FDA/MCERSI Workshop
Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?
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Ontogeny of Renal Function: Application in Population-Based Modeling for Drug Development

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Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Outline

- **Renal Maturation Models**
  - Overview
  - Evaluation with drug PK data
  - Challenges and opportunities

- **Bedside Renal Function Equations**
  - Overview
  - Evaluation with drug PK data
  - Challenges and opportunities

Focus: ***Newborns and infants / Application in drug development***

Renal Function and Glomerular Filtration Rate

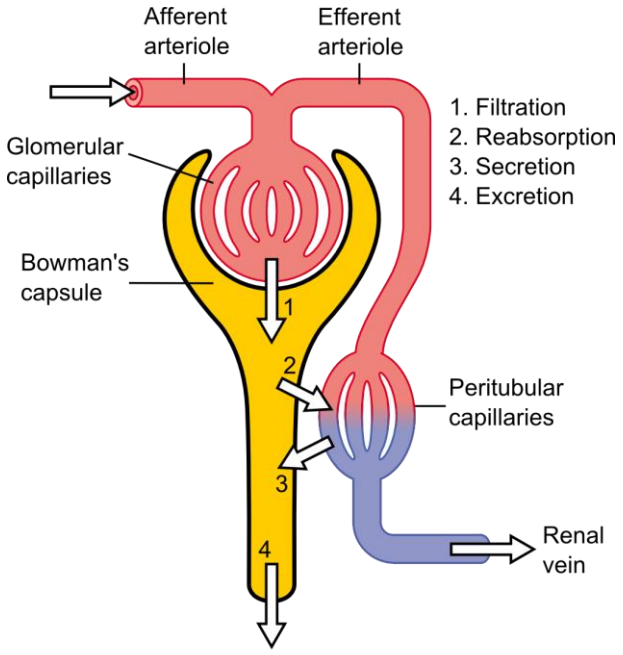
- Normal Level of GFR Varies by Age

Normal GFR in Children and Adolescents

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m²)
1 wk (males and females)	41 ± 15
2–8 wk (males and females)	66 ± 25
>8 wk (males and females)	96 ± 22
2–12 y (males and females)	133 ± 27
13–21 y (males)	140 ± 30
13–21 y (females)	126 ± 22

NKF-K/DOQI Classification of the Stages of CKD

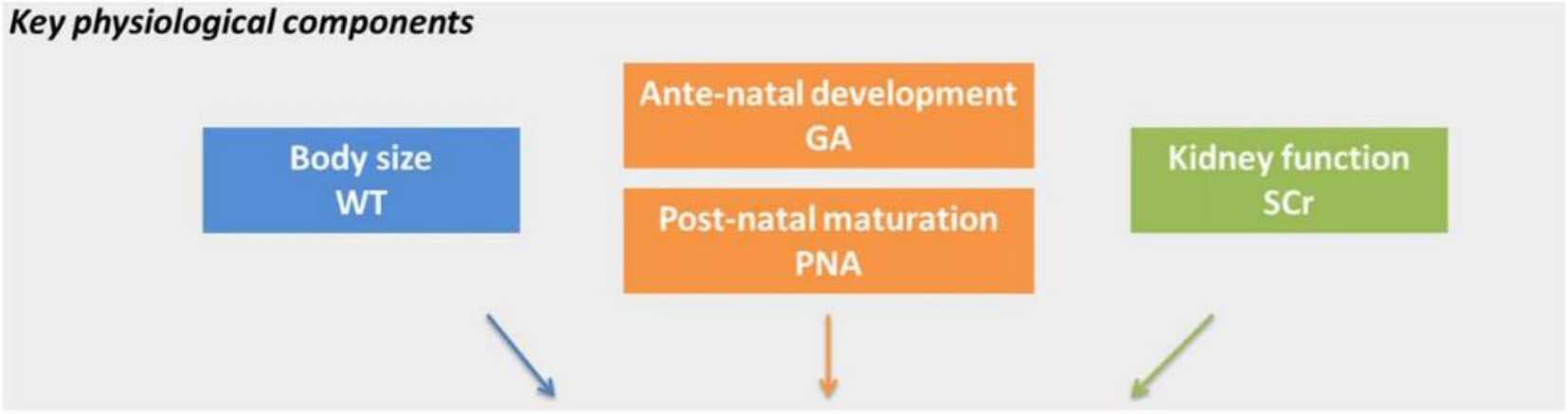
Stage	GFR (mL/min/1.73 m²)	Description
1	≥90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–29	Severe reduction of GFR
5	<15 (or dialysis)	Kidney failure



Hogg et al., Pediatrics. 2003 Jun;111(6 Pt 1):1416-21

Current Population PK Modeling Approach

- A review based on 61 articles reporting PopPK models from 13 renally eliminated drugs
- Intention: to separate the effects of body size, age and kidney function on drug clearance



Note: F_{kidney} accounts for deviation from normal kidney function, eg, due to inflammatory disease or drug-related nephrotoxicity.

Wilbaux et al, J Clin Pharm 2016, 56(8) 909–935

Key physiological components

- Body size: WT
- Ante-natal development: GA
- Post-natal maturation: PNA
- Kidney function: SCr

$$CL = \mathrm{CL}_{standard} \times F_{size} \times F_{maturation} \times F_{kidney}$$

$$F_{size} = \left(\frac{WT}{WT_{std}}\right)^{0.75}$$

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

TM_{50} = 47.7, Hill = 3.4

$$F_{kidney} = \left(\frac{GFR_{actual}}{GFR_{std}}\right)^{PWR}$$

$$F_{kidney} = \left(\frac{1}{Scr_{actual}}\right)^{PWR}$$

$$F_{kidney} = \left(\frac{Scr_{actual}}{Scr_{std}}\right)^{PWR}$$

Combined linear and power function*

$$F_{maturation} = (1 + \theta_{GACL} \cdot GA) \cdot (1 + PNA^{PWR})$$

Wilbaux et al, J Clin Pharm 2016, 56(8) 909–935
Rhodin et al., Pediatr Nephrol. 2009 Jan;24(1):67-76

