Model-informed Approaches to Support Dosage Selection in Pediatric Patients

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October 16, 2023

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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.

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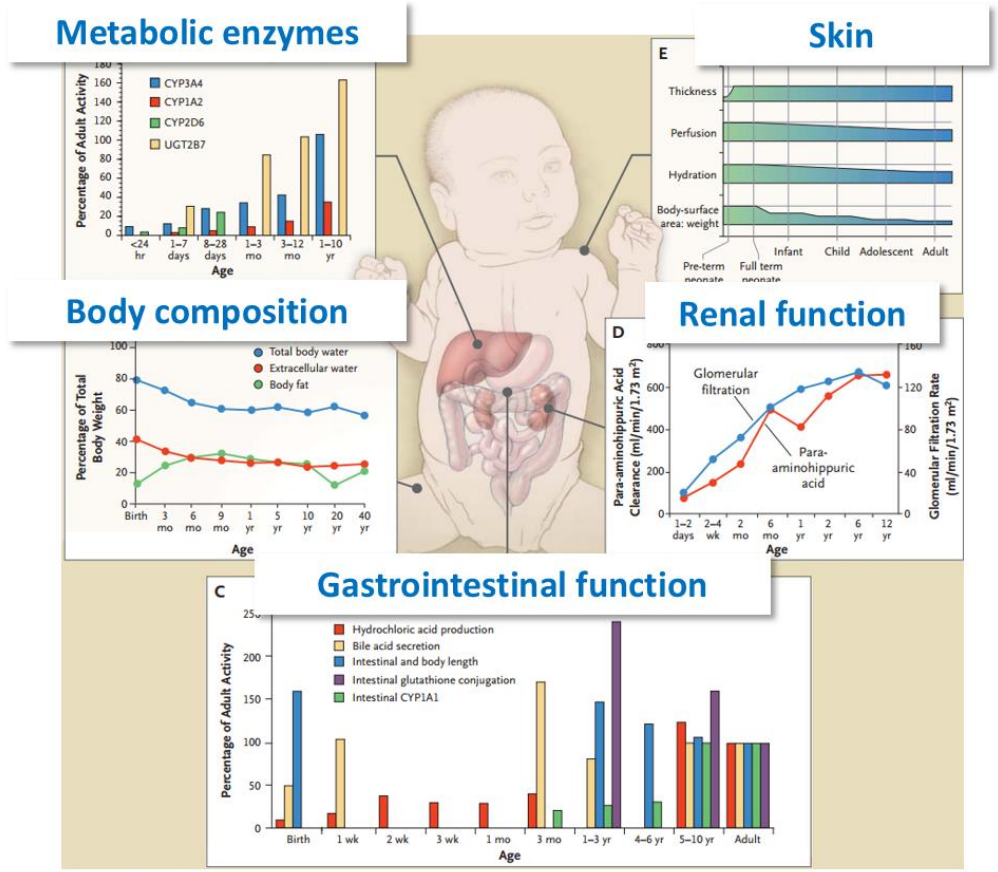
Why model-informed dose selection in pediatrics?

- 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

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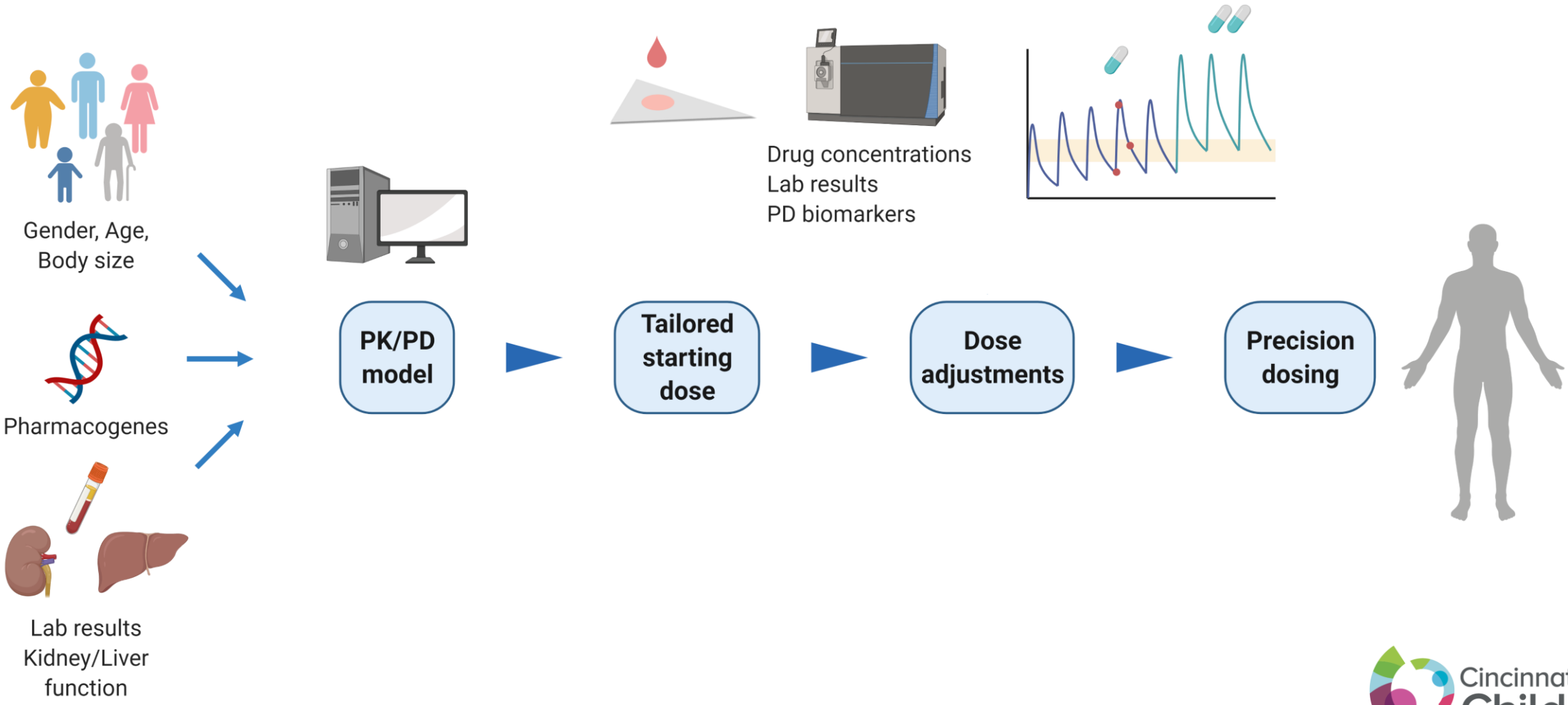
Model-informed precision dosing (MIPD)



