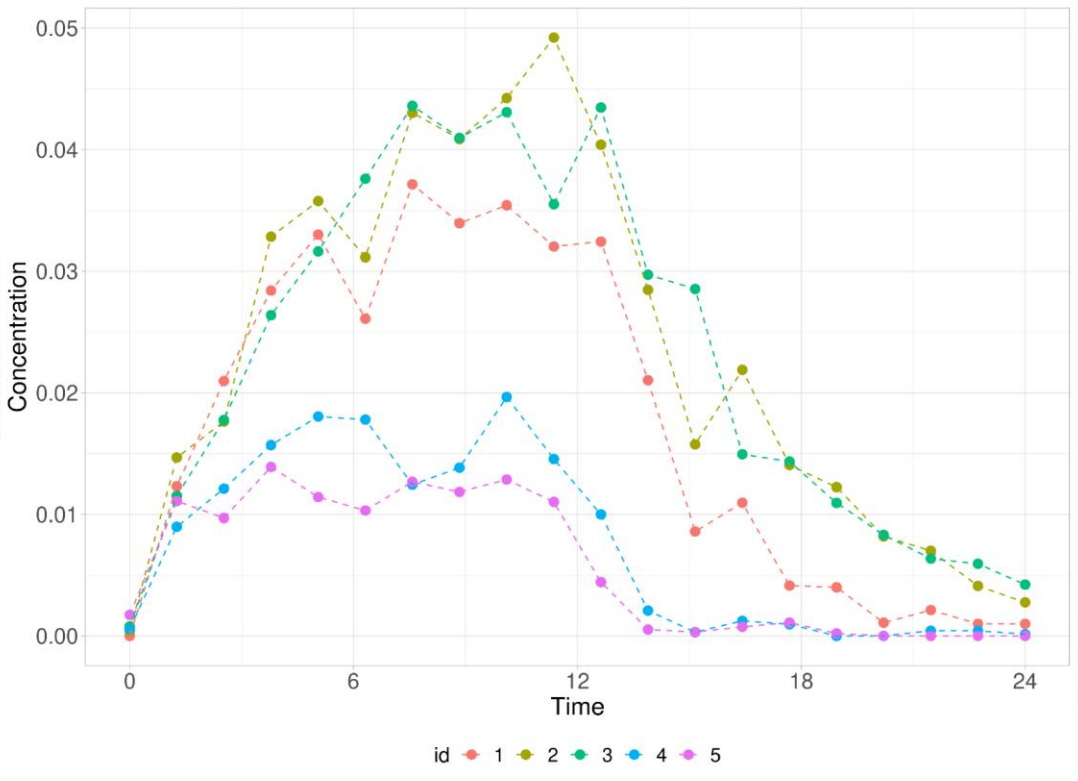
To address these challenges:

- Use a standardized, modular system to extract, process, and build PK datasets from EHR
- Borrow information using priors developed from smaller, more densely sampled studies to stabilize estimation
- Utilize automatic differentiation variational inference (ADVI) to provide quick, approximate solutions during model development and selection

We detail our approach in a Bayesian population PK analysis of the sedative dexmedetomidine which uses RWD from a pediatric cohort

Population Pharmacokinetic Models

Population PK models are nonlinear, hierarchical models used to estimate the concentration of drug in the body over time



Ex. Concentration for 5 subjects given 12 hour infusion using one-compartment model with linear elimination

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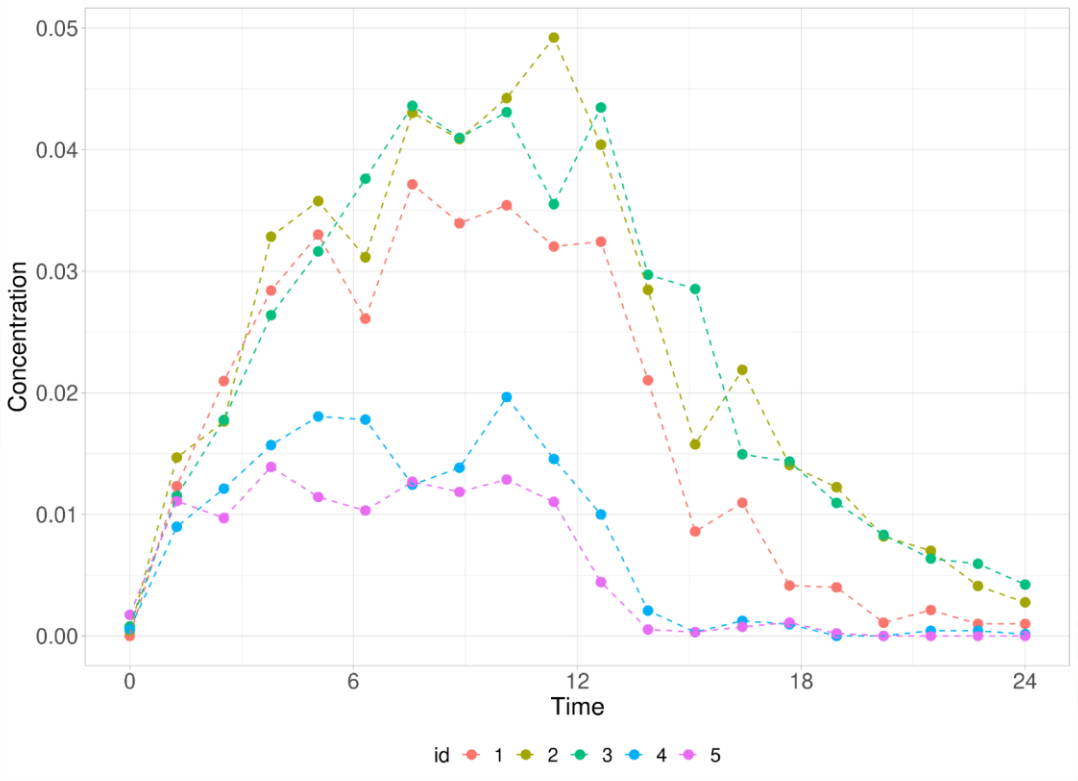
- individual level model with a structural component that describes concentration as a function of dose history, parameters, and time and a residual error component