Pediatr Nephrol (2009) 24:67–76
DOI 10.1007/s00467-008-0997-5

ORIGINAL ARTICLE

Human renal function maturation: a quantitative description using weight and postmenstrual age

Malin M. Rhodin · Brian J. Anderson · A. Michael Peters · Malcolm G. Coulthard · Barry Wilkins · Michael Cole · Etienne Chatelut · Anders Grubb · Gareth J. Veal · Michael J. Keir · Nick H. G. Holford

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

$$Fsize = \left(\frac{Wi}{Wstd}\right)^{PWR}$$

$$GFR = F_{PMA} \cdot Fsize \cdot GFRmat$$

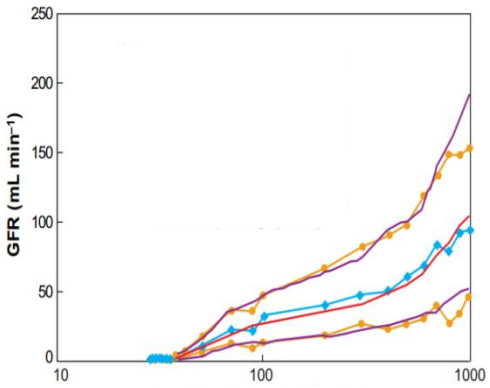
where GFRmat is the mature value for GFR (mL/min).

Table 1 Summary of pooled data used in the study

Characteristics of the study	Study							
	1	2	3	4	5	6	7	8
Method	Cr-EDTA	Cr-EDTA	Mannitol	Inulin	Inulin	Cr-EDTA	Iohexol	Sinistrin
Number	185	347	63	39	56	111	85	37
Mean PMA (range)	384 weeks (87–1652)	655 weeks (48–1461)	144 weeks (40–608)	33 weeks (28–42)	32 weeks (27–42)	762 weeks (113–1226)	581 weeks (57–924)	30 weeks (26–36)
Mean PNA (range)	6.6 years (0.9–14.2)	11.8 years (0.17–31)	2.1 years (2 days-11 years)	8 days (2–63)	9 days (1–80)	13.8 years (2.4–22.8 years)	10.4 years (0.3–17)	7.9 days (0.5–33)
Mean weight (range)	22.5 kg (8–45.4)	41.9 kg (5–120.6)	10.8 kg (2.4–36)	1.6 kg (0.68–3.71)	1.5 kg (0.64–4.65)	44.6 kg (9.6–89)	40.1 kg (5.4–98.5)	1.1 kg (0.62–1.9)
Mean GFR	107 ml/min	131 ml/min	122 ml/min	29 ml/min	25 ml/min	108 ml/min	120 ml/min	23 ml/min
Sex reported	No	No	Yes	No	Yes	Yes	Yes	No
More than one observation/ subject	No	No	No	No	Yes	No	No	Yes
Pathology	No diagnoses available	Oncology	Normal, well children	Premature	Premature	Nephrology	No known renal disease	Premature
Publication	[8]	[7]	[4]	[9]	[10]	[11]	[12]	[5]

GFR Glomerular filtration rate; *PMA* postmenstrual age; *PNA* postnatal age

- **Maturation based on PMA**
- **No efforts were made to distinguish pre-term and full-term neonates**



Collected PK Data from Renally Eliminated Drugs

Drug	Total Clearance (L/h)	Renal Clearance (L/h)	% Renal Clearance	Contribution of Non-renal Elimination Pathways
Amikacin	6.0 ± 0.5	5.0 ± 0.9	94%	<5% metabolism
Gadobutrol	6.2	6.2	>99%	No metabolism
Gadoterate	7.1	7.1	>99%	No metabolism
Vancomycin	5.9 ± 1.5	5.3 ± 2.0	>90%	~ 10% metabolism
Ampicillin	16.9 ± 3.3	10.4 ± 3.7	61%	10% Biliary elimination; Likely secretion
Gentamicin	6.0 ± 1.8	4.6 ± 1.5	~77%	No data
Meropenem	14.6 ± 8.3	10.4 ± 6.4	71%	Likely secretion; ~30% metabolism
Netilmicin	5.5 ± 0.8	4.0 ± 0.6	72%	No data

