

Model-informed Approaches to Support Dosage Selection in Pediatric Patients

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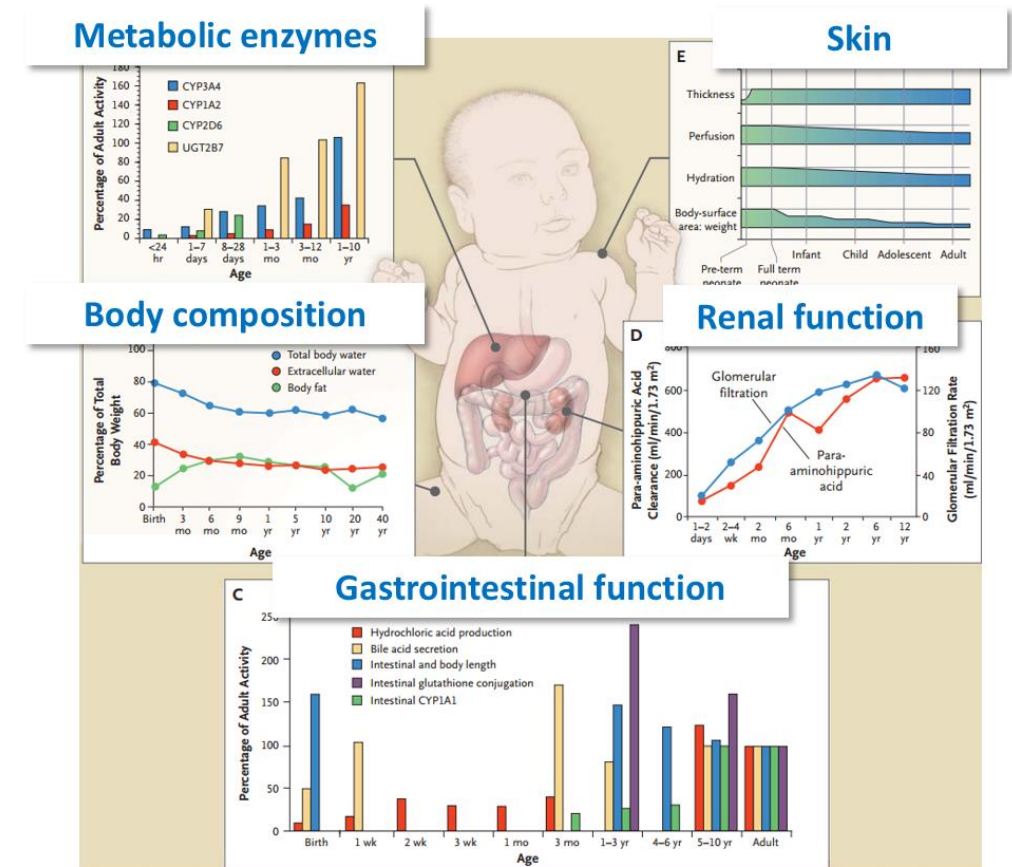


Outline

- Highlight the ongoing challenges in identifying appropriate dosing regimens for pediatric patients across a wide age spectrum from newborns to young adults.
- Overview model-informed precision dosing approaches in support of designing and expediting oncology drug development in pediatrics.
- Describe examples of the application of model-informed approaches to support dosage selection of oncology drugs in pediatric patients.

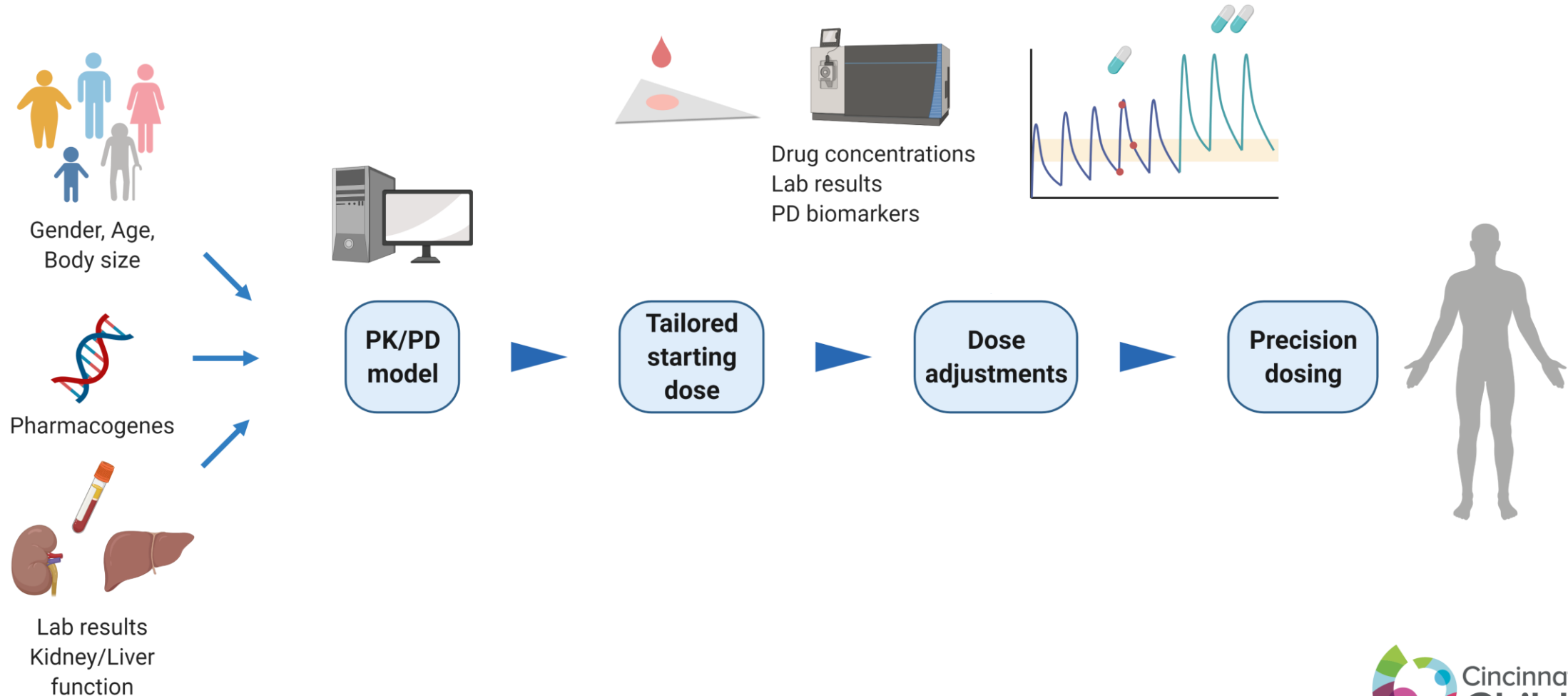
Why model-informed dose selection in pediatrics?