Mizuno T et al. Br J Clin Pharmacol, 2021

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

Extrapolation from adults to children

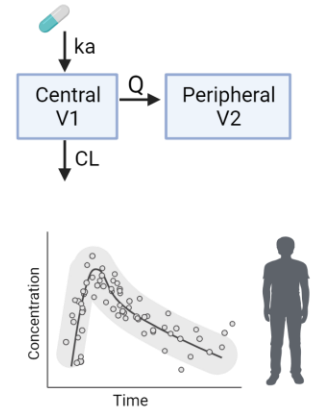
Simulation using pediatric models

Identify age-appropriate dosing regimens

Determine optimal time points and sample size

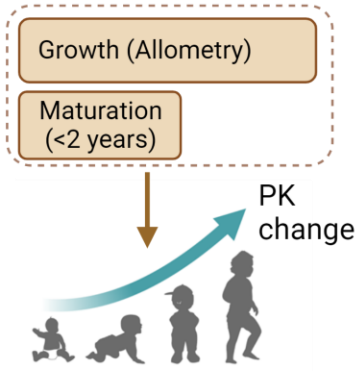
Confirm results with simulations

Population PK modeling



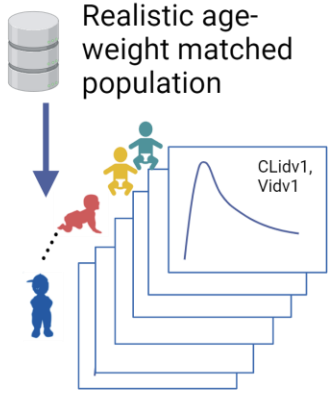
- Prior knowledge
- Rich adult PK data in healthy volunteers/ patients

Pediatric PK modeling



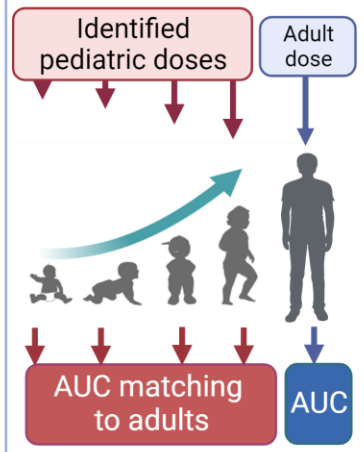
- Incorporation of covariates

Monte Carlo Simulations



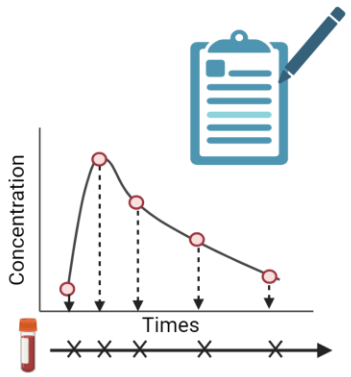
- Individual PK simulation in realistic age-matched population

Dose selection by exposure matching



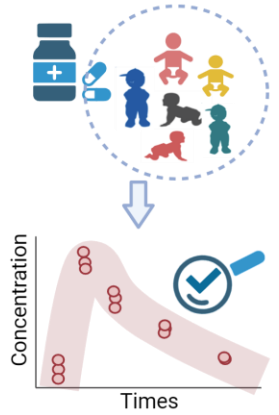
- Age-appropriate doses to match adult exposures

Trial design



- Sample size and power evaluation
- D-optimal sampling design

Phase I Study



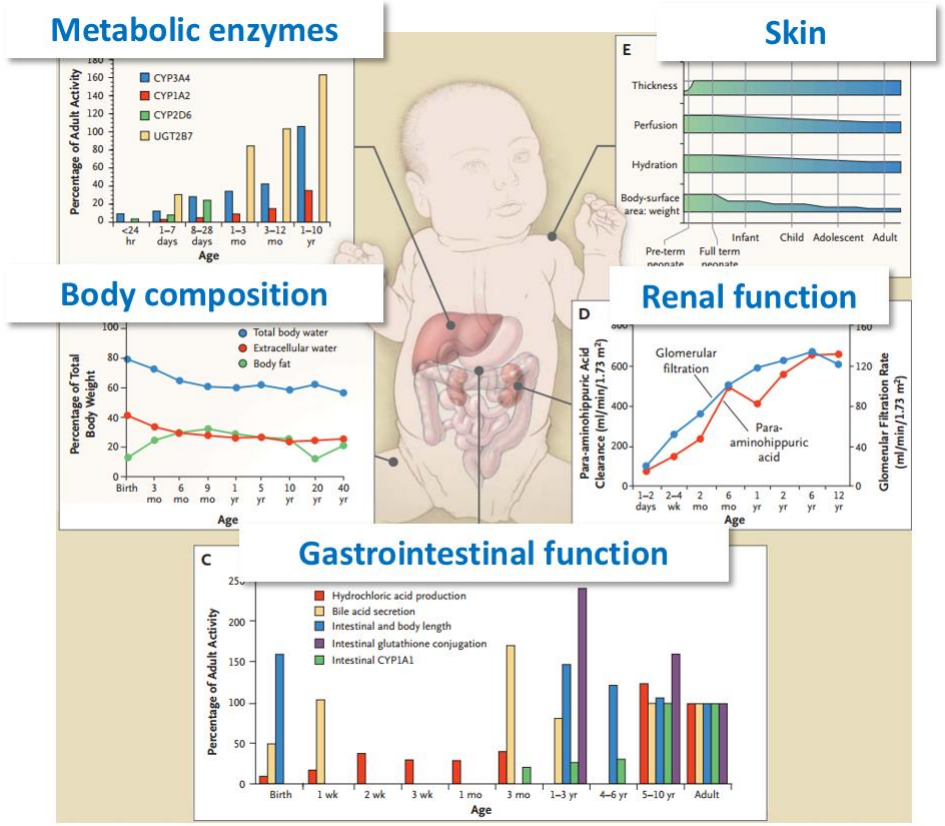
- Conduct Phase I clinical trial
- Confirm results with simulations