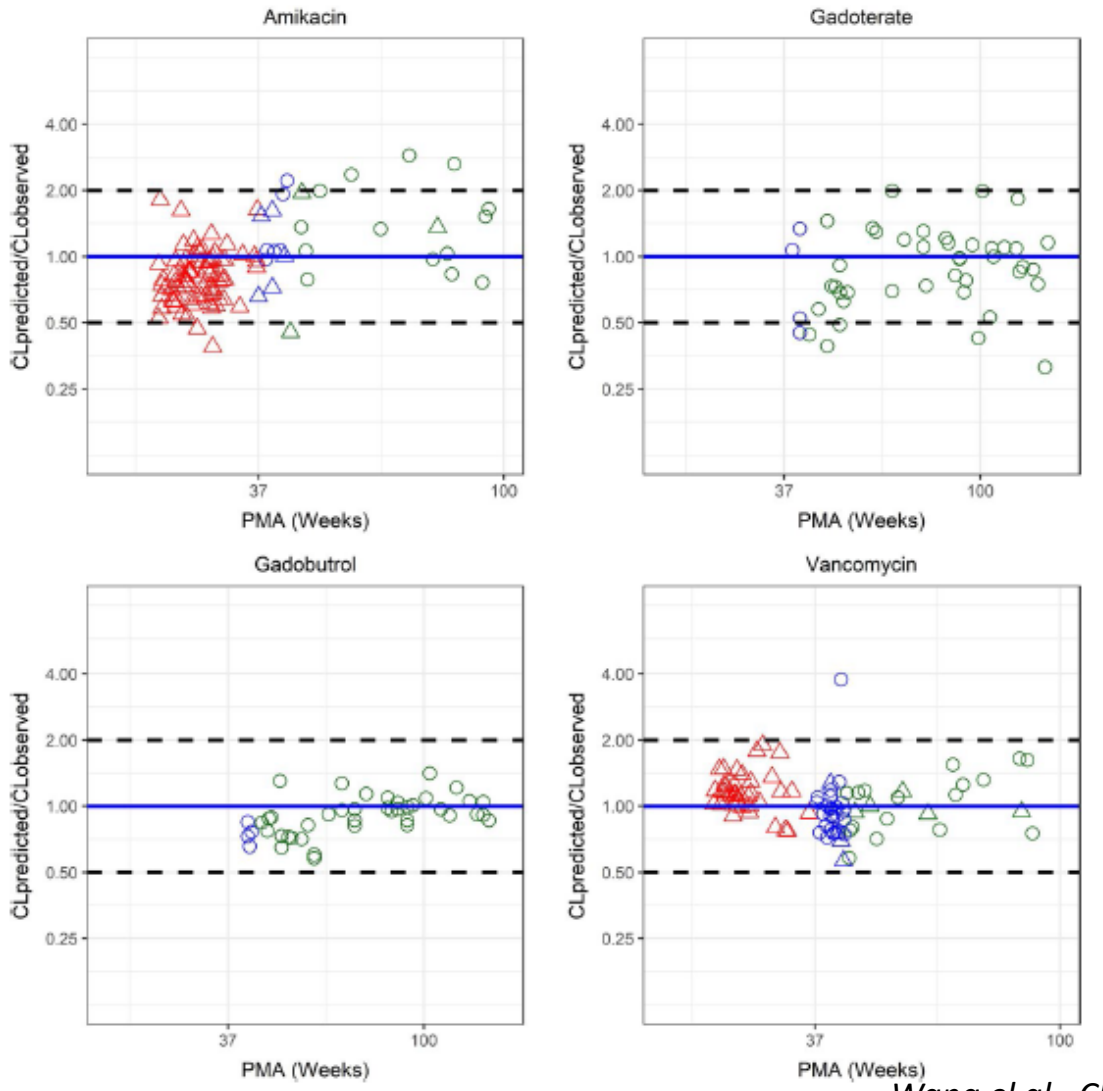
Wang el al., Clin Pharmacol Ther. 2018

Distribution of Newborns and Infants in Age Categories

Drugs (n)	≥ 42 weeks PMA (n)	37 to <42 weeks PMA (n)	<37 weeks PMA (n)	PNA (Days)	GA (Weeks)	PMA (Weeks)	Body Weight (kg)	SCR (mg/dL)*
Amikacin (108)	22	11	75	10 (3-625)	29 (23-41)	31 (25-127)	1.29 (0.45-11.28)	0.38 (0.2-0.96)
Gadobutrol (43)	39	4	0	212 (6-696)	40 (40-40)	70 (41-139)	7.2 (2.80-14.20)	0.27 (0.1-0.66)
Gadoterate (45)	41	4	0	266 (4-721)	40	78 (39-143)	8.00 (3.00-15.00)	0.24 (0.14-0.42)
Vancomycin (92)	22	31	39	13 (2-367)	36 (24-41)	39 (25-89)	2.61 (0.53-8.26)	0.5 (0.18-1.67)
Ampicillin (73)	5	31	37	2 (0-24)	36 (24-41)	37 (25-43)	2.47 (0.50-4.19)	0.6 (0.2-2.5)
Gentamicin (143)	46	48	49	1 (0-711)	37 (23-43)	38 (23-135)	3.12 (0.40-12.00)	0.6 (0.18-5.5)
Meropenem (200)	13	31	156	21 (1-92)	28 (23-40)	32 (24-51)	1.54 (0.39-6.50)	0.5 (0.1-1.9)
Netilmicin (83)	1	3	79	10 (2-121)	27 (23-41)	29 (24-43)	1.00 (0.47-3.00)	0.77 (0.27-1.67)
All drugs (787)	189	163	435	13 (0-721)	33 (23-43)	35 (23-143)	2.16 (0.39-15.00)	0.5 (0.1-5.5)