- Children are not small adults
- Rapid growth and development (maturation) in size and organ functions impact drug response
- Clinical PK/PD data are limited in children
- Large inter-patient variability
- “One size does not fit all”
- To better predict and control exposure and response in pediatric population and individual patients

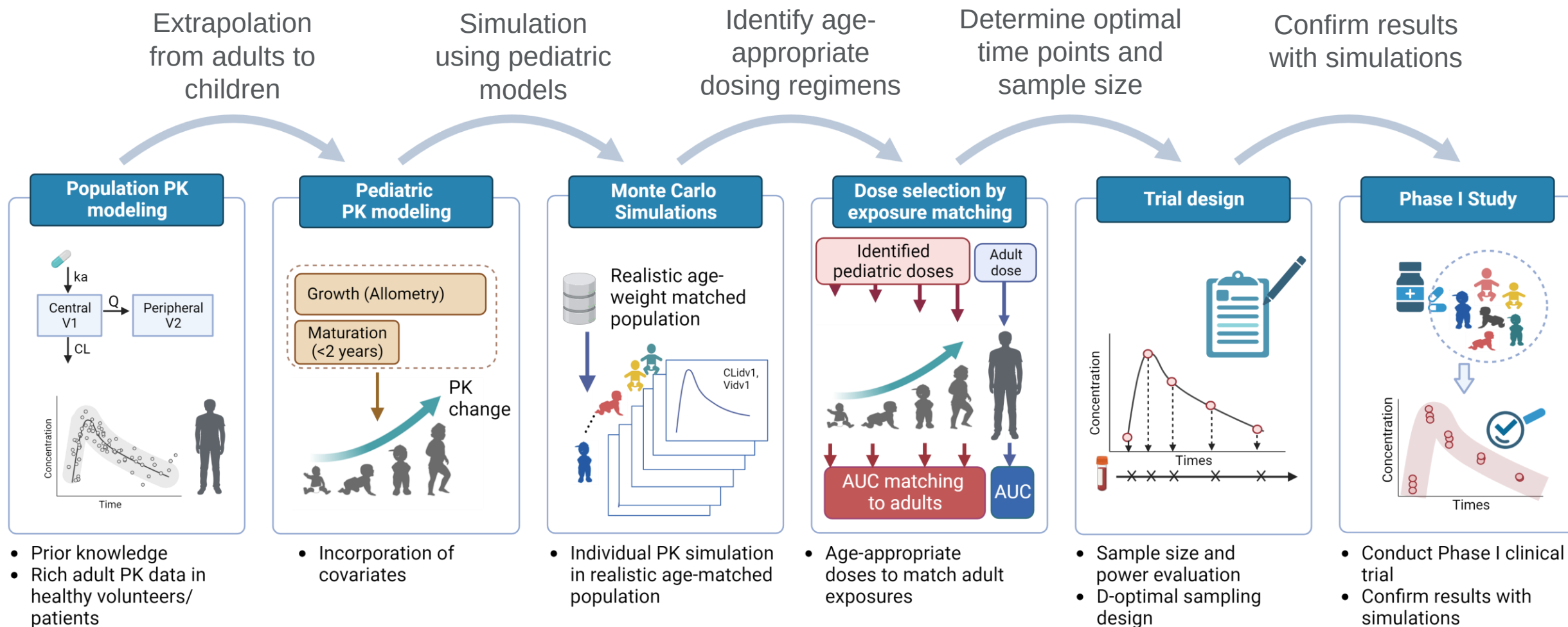


Kearns GL et al. N Engl J Med. 2003;349(12):1157-67

Model-informed precision dosing (MIPD)



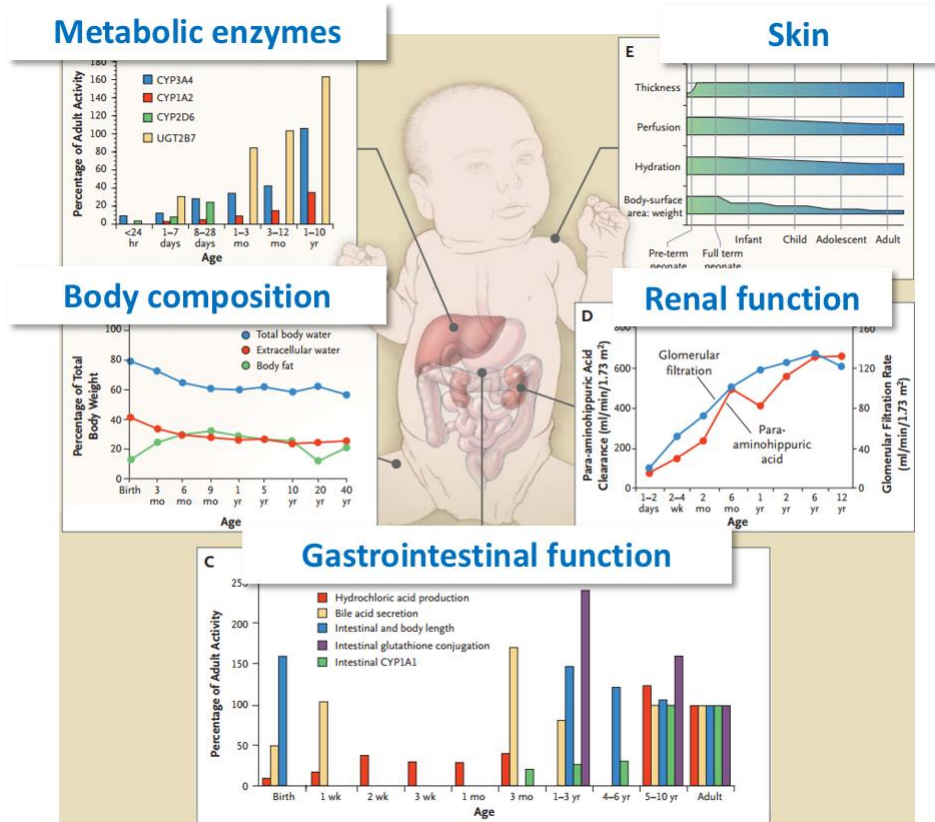
Model-informed approaches to support dose selection and clinical trial design in pediatric drug development