$$Y_{ij} = f_1(D_i, \psi_i, t_{ij}) + \varepsilon_{ij}$$
$$\varepsilon_{ij} \sim N(0, \sigma_{ij}^2), \quad \sigma_{ij}^2 = f(D_i, \boldsymbol{\psi_i}, t_{ij})^{\gamma}\sigma_y^2, \quad \gamma \geq 0,$$



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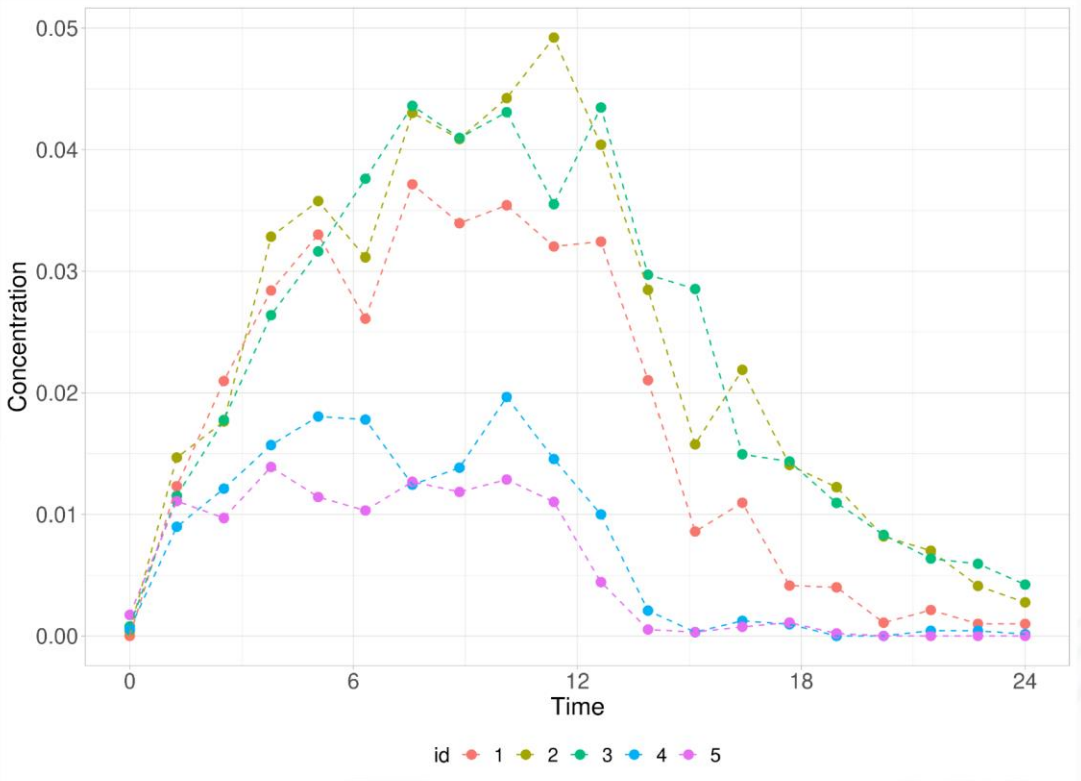
- population level model describes the multivariate distribution of the individual-level parameters with **population regression coefficients and covariates** (fixed effects) and **individual-specific deviations** (random effects)

$$\boldsymbol{\psi_i} = \boldsymbol{f_2}(\boldsymbol{\mu}, \boldsymbol{X}_i) + \boldsymbol{\eta_i}, \quad \boldsymbol{\eta} \sim N(0, \boldsymbol{\Omega})$$



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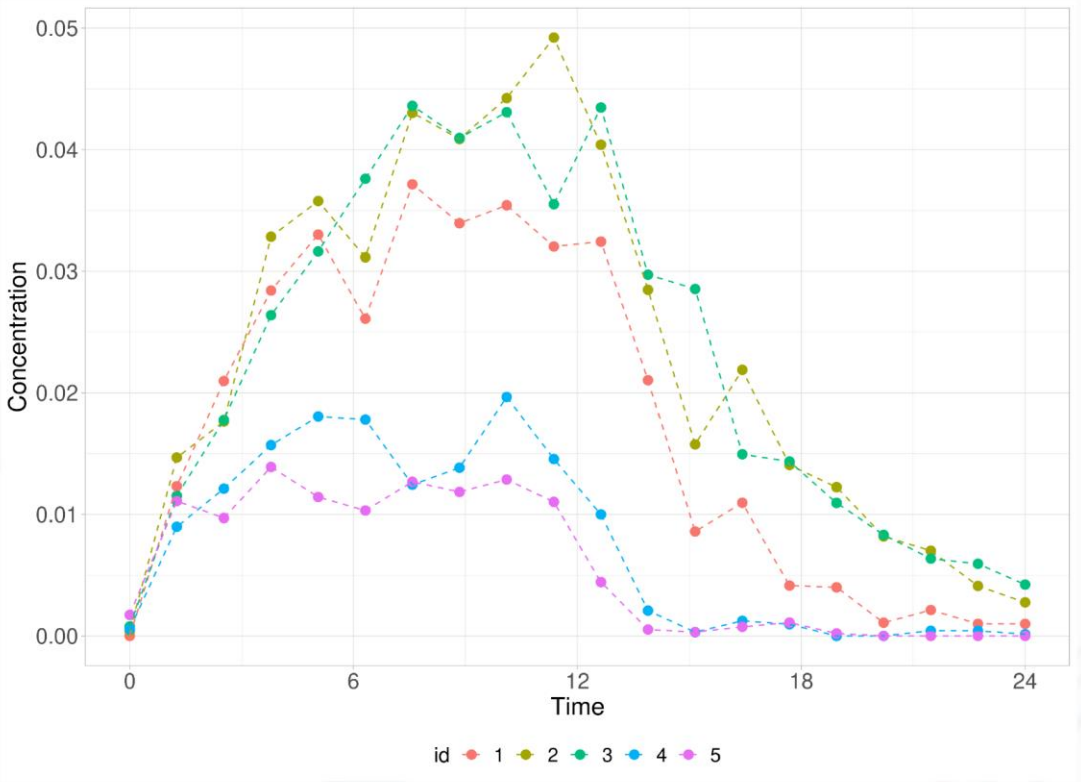
- **priors** describe uncertainty in unknown parameters