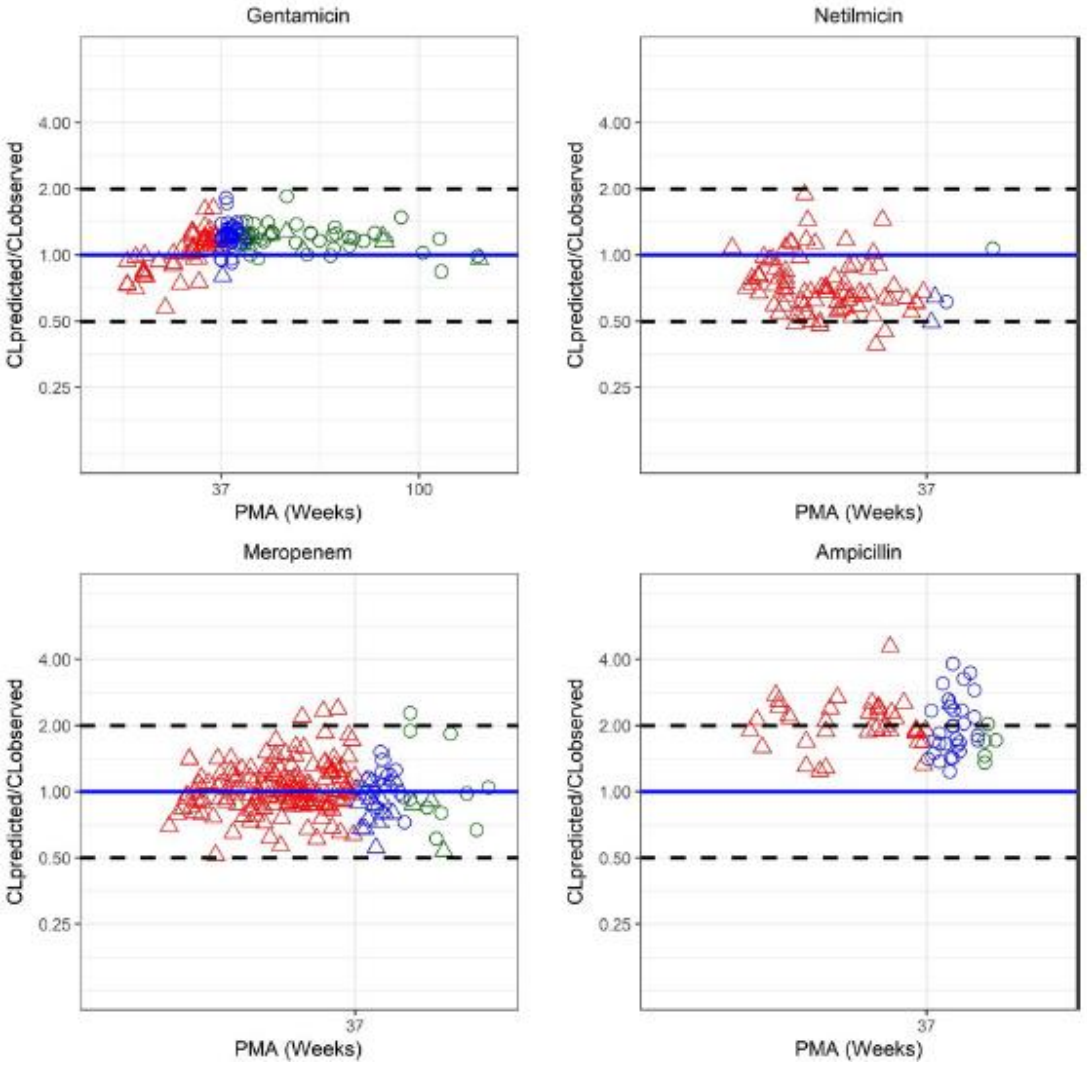
Wang el al., Clin Pharmacol Ther. 2018

Predictive Performance for Drug Clearance Using PMA based Model (1)



Wang el al., Clin Pharmacol Ther. 2018

Predictive Performance for Drug Clearance Using PMA based Model (2)



Wang el al., Clin Pharmacol Ther. 2018

Renal Maturation Model in Drug Development

- **Case Example:**
  - Gadobenate dimeglumine; gadolinium-based contrast agent with ~95% renal elimination
  - PK simulations based on the PMA-based maturation model were used to inform the dose selection in infants

Pediatric: A population pharmacokinetic analysis incorporated data from 25 healthy subjects (14 males and 11 females) and 15 subjects undergoing MR imaging of the central nervous system (7 males and 8 females) between ages of 2 and 16 years. The subjects received a single intravenous dose of 0.1 mmol/kg of MultiHance. The geometric mean C_{max} was 62.3 µg/mL (n=16) in children 2 to 5 years of age, and 64.2 µg/mL (n=24) in children older than 5 years. The geometric mean AUC $_{0-\infty}$ was 77.9 µg·h/mL in children 2-5 years of age (n=16) and 82.6 µg·h/mL in children older than 5 years (n=24). The geometric mean half-life was 1.2 hours in children 2 to 5 years of age and 0.93 hours in children older than 5 years. There was no significant gender-related difference in the pharmacokinetic parameters in the pediatric patients. Over 80% of the dose was recovered in urine after 24 hours. Pharmacokinetic simulations indicate similar AUC and C_{max} values for MultiHance in pediatric subjects less than 2 years when compared to those reported for adults; no age-based dose adjustment is necessary for this pediatric population.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021357s016s017,021358s015s016lbl.pdf

Renal Maturation Model in Drug Development

- Opportunities:
  - Age based renal maturation models, in combination with body weight- based scaling, can be used in population modeling for drugs that are primarily eliminated via renal pathway to inform **initial dose selection** for newborns and infants in clinical trials.

- Challenges:
  - The current models do not incorporate renal ontogeny of **reabsorption and secretion**. Better understanding of the ontogeny of drug transporters and metabolism in kidney are needed.
  - The model does not account for **renal impairment** (due to *kidney disease or drug-related nephrotoxicity).*

Outline

- Renal Maturation Models
  - Overview of models (Filtration, Reabsorption, Secretion)
  - Evaluation with drug PK data
  - Challenges and opportunities

- **Bedside Renal function Models**
  - Overview
  - Evaluation with drug PK data
  - Challenges and opportunities

Estimation of GFR

- Traditionally used methods
  - Inulin
  - PAH (para-aminohippurate)
  - DTPA (diethylenetriamine penta-acetic acid)
- Methodology can be based on urinary accumulation or plasma disappearance
- Newer substances that have been studied in children
  - Iothalamate—non-radioactive, actively secreted by renal proximal tubule
  - Iohexol—non-radioactive, less allergenic potential

The Case for Creatinine

- Metabolic product of muscle
- Generally produced at a constant rate by the body
- Freely filtered
- Not metabolized
- BUT, is secreted by the proximal tubule
- Attractive as an estimate of GFR because injection is not necessary and steady state plasma creatinine can be used without need for collection of urine

Lynne Yao, FDA presentation, 2016

Limitations of Creatinine

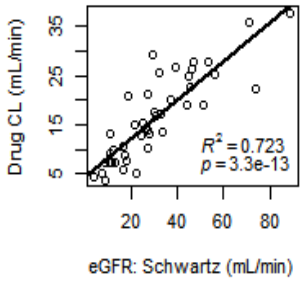
- Serum creatinine affected by
  - Muscle mass
  - Muscle breakdown
  - Maternal transfer
  - Tubular secretion
  - Diet
  - Disease (e.g. neuromuscular disease, anorexia nervosa)
- These factors produce variability in specific situations, especially in preterm and newborn infants

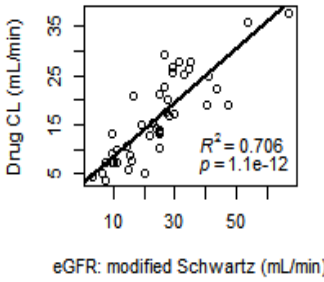
Serum-Creatinine (SCR)-based equations for Estimation of GFR