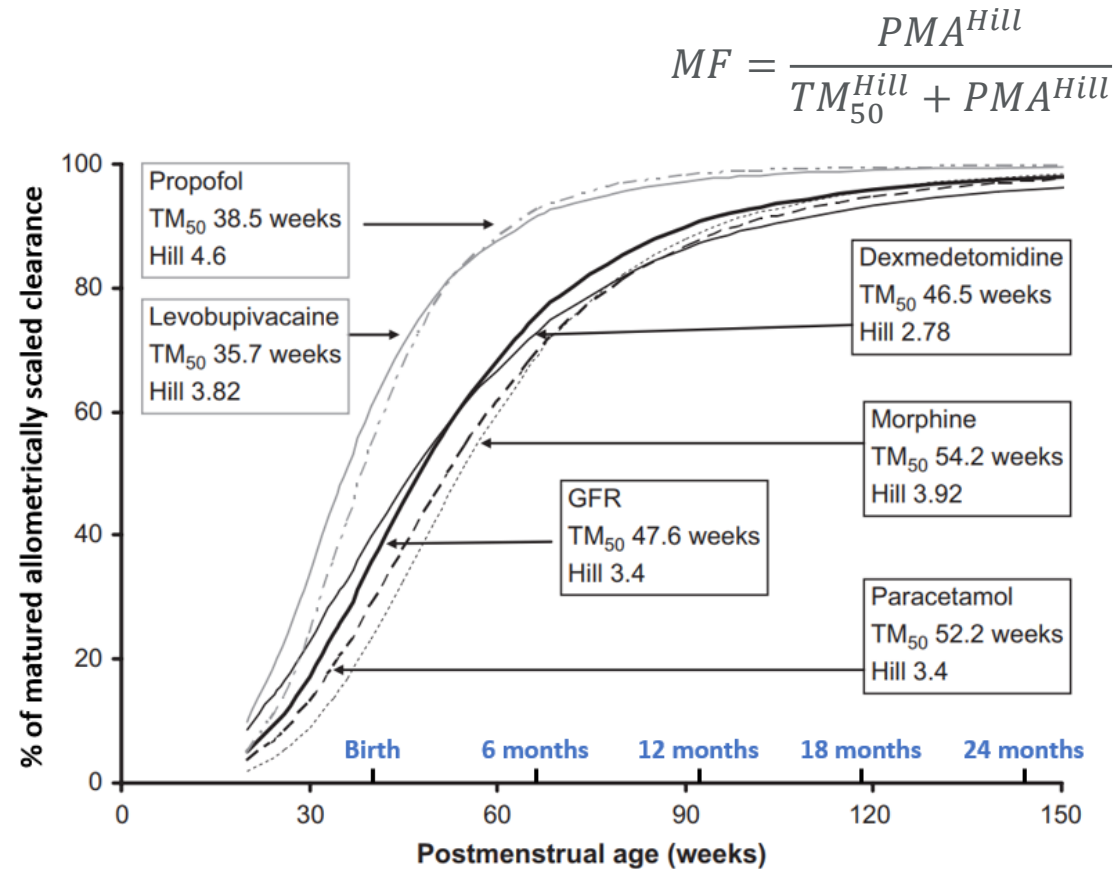
Case study 1

Model-informed pediatric dose selection for sirolimus in infants with vascular tumors and malformations

Implications of maturation on drug response in infants



Kearns GL et al. N Engl J Med. 2003;349(12):1157-67



Anderson and Holford, Pediatric Anesthesia 21 (2011) 222–237

Neonates and infants experience rapid physiological changes in their organ function, in addition to the growth in body size.

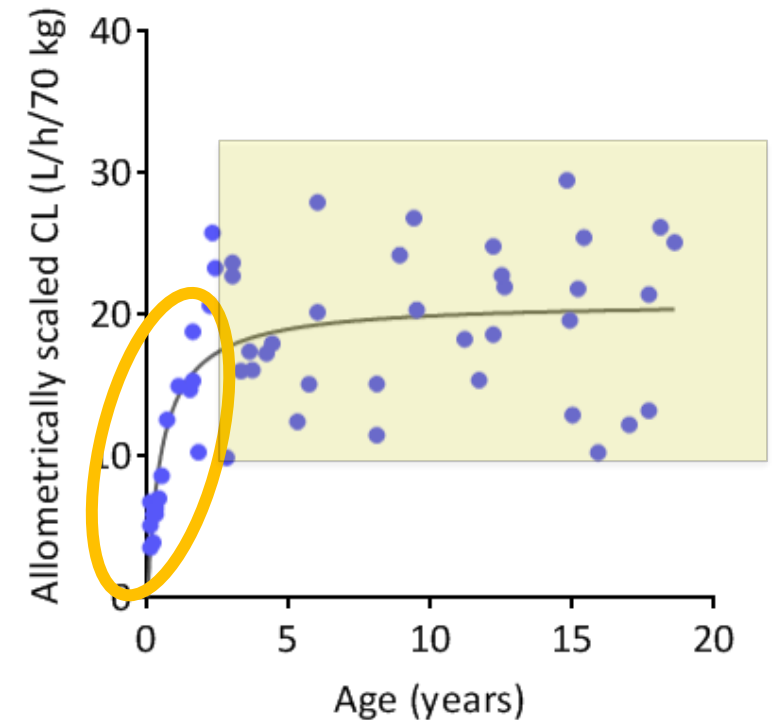
Effect of body size and maturation on sirolimus clearance in children