$$p_3(\boldsymbol{\mu}, \boldsymbol{\Omega}, \sigma_y^2) = p(\boldsymbol{\mu})p(\boldsymbol{\Omega})p(\sigma_y^2)$$



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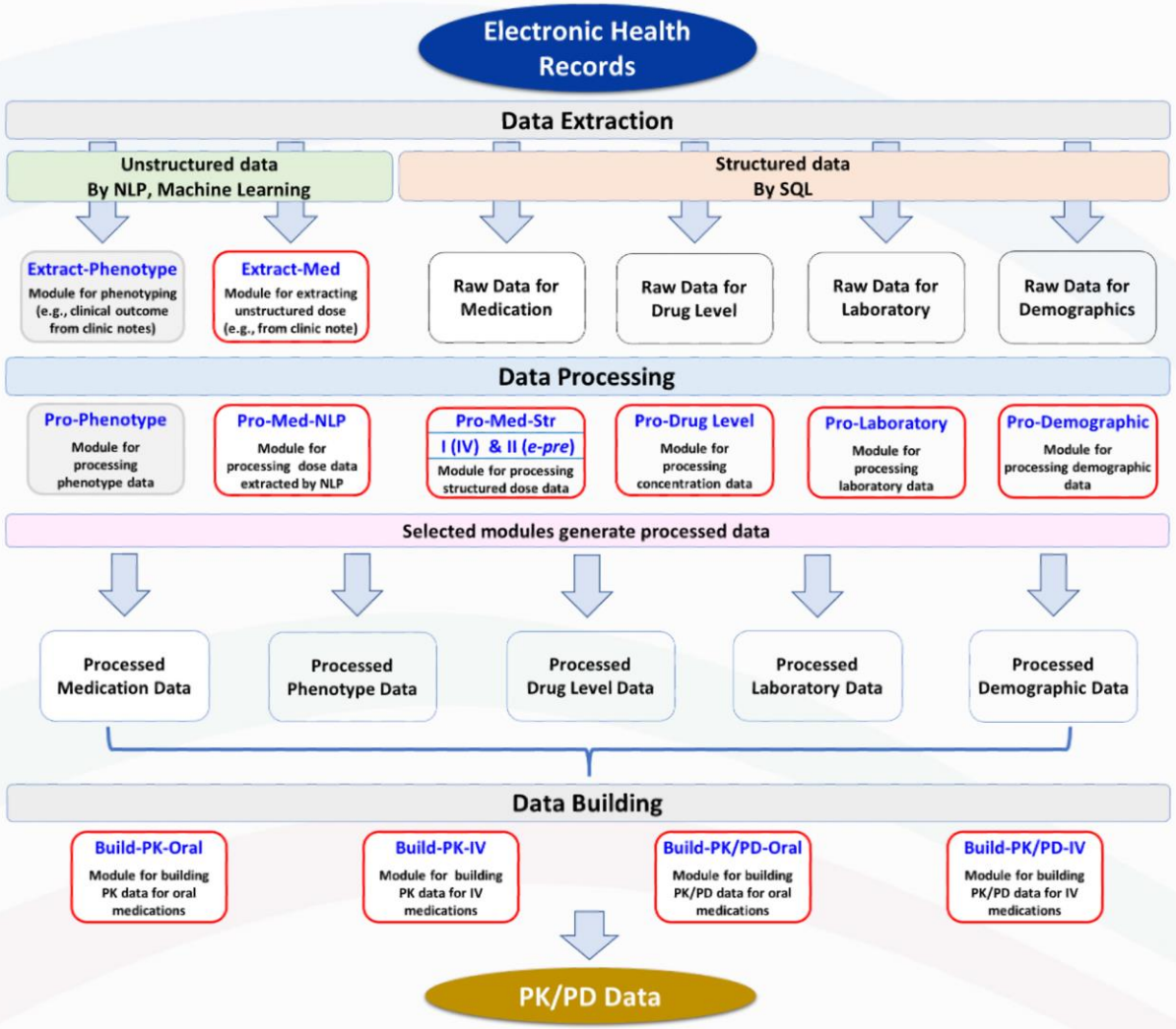
Population Pharmacokinetics: RWD from EHR and remnant samples