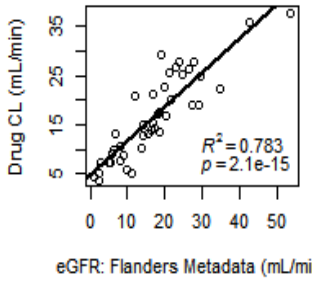
- **Schwartz (Original)**
  - eGFR (mL/min/1.73m2)=k*HT (cm)/SCR (mg/dL) (k=0.33 for LBW<1yr, 0.45 for Term <1 yr, 0.55 for >= 1 yr female, 0.70 for >= 1 yr male)
  - k values from FDA Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, 2014
- **Modified Schwartz (Bedside Schwartz)**
  - eGFR (mL/min/1.73m2)=k*HT (cm)/SCR (mg/dL) (k=0.413)
- Counahan-Barratt
  - eGFR (mL/min/1.73m2)=k*HT (cm)/SCR (mg/dL) (k=0.43)
- Flanders Metadata
  - eGFR (mL/min/1.73m2) = (0.0414*log(AGE) + 0.3018) *HT/SCR
- Leger
  - eGFR (mL/min) = (56.7*WT+0.142*(HT^2))/(SCR*88.4)
- British Columbia Children's Hospital
  - eGFR (mL/min/1.73m2) = exp(1.18+0.0016*WT+0.01*HT+149.5/(SCR*88.4)-2141/((SCR*88.4)^2))
- Lund-Malmo, applicable if SCr < 1.70 mg/dL
  - Male: eGFR (mL/min/1.73m2) = exp(4.62-0.0112*SCR*88.4-0.0124*AGE+0.339*log(AGE)
  - Female: eGFR (mL/min/1.73m2) = exp(4.62-0.0112*SCR*88.4-0.0124*AGE+0.339*log(AGE-0.226)
- Cockcroft-Gault
  - Male: eGFR (mL/min) = (140-AGE)*WT/(SCR*72)
  - Female: eGFR (mL/min) = (140-AGE)*WT/(SCR*72)*0.85
- Simcyp default model
  - eGFR (mL/min) = (-6.616*BSA^2) + (99.054*BSA) - 17.74
- Rhodin model
  - eGFR (L/hr) =(WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*7.26

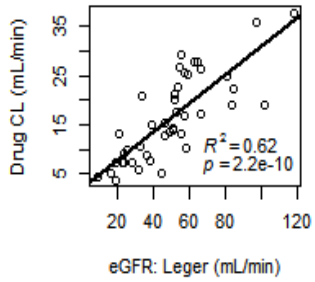
Maturation-based models for comparison

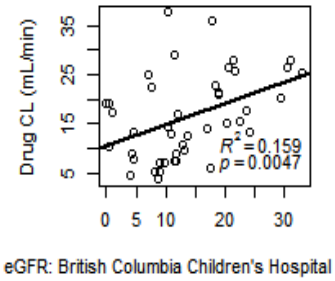
How Well Does eGFR Predict Gadobutrol CL?