Sirolimus clearance estimated using Phase 2 clinical trial for pediatric patients with vascular tumors and malformations

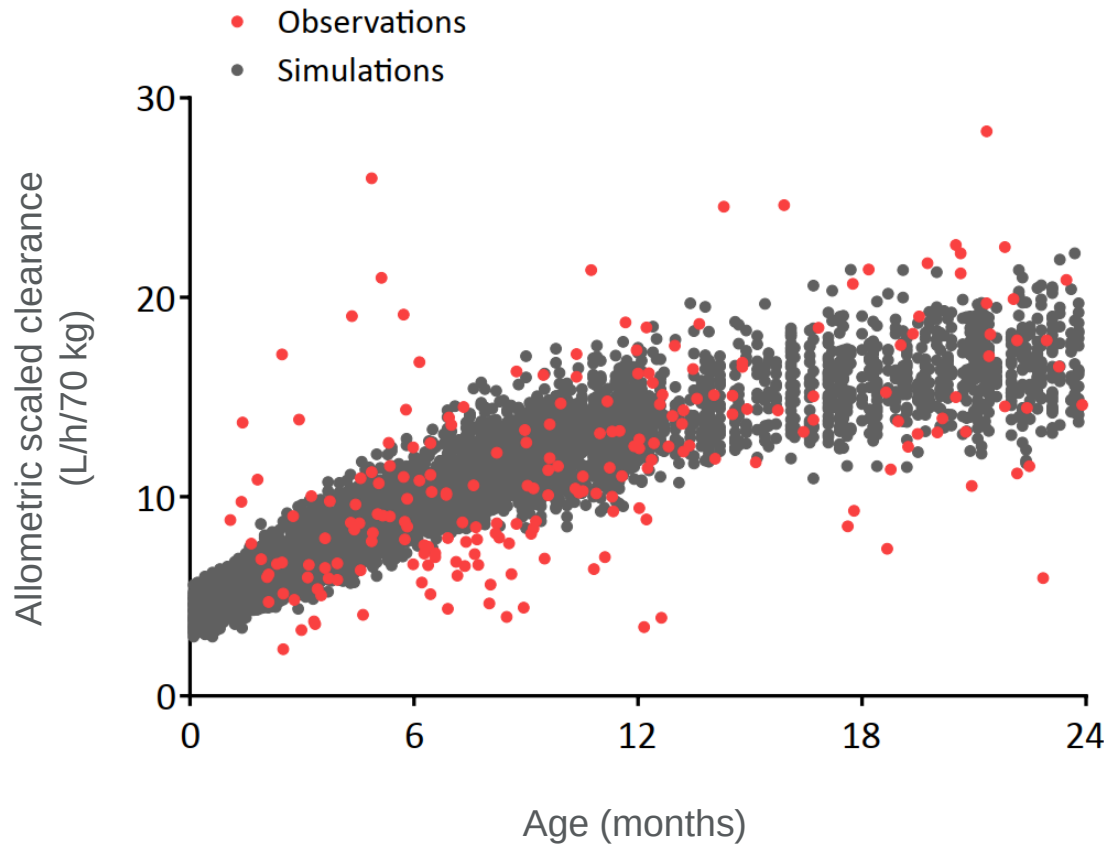


Denise Adams, MD
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- Increased sirolimus clearance in older children can be described using allometrically scaled body weight (growth of body size)
- There is a rapid maturation in clearance in younger children <2 years old
- Need to optimize dosing regimens in young children



Development of a model to describe clearance maturation in young children



Maturation model

$$CL_{\text{pediatric}} = CL_{\text{adult}} \cdot \left(\frac{BW}{70} \right)^{0.75} \cdot MF$$

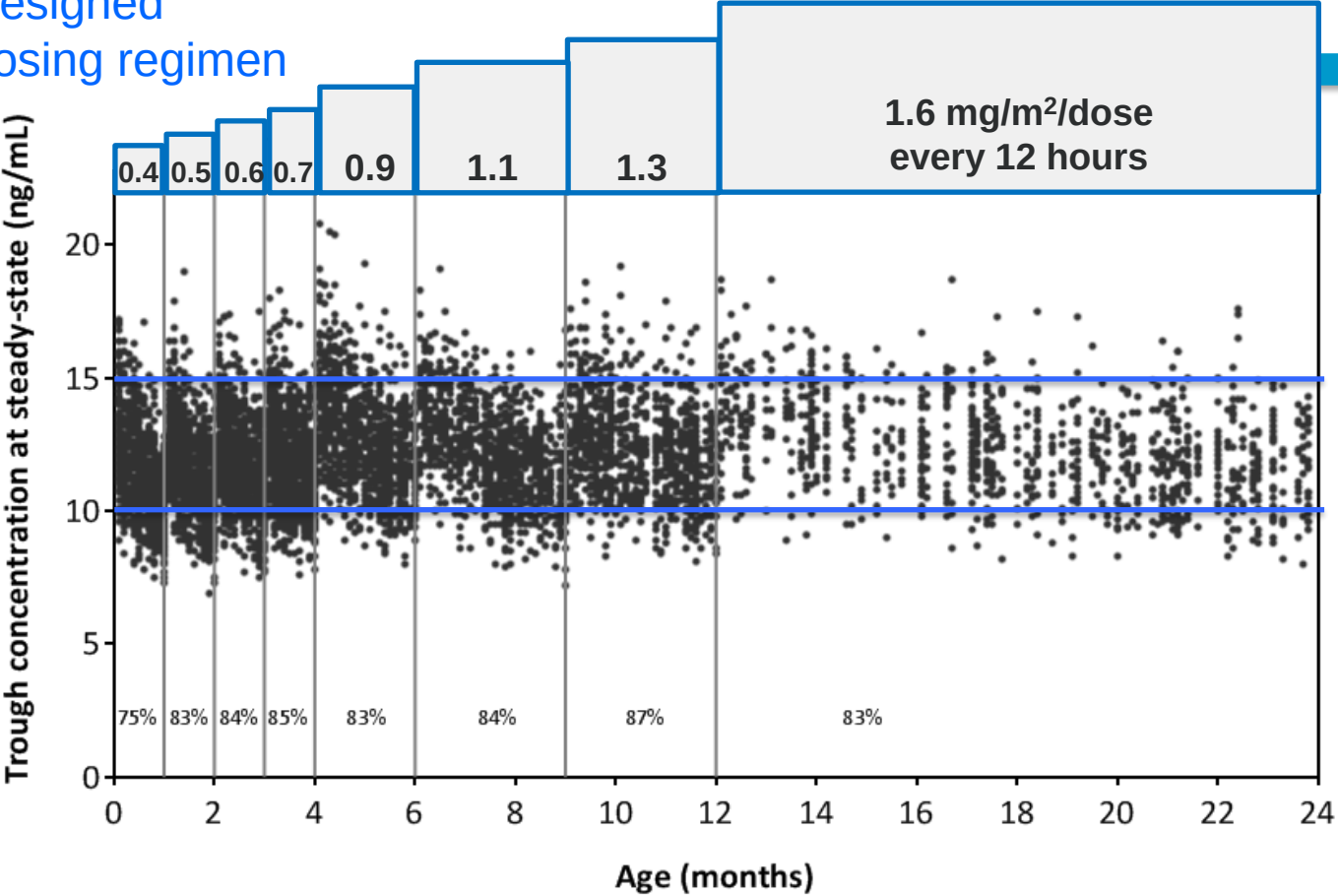
$$MF = \frac{PMA^{\text{Hill}}}{TM_{50}^{\text{Hill}} + PMA^{\text{Hill}}}$$