Adapted with modification from Vinks and Barrett. J Clin Pharmacol. 2021 Jun;61 Suppl 1:S52-S59.

Case study 1

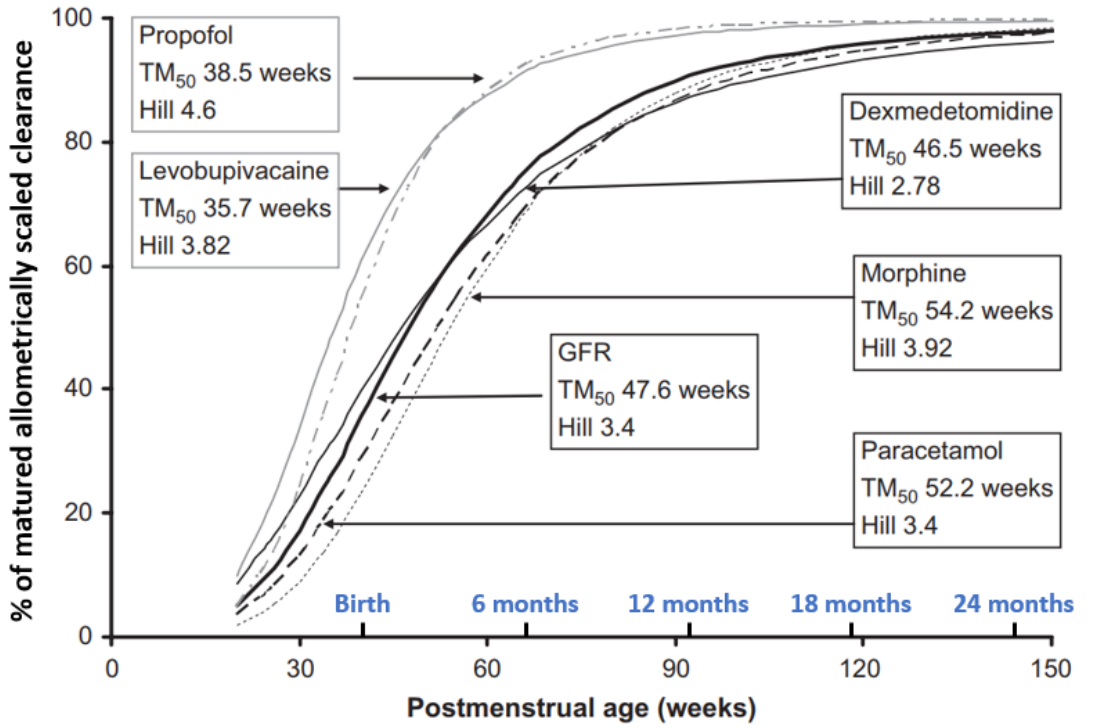
Model-informed pediatric dose selection for sirolimus in infants with vascular tumors and malformations

Implications of maturation on drug response in infants



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

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



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.

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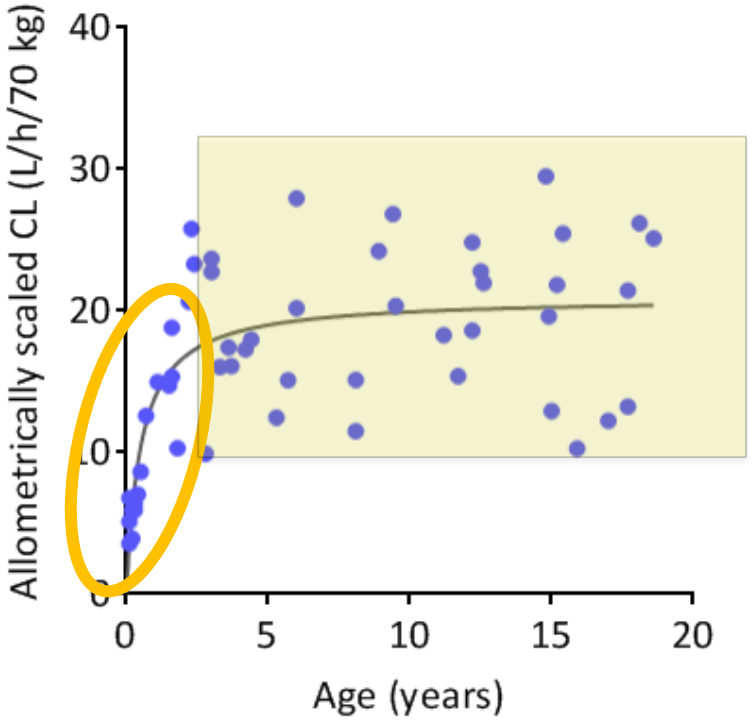
Effect of body size and maturation on sirolimus clearance in children