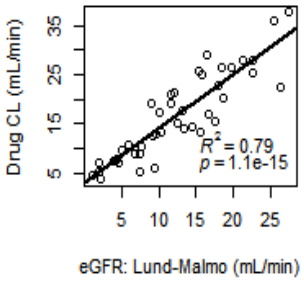


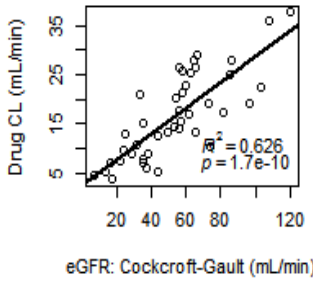


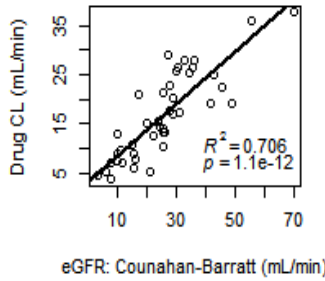


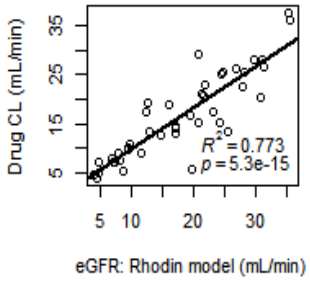


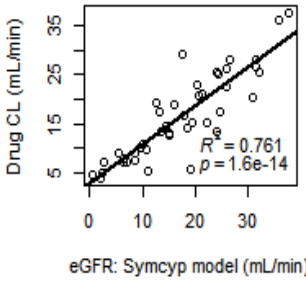








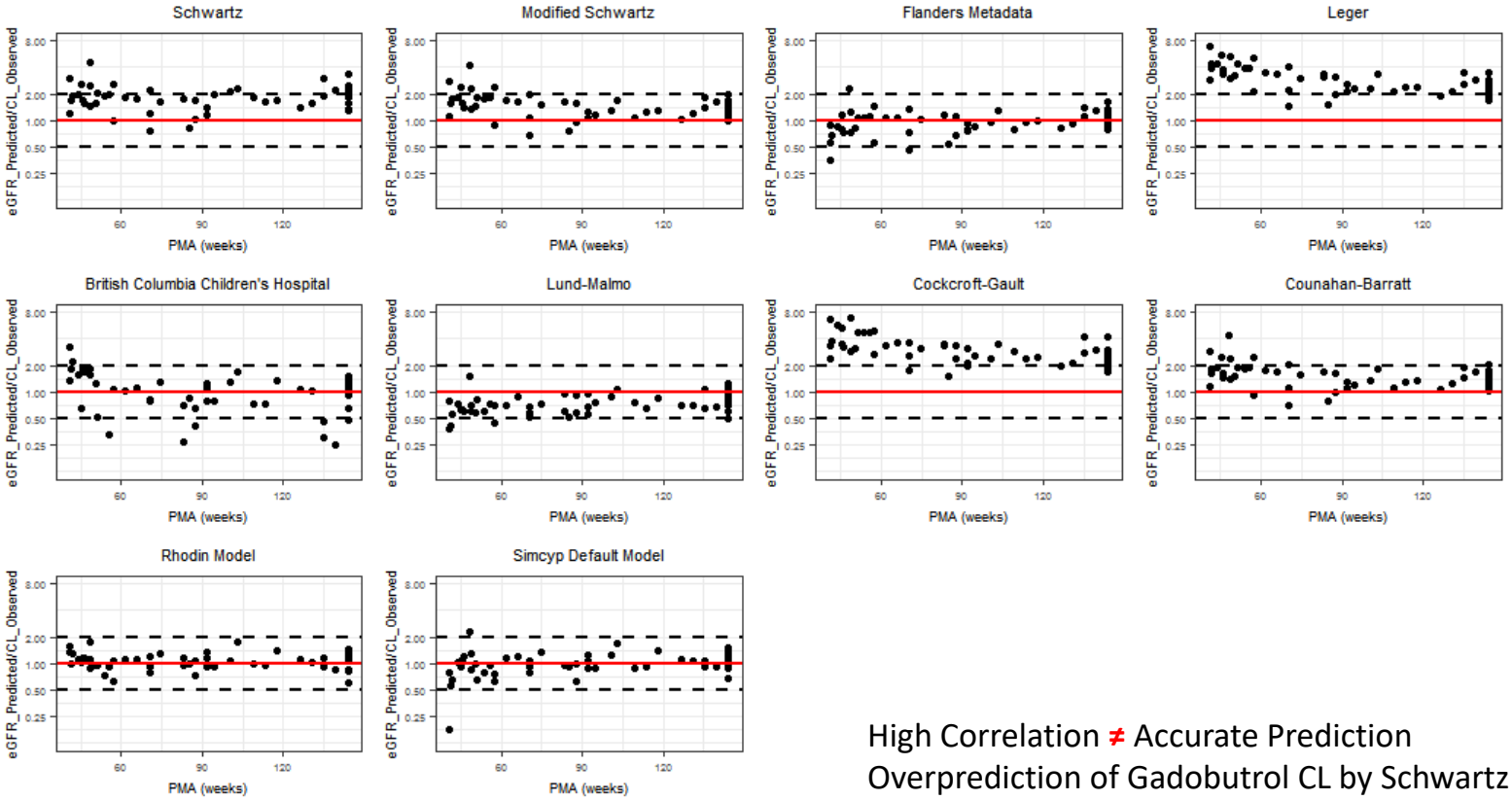




Gadobutrol: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism

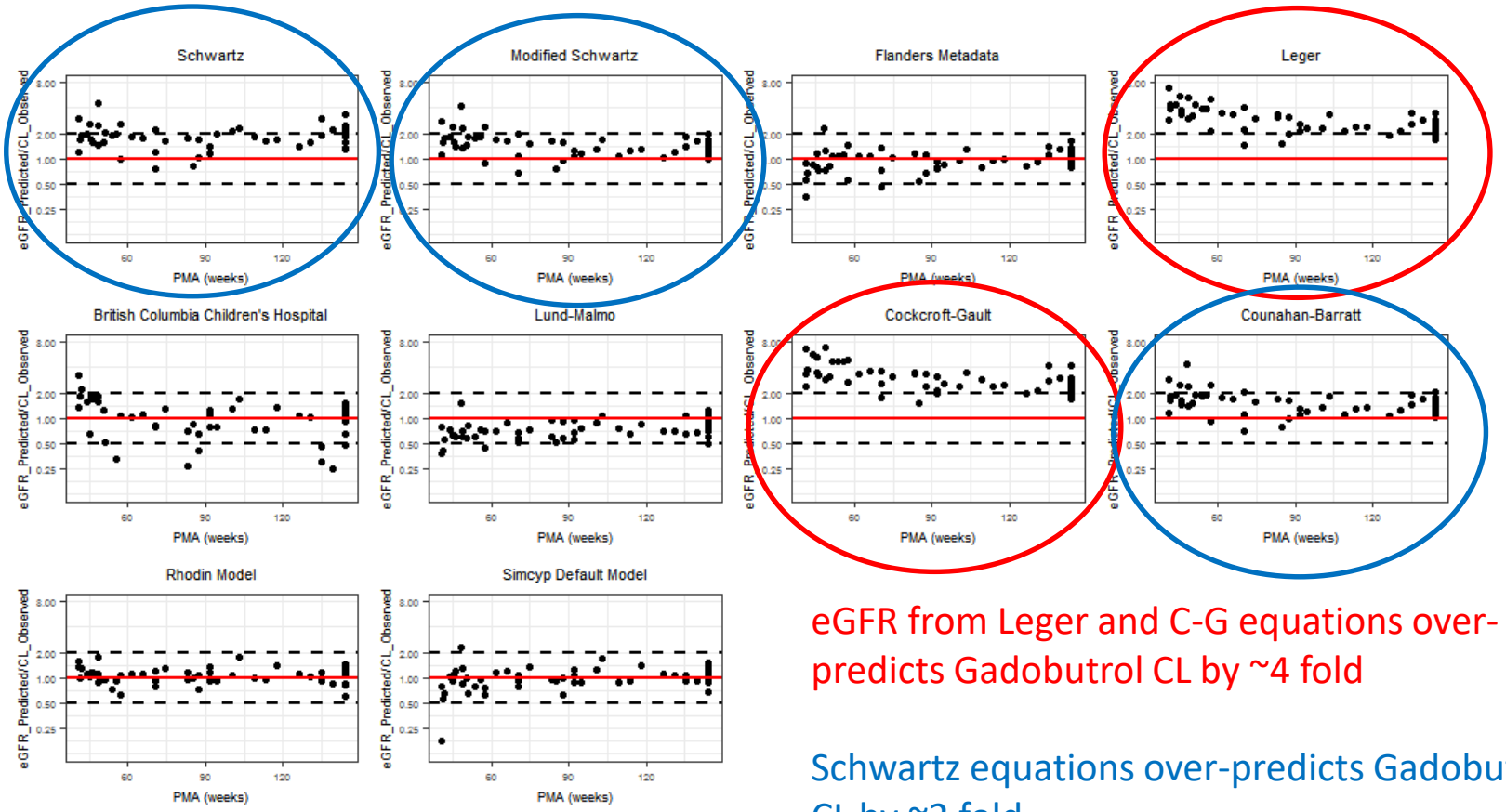
eGFR from equation of British Columbia Children's Hospital shows low correlation with Gadobutrol CL

How Well Does eGFR Predict Gadobutrol CL?