Clinical trial simulations to identify age-appropriate dosing regimens

Clinical trial simulations to identify age-appropriate dosing regimens to optimally achieve target attainment

Designed dosing regimen



Age groups	Dosing regimens (mg/m ² BID)
0–1 months	0.4
1–2 months	0.5
2–3 months	0.6
3–4 months	0.7
4–6 months	0.9
6–9 months	1.1
9–12 months	1.3
12–24 months	1.6

Clinical trial of sirolimus in infants with tuberous sclerosis complex

Stopping TSC Onset and Progression 2B: Sirolimus TSC Epilepsy Prevention Study (TSC-STEPPS)

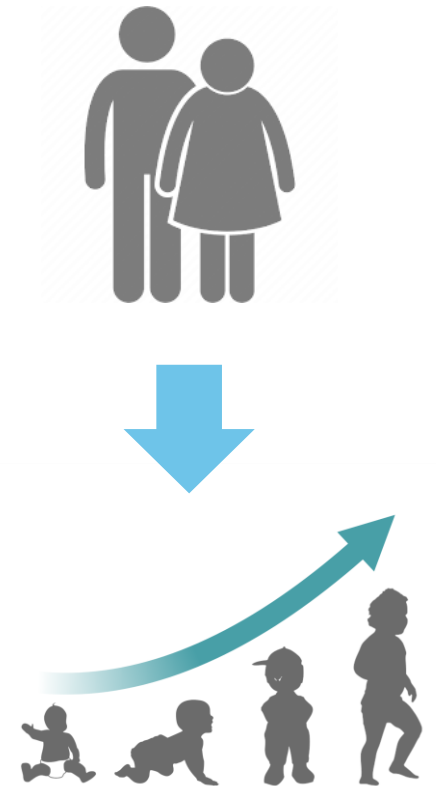
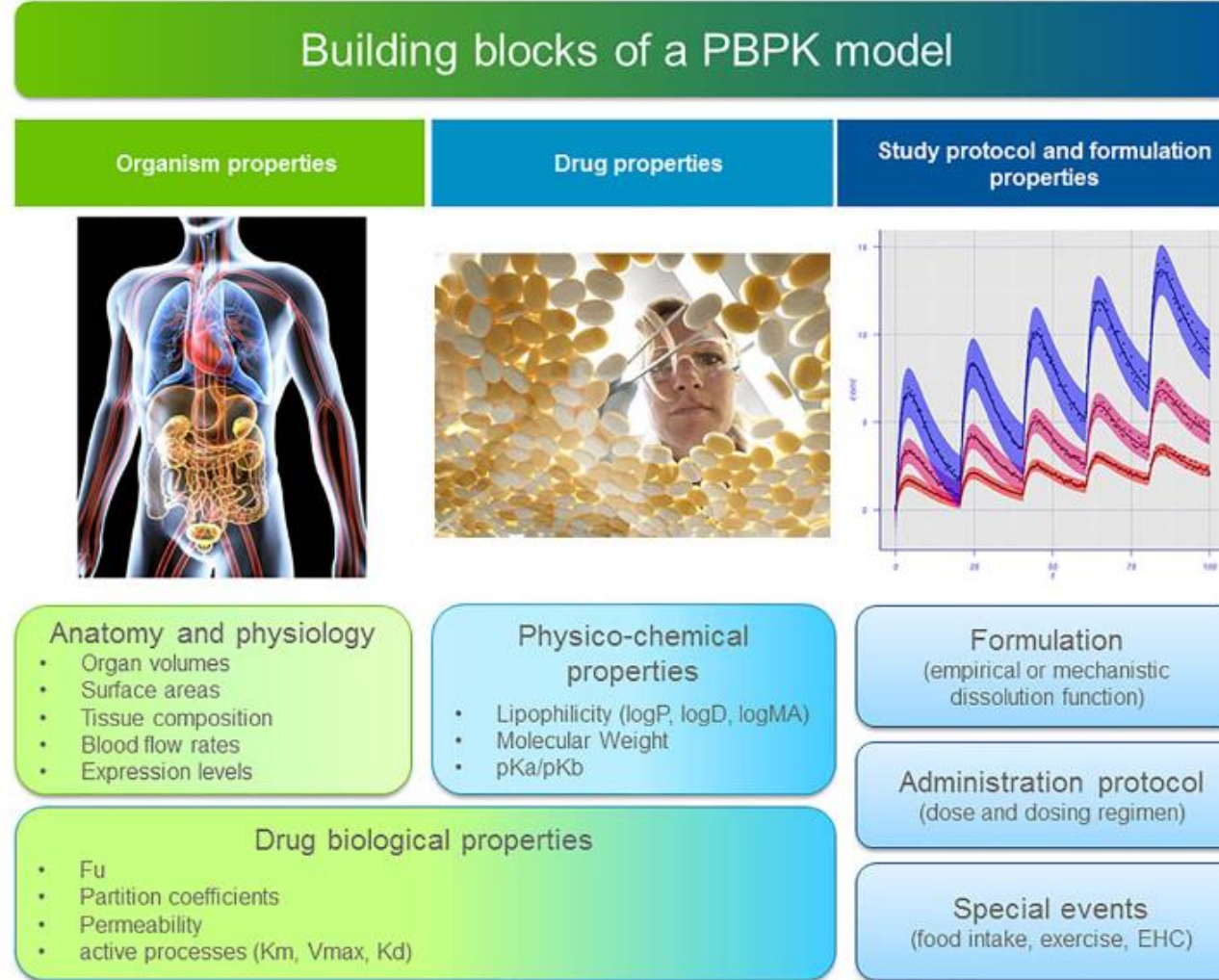
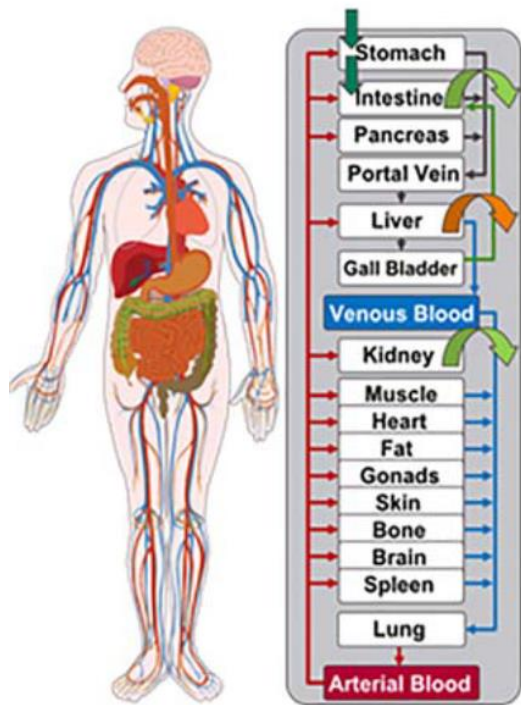
ClinicalTrials.gov Identifier: NCT05104983