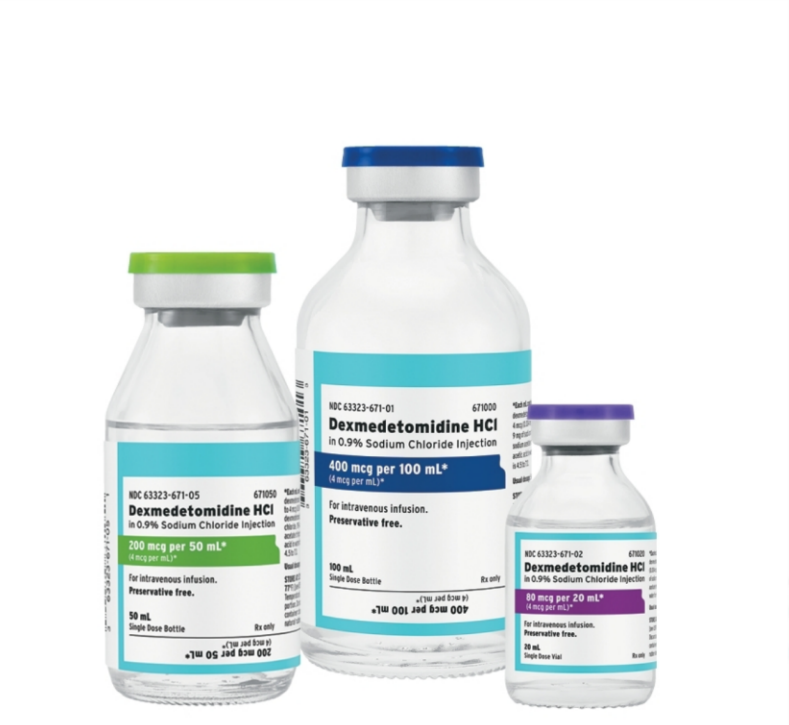
Modified from: Choi et al. (2020) Development of a System for Post-marketing Population Pharmacokinetic and Pharmacodynamic Studies using Real-World Data from Electronic Health Records. *Clinical Pharmacology & Therapeutics*

Standardized software to extract, clean, and combine EHR data

1. Obtain raw data from EHR, separate files for
    - Demographics, surgical and clinical data
    - Dexmedetomidine dosing history
    - Plasma concentration data from remnant plasma specimens ≥ 100 µL collected for usual clinical care
    - Additional clinical laboratory values related to drug metabolism
2. Process raw data
    - standardize data and apply interactive data quality checks to reconcile missing, duplicate, and other erroneous concentration or dosing information
3. Build PK IV infusion data
    - combine data on concentration with sample collection
    - merge demographic, dosing, concentration and other data
4. Remove data that is erroneous, incomplete, or meets exclusion criteria using pre-defined algorithm followed by manual review

Population PK Analysis of Dexmedetomidine

- Dexmedetomidine is a sedative routinely used as part of intraoperative anesthetic management during pediatric congenital heart surgery and in the postoperative period in the intensive care unit



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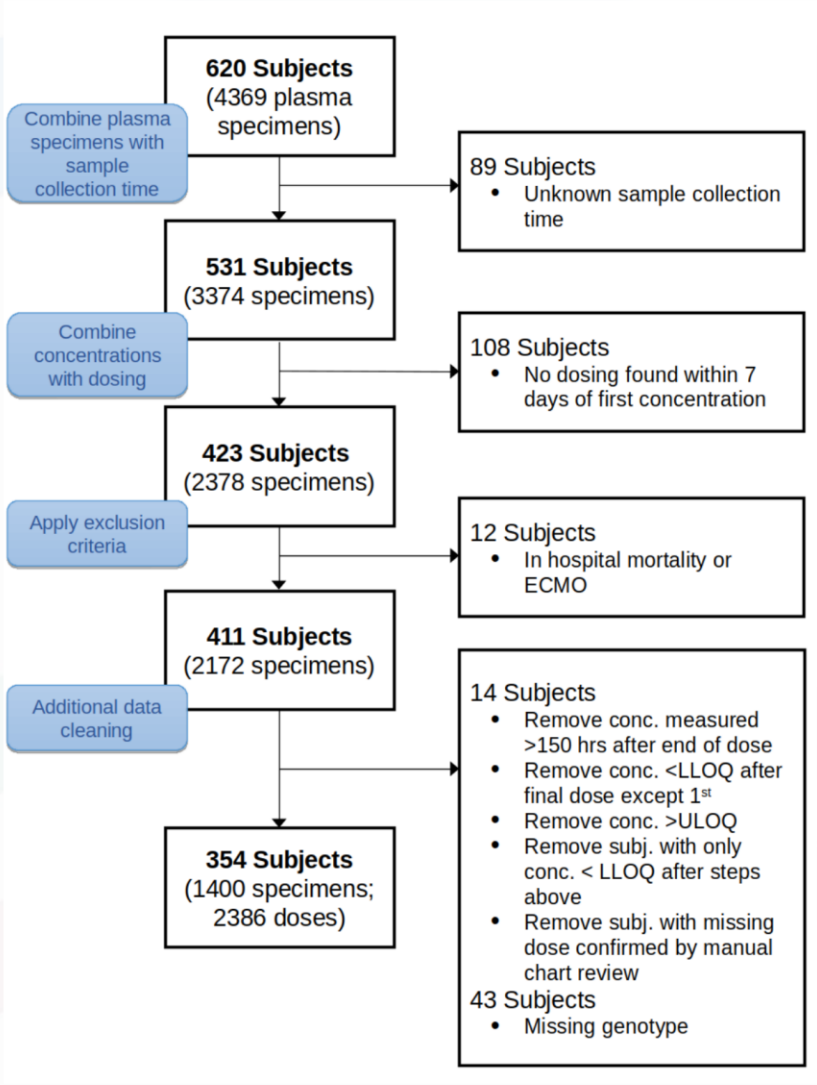
- Objectives:
  - perform a population PK analysis of dexmedetomidine in children using remnant specimens and electronic health records (EHRs)
  - explore the impact of patient's characteristics and novel pharmacogenetics on dexmedetomidine clearance