High Correlation ≠ Accurate Prediction
Overprediction of Gadobutrol CL by Schwartz Equation

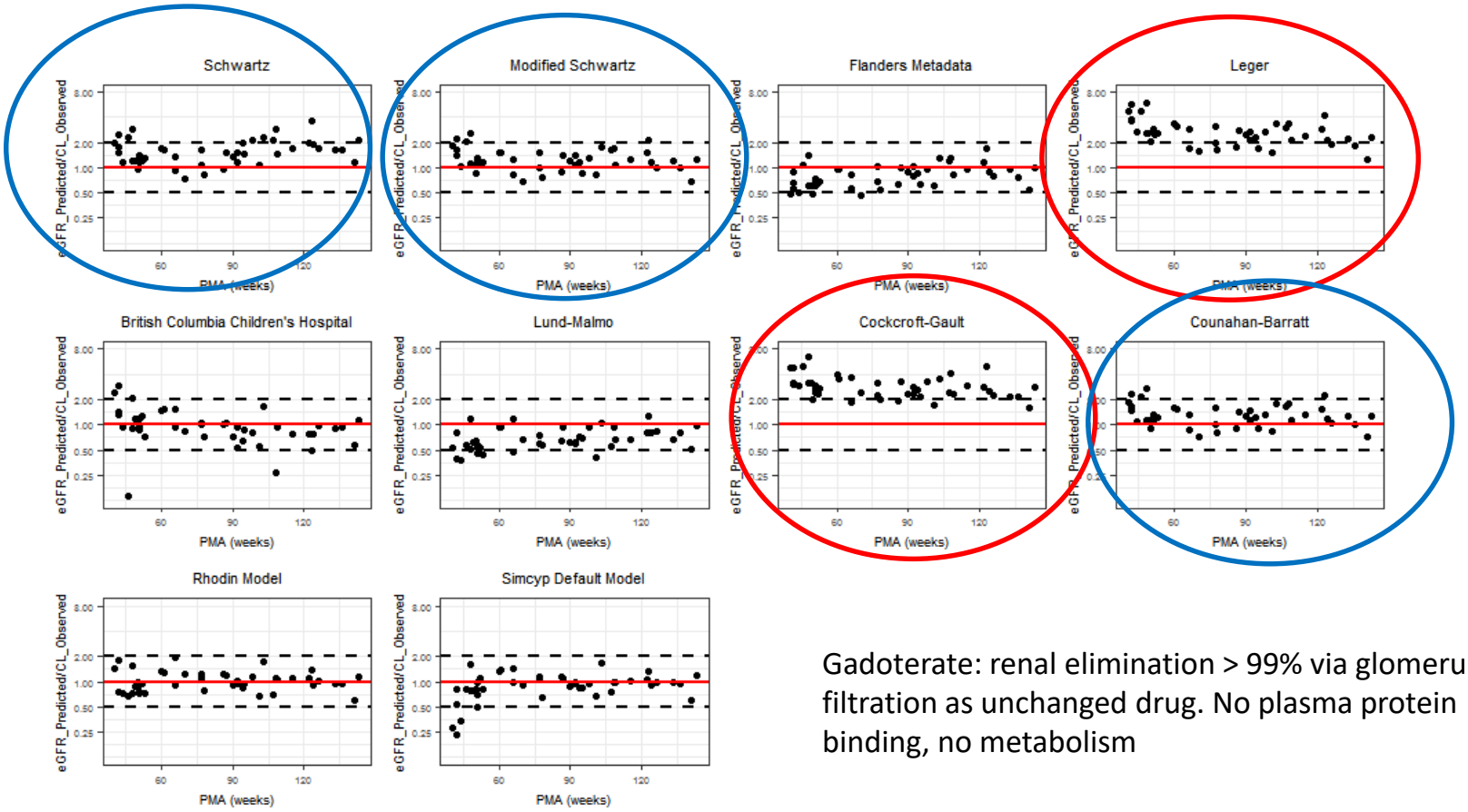
How Well Does eGFR Predict Gadobutrol CL?



eGFR from Leger and C-G equations over-predicts Gadobutrol CL by ~4 fold

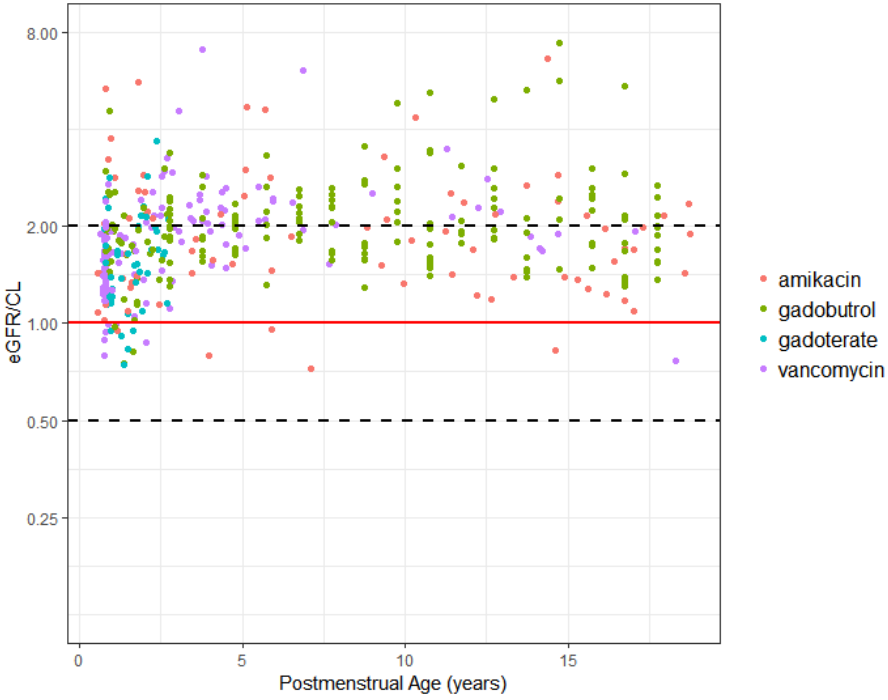
Schwartz equations over-predicts Gadobutrol CL by ~2 fold