Denise Adams, MD
Children's Hospital of Philadelphia

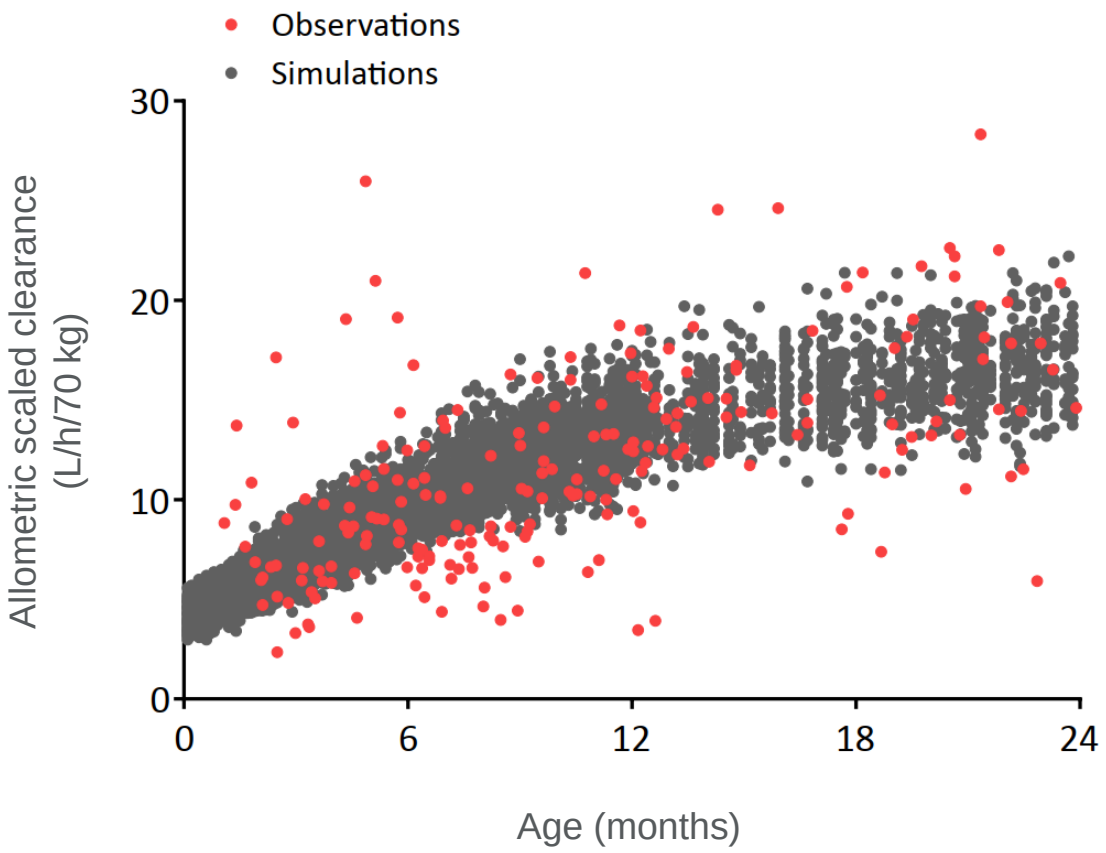
Sirolimus clearance estimated using Phase 2 clinical trial for pediatric patients with vascular tumors and malformations

- 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



Adams et al. Pediatrics, 2016, Mizuno et al. Eur J Pharm Sci. 2017.

Development of a model to describe clearance maturation in young children



Maturation model

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

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

Clinical trial simulations to identify age-appropriate dosing regimens

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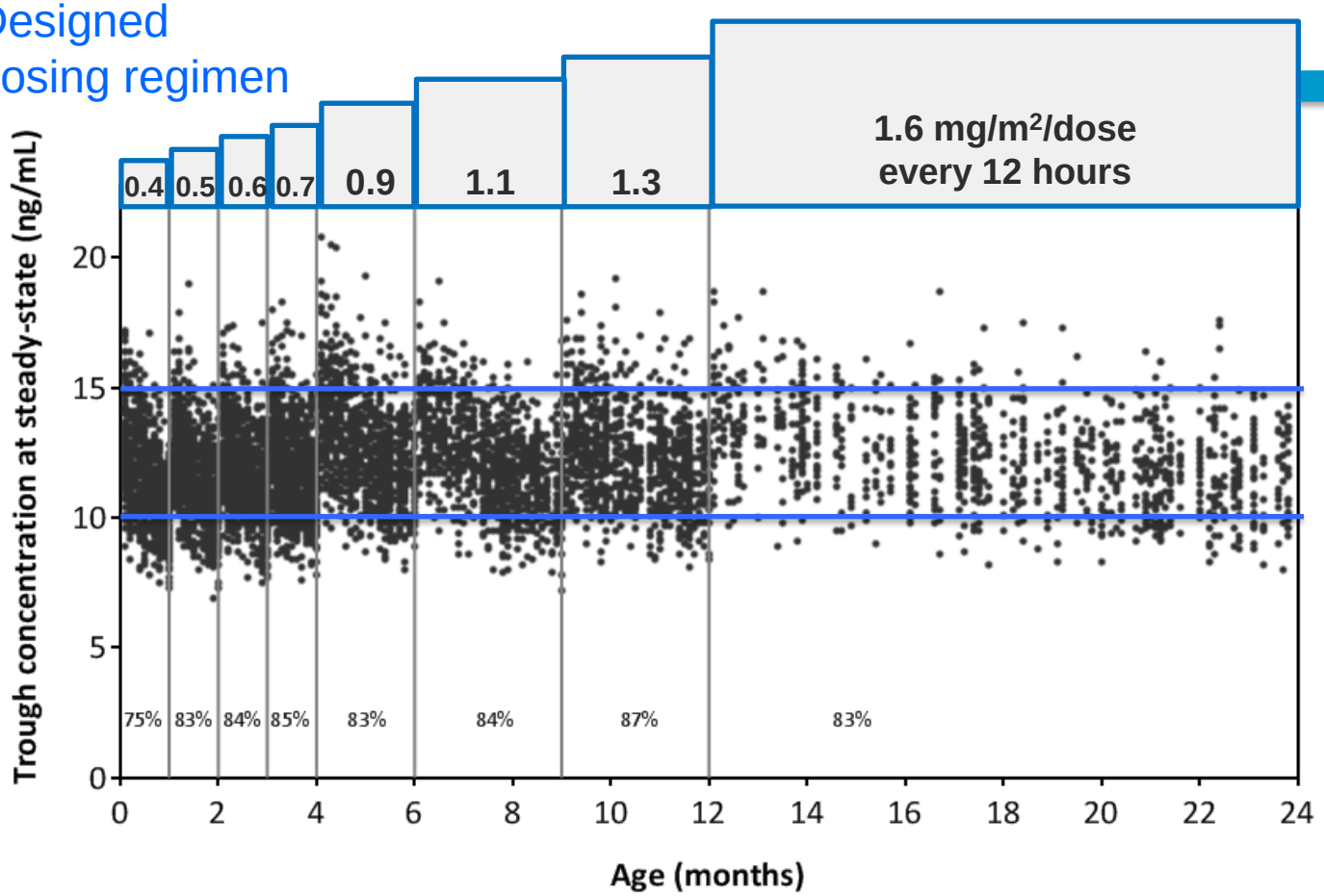
Mizuno et al. Pediatr Blood Cancer. 2017;64:e26458.