Dexmedetomidine Pop. PK: Frequentist Analysis



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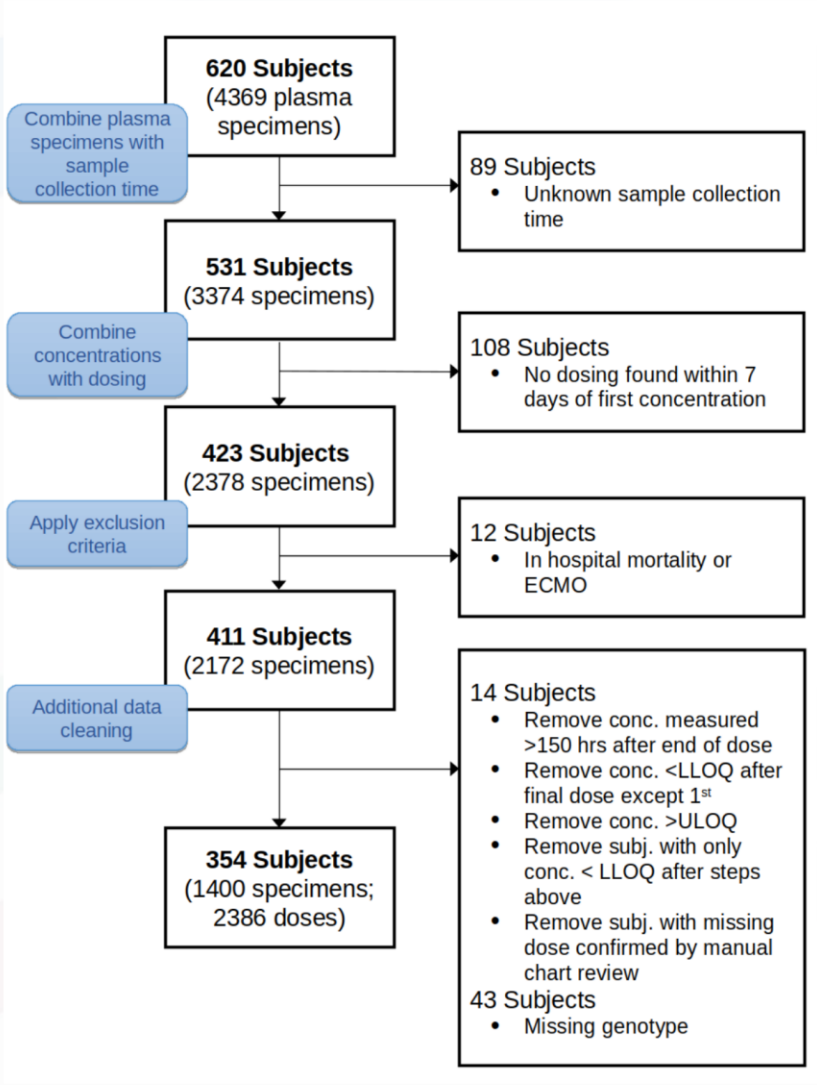

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- A frequentist analysis examined multiple structural, error, and variance models and association between PK and patient characteristics (weight, postmenstrual age, sex, cardiac bypass time, etc.) and genotype variables (*UGT1A4* and *UGT2B10* variants, novel *CYP2A6* risk score).

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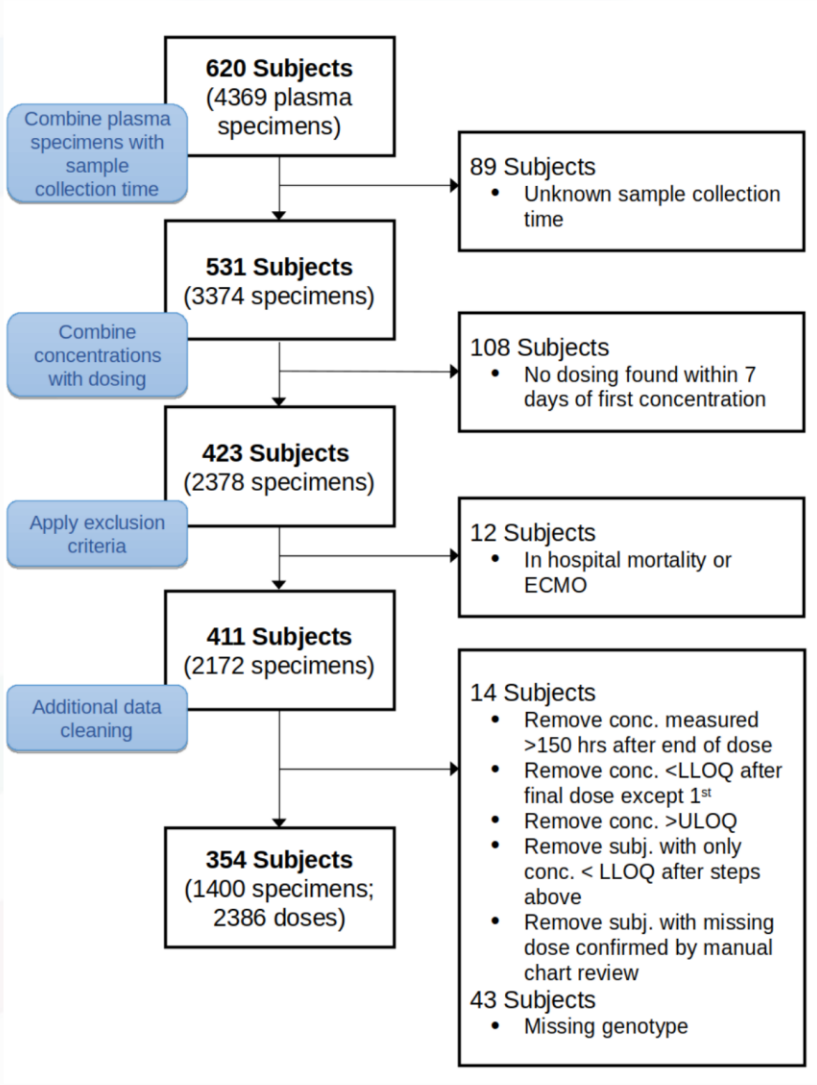