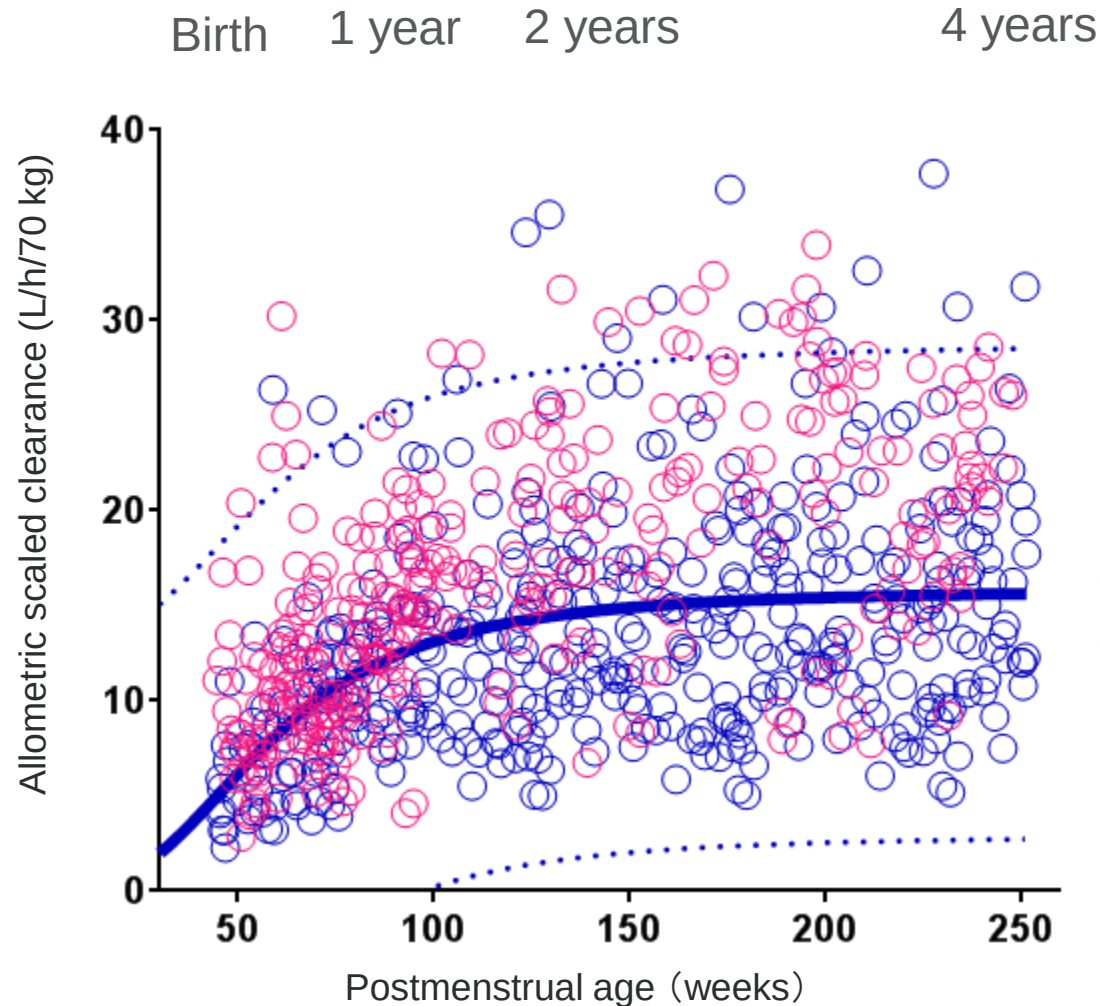
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- The developed age-appropriate dosing regimens have been used as the initial dose for all participants
- Subsequent dose is adjusted based on concentration measurements with Bayesian estimation