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

Designed dosing regimen



Age groups	Dosing regimens (mg/m² 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

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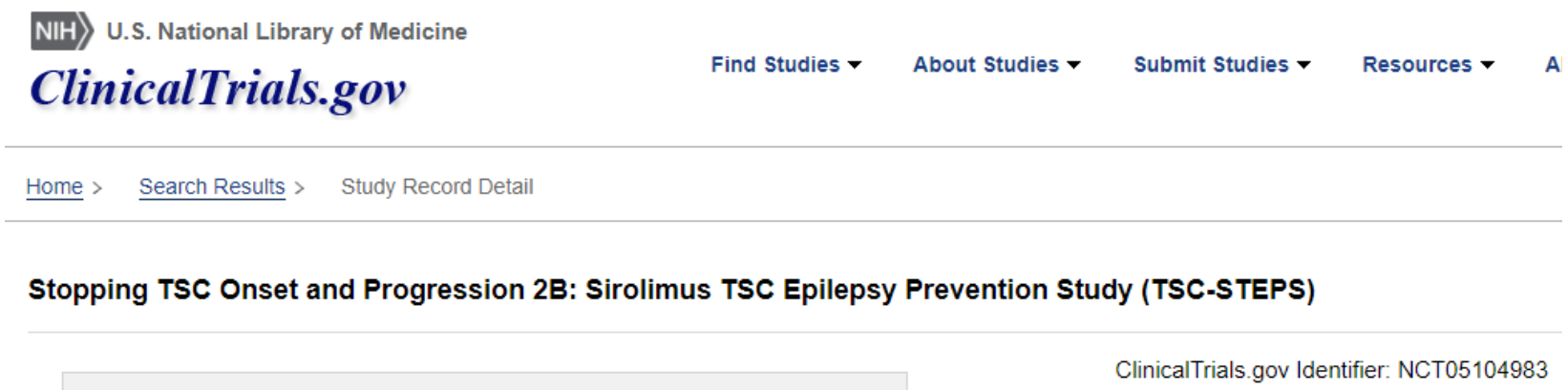
Mizuno T et al. Pediatr Blood Cancer. 2017;64:e26458.

Clinical trial of sirolimus in infants with tuberous sclerosis complex



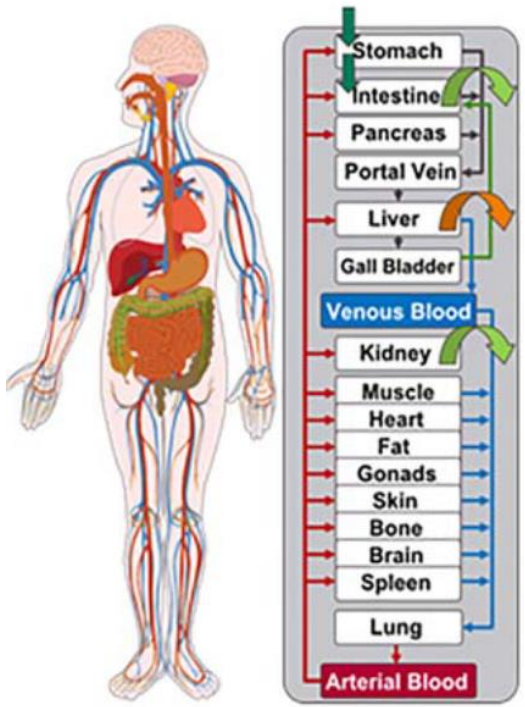
Darcy Krueger, MD, PhD

Neurology, CCHMC

- 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

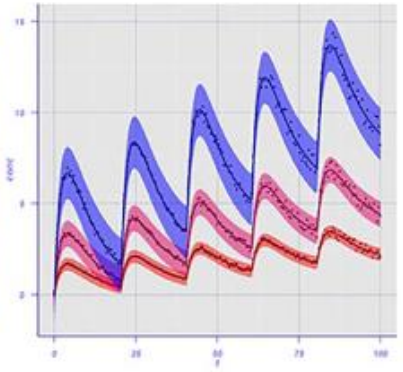
https://clinicaltrials.gov/ct2/show/NCT05104983