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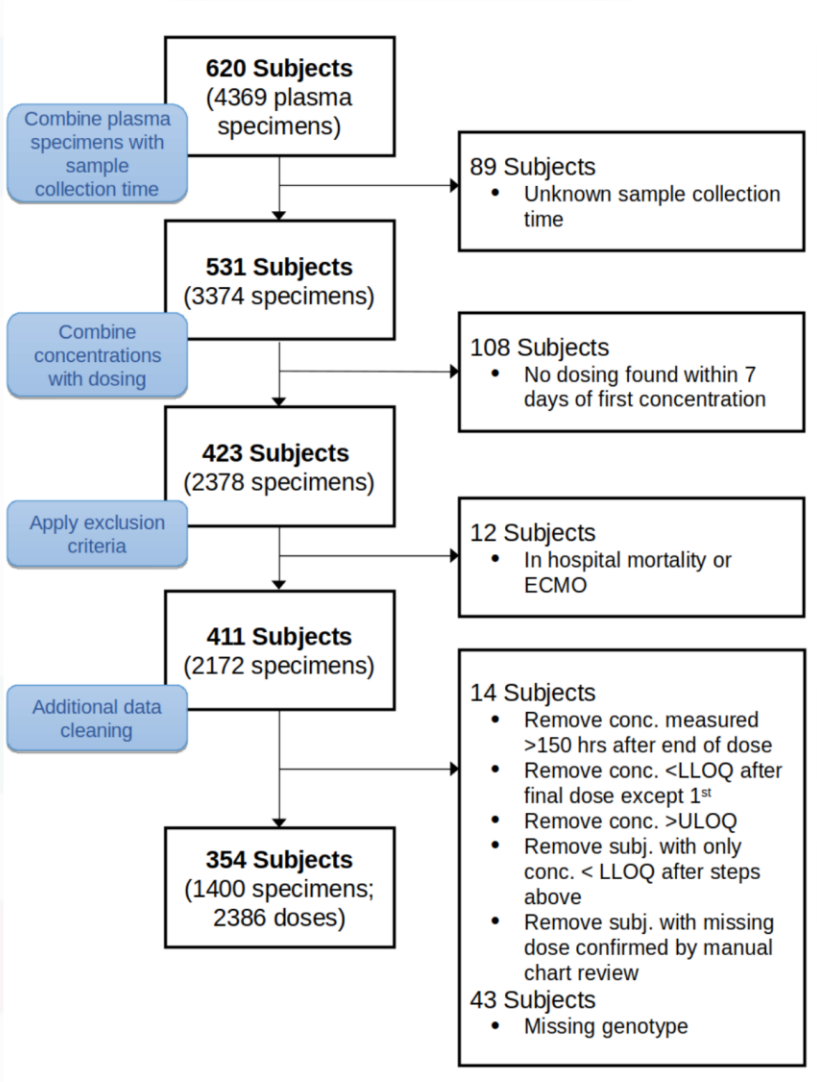

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  - The data were best described with a two-compartment model with allometric scaling for weight and Hill maturation function for postmenstrual age.
  - Weight and age were important predictors of clearance; did not find evidence for pharmacogenetic effects of *UGT1A4* or *UGT2B10* genotype or *CYP2A6* risk score.

Dexmedetomidine Pop. PK: Bayesian Analysis

- The frequentist analysis had several limitations:
  - required simplifications (e.g., fixing most random effects correlations at zero) to avoid convergence problems
  - produced some population PK estimates which differed substantially from previous studies in similar populations