Physiologically based pharmacokinetics (PBPK) modeling



Developmental changes in sirolimus clearance



PBPK model-based simulations
n= 400 virtual pediatric subjects

Observations (Bayesian estimates)
316 data from 24 patients

Maturation model

$$CL_{\text{pediatric}} = CL_{\text{adult}} \cdot \left(\frac{BW}{70} \right)^{0.75} \cdot MF$$

$$MF = \frac{PMA^{\text{Hill}}}{TM_{50}^{\text{Hill}} + PMA^{\text{Hill}}}$$

Case study 2

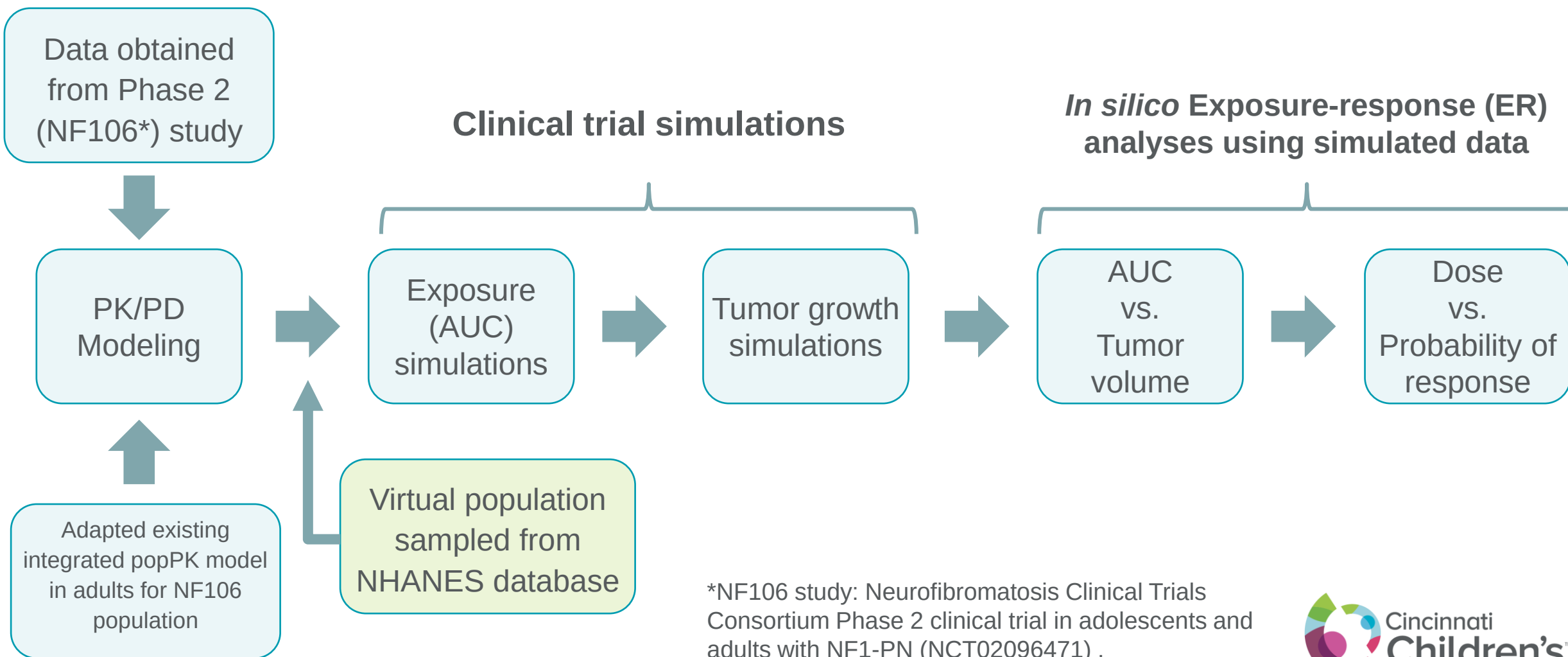
Population PK/PD modeling and ER analysis of mirdametinib in adolescents and adults with neurofibromatosis type-1 (NF1) related plexiform neurofibromas (PN)

NF1-related PN and MEK inhibitor mirdametinib

- Plexiform neurofibromas (PNs) are nerve sheath tumors that develop in ~40% of patients with neurofibromatosis type 1 (NF1).^{1,2}
- PNs are associated with morbidities and complications such as severe pain, disfigurement, reduced quality of life, and malignant transformation.¹⁻³
- Mirdametinib is an investigational oral MEK1/2 inhibitor that was evaluated in the Neurofibromatosis Clinical Trials Consortium Phase 2 NF106 clinical trial (NCT02096471) in adolescents and adults with NF1-PN.¹

1) Weiss BD et al. J Clin Oncol. 2021;39(7):797-806. 2) Wolters PL et al. Am J Med Genet A. 2015;167a(9):2103-2113.
3) Dombi E et al. N Engl J Med. 2016;375(26):2550-2560.