Physiologically based pharmacokinetics (PBPK) modeling



Building blocks of a PBPK model

Organism properties	Drug properties	Study protocol and formulation properties



Anatomy and physiology
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

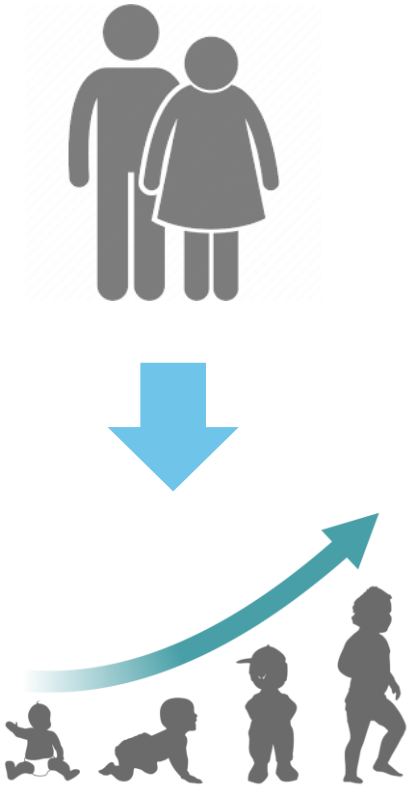
Physico-chemical properties
- Lipophilicity (logP, logD, logMA)
- Molecular Weight
- pKa/pKb

Drug biological properties
- Fu
- Partition coefficients
- Permeability
- active processes (Km, Vmax, Kd)

Formulation
(empirical or mechanistic dissolution function)

Administration protocol
(dose and dosing regimen)

Special events
(food intake, exercise, EHC)



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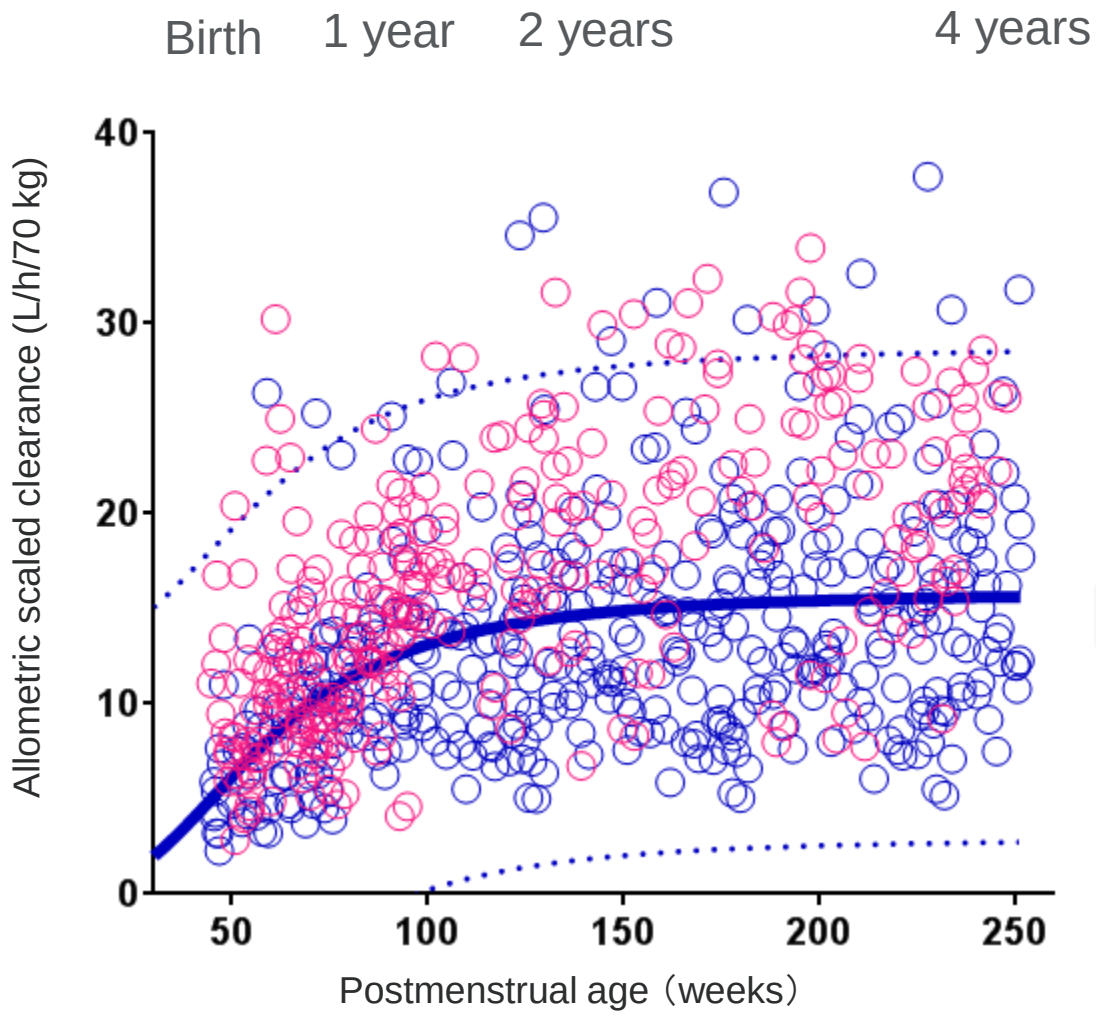
Kuepfer et al. CPT Pharmacometrics Syst. Pharmacol. (2016)

Mizuno T. Presented at FDA-ISoP public workshop, Silver Spring, MD, Oct 16, 2023.

Developmental changes in sirolimus clearance



PBPK model-based simulations

n= 400 virtual pediatric subjects

Observations (Bayesian estimates)

316 data from 24 patients

Maturation model

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

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

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Emoto et al., CPT-PSP. 2015 & 2016

Courtesy: Alexander Vinks, PhD, PharmD

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.