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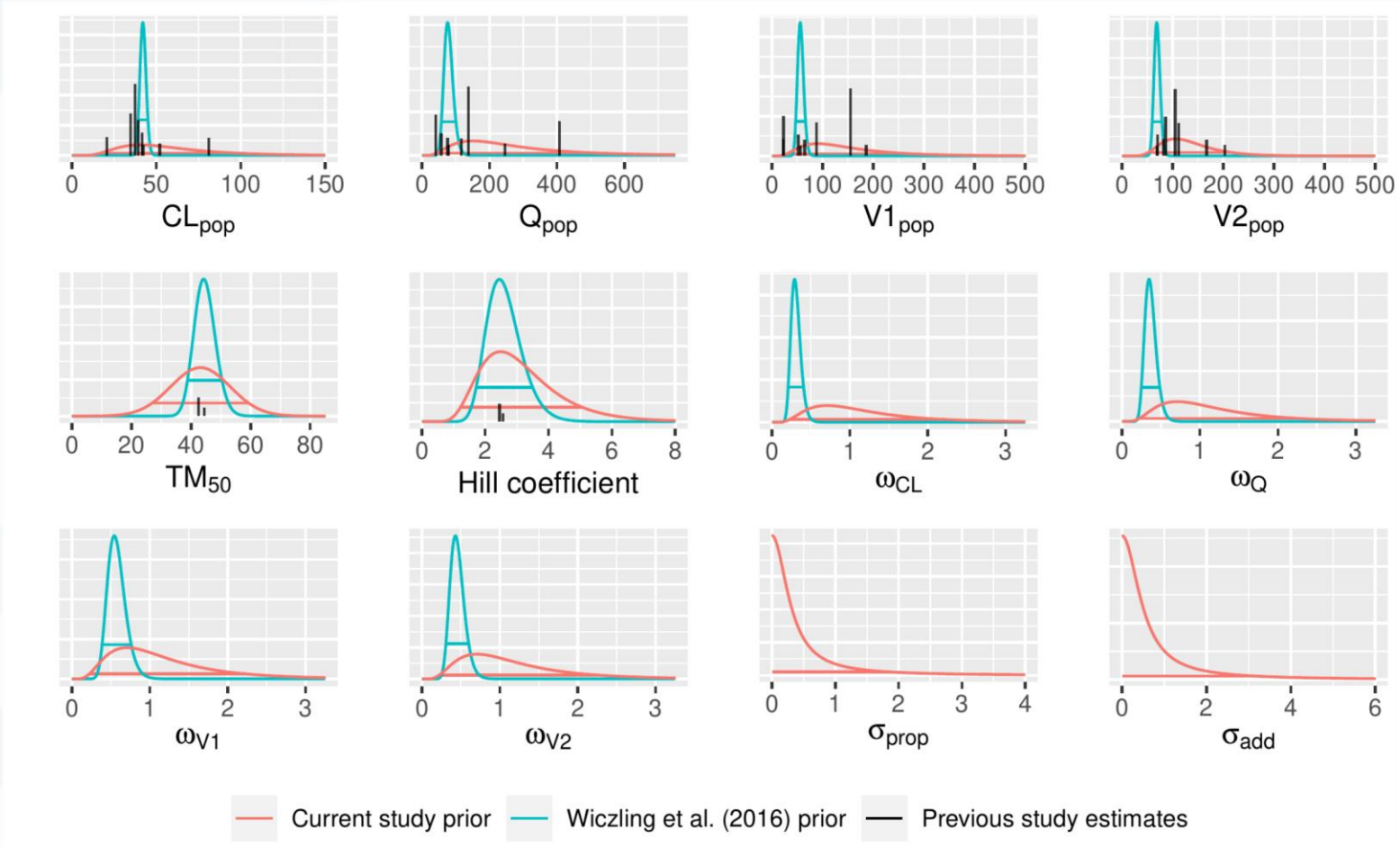
- Use a Bayesian framework to combine prior information from small, designed clinical studies with the larger observational RWD to more precisely estimate parameters and the entire model

Dexmedetomidine Pop. PK: Priors

Informative prior developed from recently published pediatric dexmedtomidine PK studies using a weighted average of study estimates



The current study priors are less informative than a previous Bayesian analysis which had fewer subjects but more regular, intensive sampling

Dexmedetomidine Pop. PK: Model Development

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- For population parameters, posterior medians can be fairly accurate but credible intervals are underestimated with ADVI, therefore selected models were refit using MCMC estimation to produce final posterior parameter estimates and perform posterior checks

Dexmedetomidine Pop. PK: Results

- Allometric scaling and Hill maturation model was not improved by adding serum creatinine, sex, STAT score[1], cardiac bypass time, length of ICU stay, or *UGT1A4* or *UGT2B10* variant effects to model

[1] Society of Thoracic Surgery–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality score

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- Among the 350 subjects with *CYP2A6* score, the allometric scaling and Hill maturation factor model $(lppd_{cv} = \mathbf{780.3})$ was improved by adding *CYP2A6* effect to model $(lppd_{cv} = \mathbf{803.3})$

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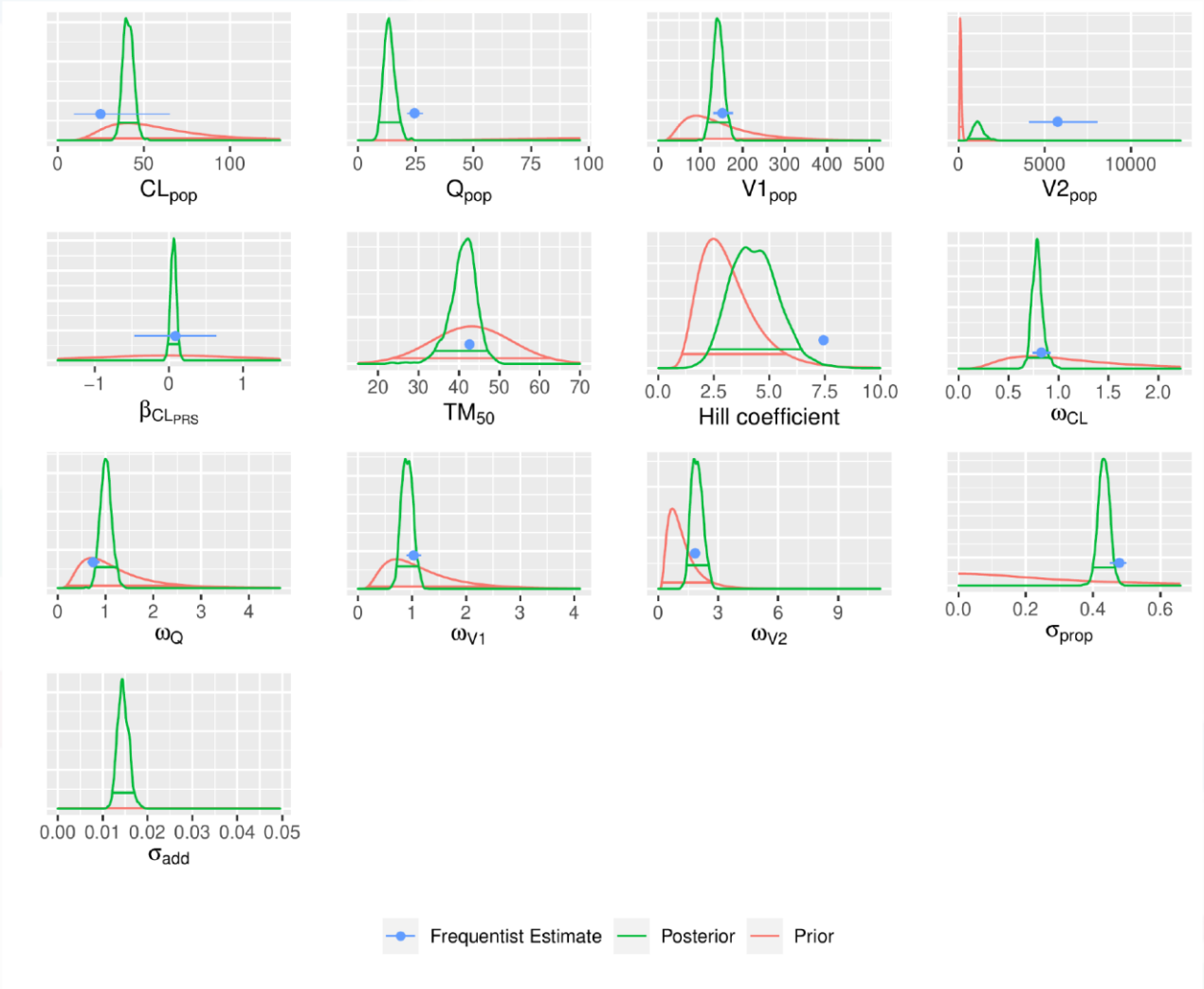
Dexmedetomidine Pop. PK: Results