Project flow chart

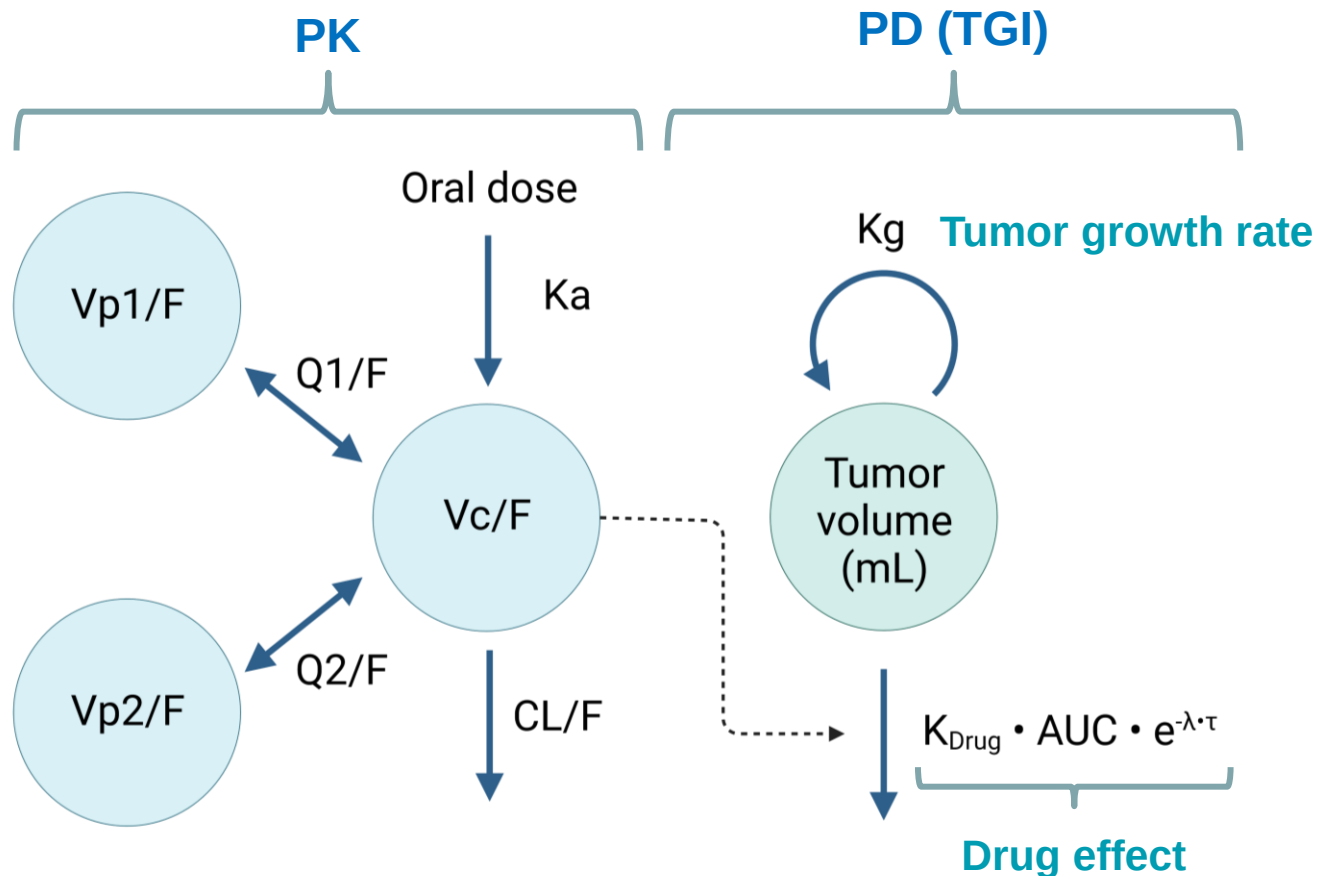


*NF106 study: Neurofibromatosis Clinical Trials Consortium Phase 2 clinical trial in adolescents and adults with NF1-PN (NCT02096471) .

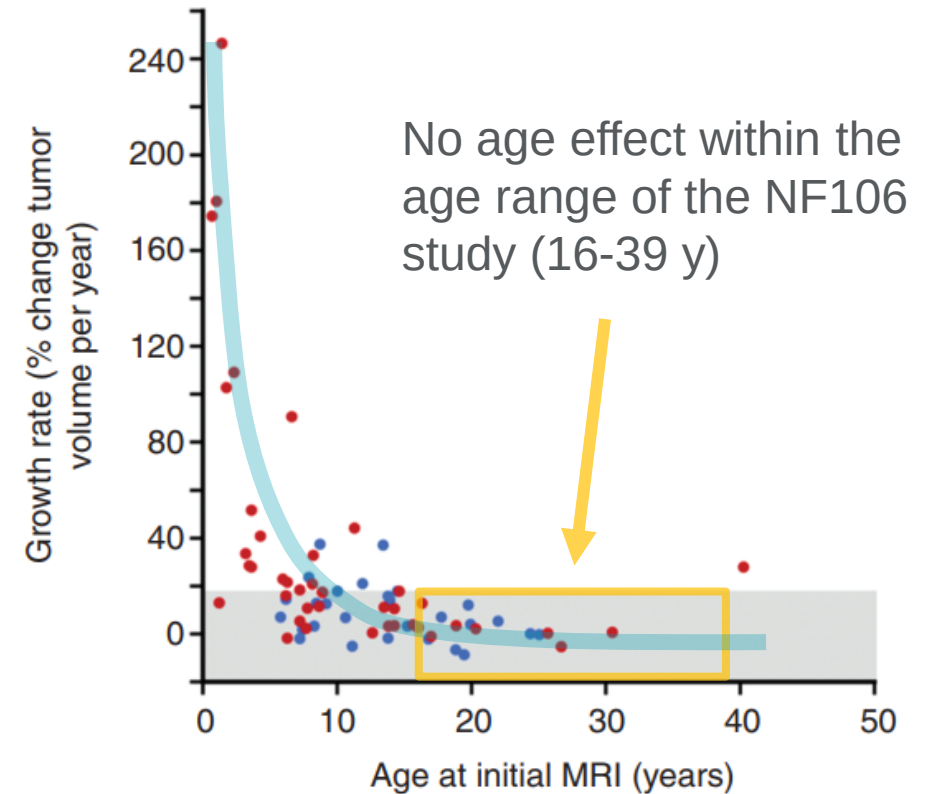


Mirdametinib PK/PD model development using tumor growth inhibition (TGI) modeling

PK/PD model structure



Effect of age on tumor growth rate¹



¹Akshintala et al. Neuro Oncol. 2020

Simulations of tumor growth profile for various dosing regimens

Unpublished data

ER relationship between AUC and tumor volume

Unpublished data

ER relationship between dose and probability of response ($\geq 20\%$ tumor volume reduction)

Unpublished data

Summary- mirdametinib case study

- Mirdametinib PK/PD model has been successfully developed by linking drug exposure and dynamic tumor volume changes.
- ER relationship was characterized by clinical trial simulations using the developed TGI model.
- Safety data (i.e. risk of adverse drug reactions) and the exposure-response for safety relationship should be considered to determine the optimal dose and/or regimen.
- Developed modeling and simulation framework will provide a foundation and could help in the design of future studies.

Conclusion

- Drug disposition and response in pediatric patients can be described with a quantitative pharmacometric approach by considering growth and maturation.
- Model-informed precision dosing is feasible and helpful in supporting dose selection in pediatric patients.
- Multidisciplinary collaboration and integration of advanced technologies are essential to facilitate the implementation of model-informed precision dosing.

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