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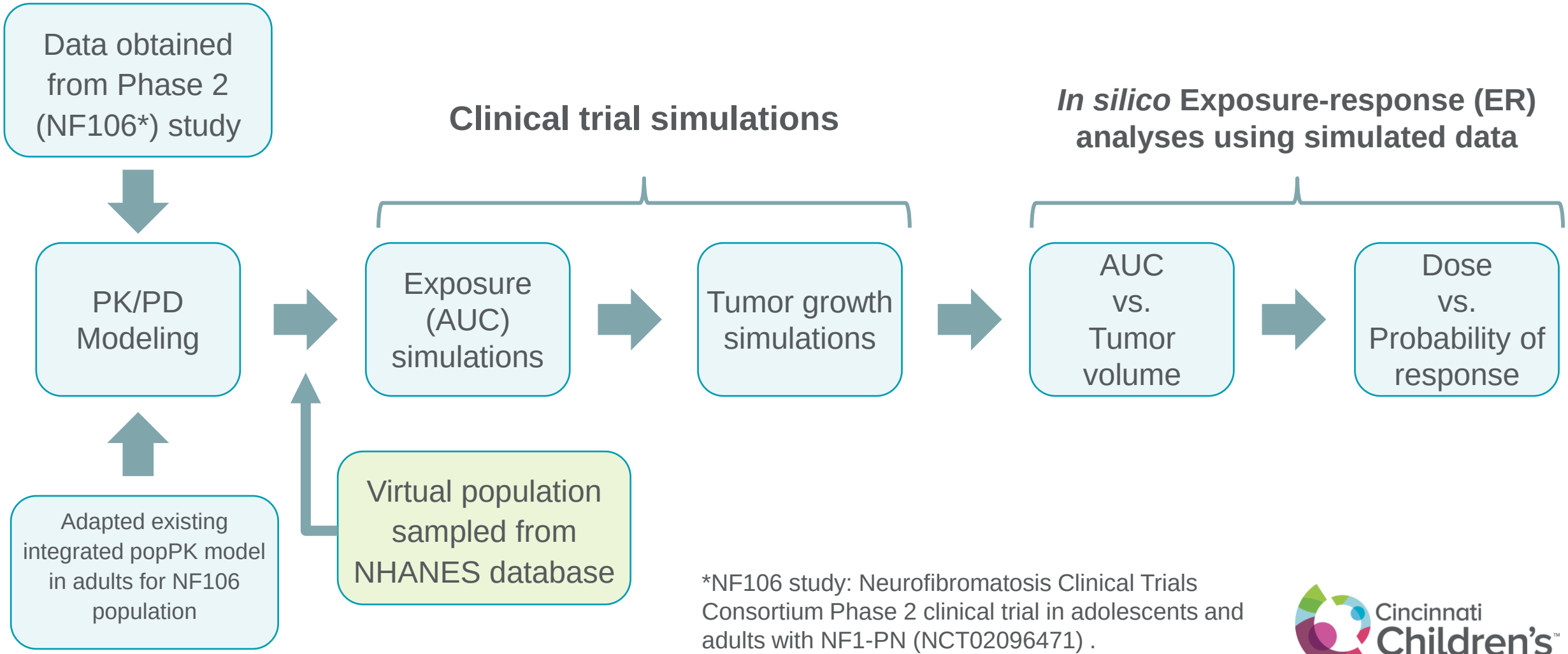
Project flow chart