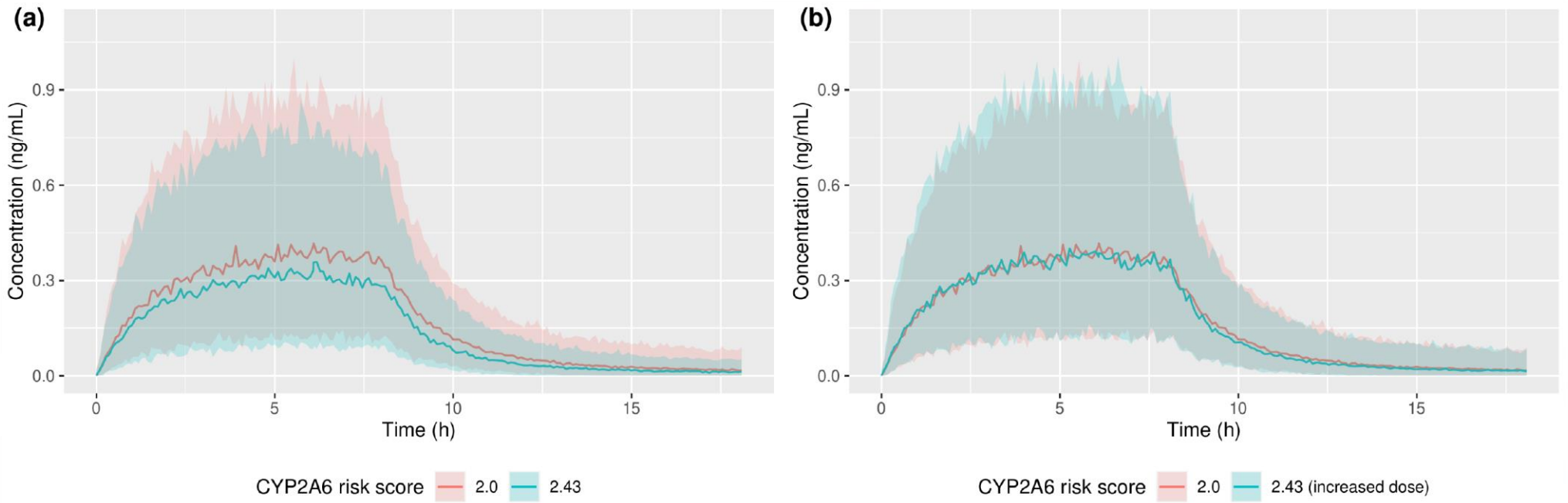
Incorporating prior information stabilized estimation and produced results much closer to the previous literature for most parameters compared to the frequentist analysis



Dexmedetomidine Pop. PK: Results

Including predicted *CYP2A6* enzyme activity can potentially make a clinically meaningful difference in dosing

A one standard deviation increase in *CYP2A6* score was associated with approximately 6% higher total clearance, so a subject with a high *CYP2A6* score will require a larger dose to achieve the same concentration as a subject with lower *CYP2A6* score, holding other covariates constant



Posterior predictions for hypothetical subjects with median weight and postmenstrual age and *CYP2A6* scores of 2.0 and 2.43. (a) dosing same for both subjects; (b) dosing for high *CYP2A6* subject increased by 0.1 mcg/kg

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- Using ADVI reduced modeling time, e.g. for final model ADVI fit time was 6 minutes, MCMC fit time was 595 minutes (9 hours, 55 minutes)
- Including *CYP2A6* improved estimated predictive accuracy and effect is potentially clinically meaningful

Acknowledgements

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- PI: Leena Choi, PhD
- Cole Beck
- Elizabeth McNeer, MS
- Michael Williams, PhD
- Hannah Weeks

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- Sara Van Driest, MD, PhD
- Prince Kannenkeril, MD

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