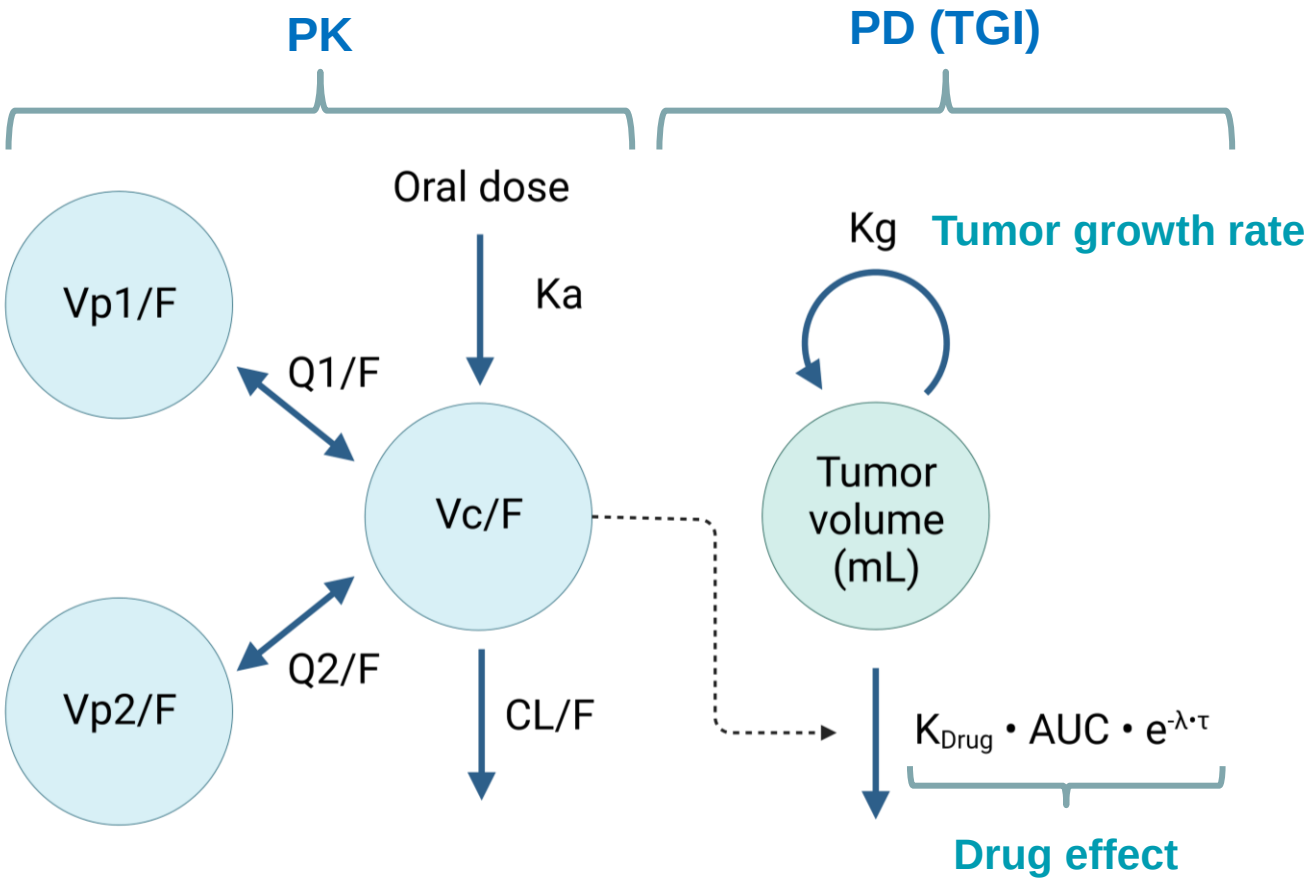


*NF106 study: Neurofibromatosis Clinical Trials Consortium Phase 2 clinical trial in adolescents and adults with NF1-PN (NCT02096471) .

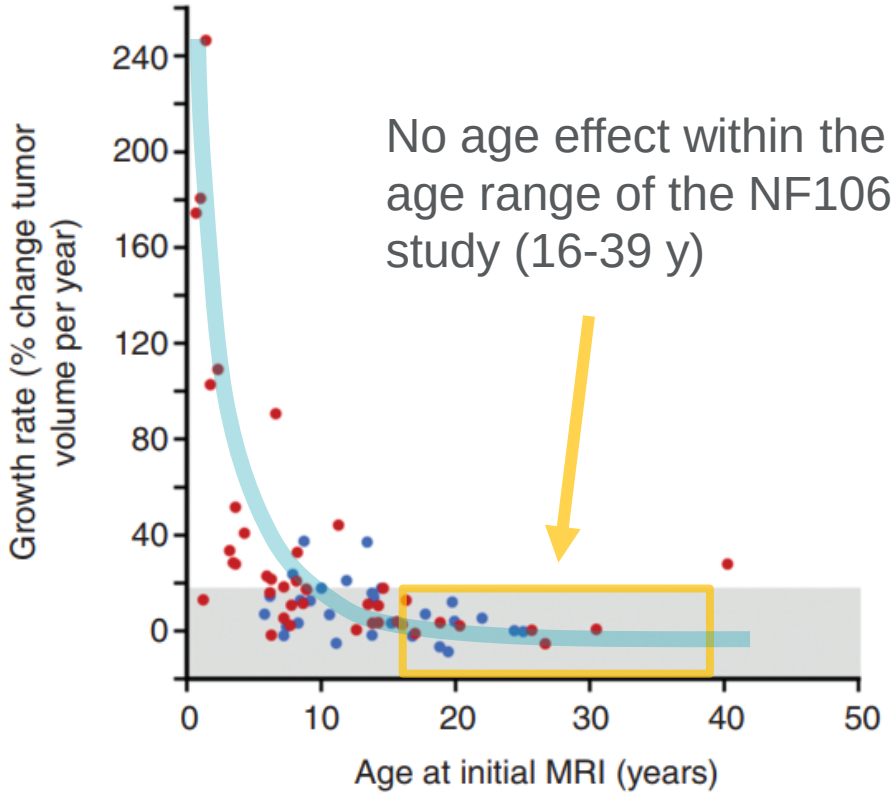
Shearer et al. NF conference 2022; Mizuno et al. ACCP 2022

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

PK/PD model structure



Effect of age on tumor growth rate[1]



No age effect within the age range of the NF106 study (16-39 y)

[1]Akshintala et al. Neuro Oncol. 2020

Shearer et al. NF conference 2022; Mizuno et al. ACCP 2022

Simulations of tumor growth profile for various dosing regimens

Unpublished data

Shearer et al. NF conference 2022; Mizuno et al. ACCP 2022

ER relationship between AUC and tumor volume

Unpublished data

Shearer et al. NF conference 2022; Mizuno et al. ACCP 2022

ER relationship between dose and probability of response (≥20% tumor volume reduction)

Unpublished data

Shearer et al. NF conference 2022; Mizuno et al. ACCP 2022

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.

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Shearer et al. NF conference 2022; Mizuno et al. ACCP 2022

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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Acknowledgments

CCHMC

Clinical Pharmacology

Alexander Vinks, Pharm D, PhD, FCP

Tracy Glauser, MD

Min Dong, PhD

Kana Mizuno, PhD

Sonya Tang Girdwood, MD, PhD

Zachary Taylor, PhD

Laura Ramsey, PhD

Brooks McPhail, PhD

Keizo Fukushima, PhD

Ryota Tanaka, PhD

Kei Irie, PhD

Ronaldo Morales Junior, PhD

Wen Rui Tan, MS

Sanjana Parikh, MS

And all other members!!

Cancer and Blood Disease Institute

Brian Weiss, MD

Adrienne Hammill, MD, PhD

Paula Mobberley-Schuman, MS

Neurology

Darcy Krueger, MD, PhD

David Ritter, MD, PhD

Children's Hospital of Philadelphia

Denise Adams, MD

Medimatics

Nieko Punt, MS

SpringWorks Therapeutics

Todd Shearer, PhD

Abraham Langseth, PhD

Thuy Hoang, PhD

Patients and their families

All medical staffs for patient care

Sirolimus clinical trial was supported by the FDA Office of Orphan Products (R01FD003712 and R01FD004363, PI: Dr. Adams). Pfizer Inc. provided sirolimus for the clinical study but had no role in designing or conducting the study or in analyzing or reporting the data. Funding for mirdametinib PK/PD analysis was provided by SpringWorks Therapeutics, Inc. The NF106 study, an NF Clinical Trials Consortium study, was supported by DOD award W81XWH-12-1-0155.