Similar Observations in Gadoterate (0-2yr)



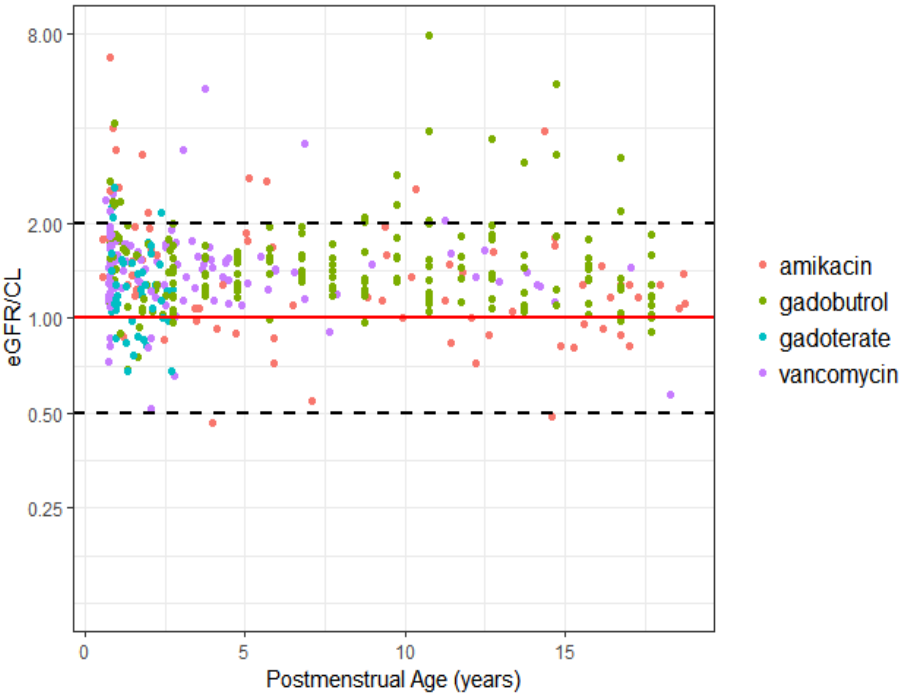
Gadoterate: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism

Over-Estimating Drug Clearance Using Schwartz Equations



Schwartz equation adopted by **FDA 2014 Clin Pharm Guidance**: k=0.33 for LBW<1yr, 0.45 for Term <1 yr, 0.55 for >= 1 yr female, 0.70 for >= 1 yr male

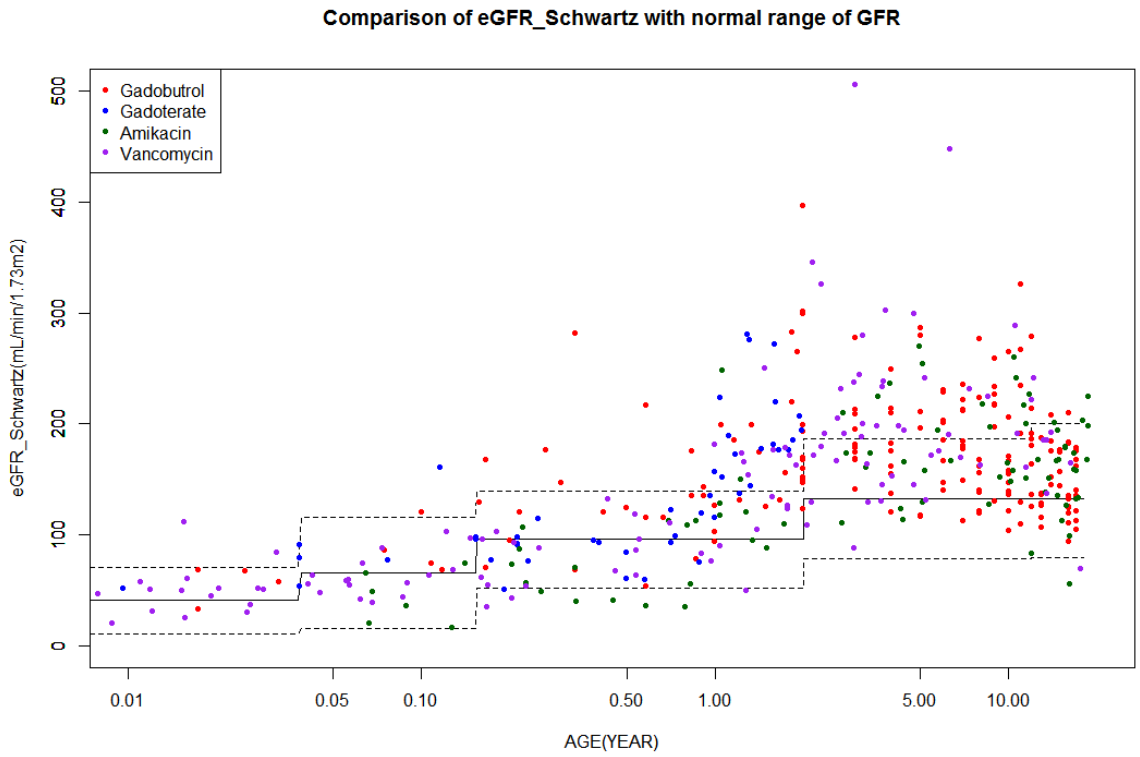
https://www.fda.gov/media/90358/download



Bedside Schwartz equation: k=0.413

J Am Soc Nephrol. 2009 Mar;20(3):629-37

eGFR Calculated from Schwartz Equation Exceeds Upper Limit of Normal Range



Normal GFR in Children and Adolescents

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m²)
1 wk (males and females)	41 ± 15
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Solid line: mean value of normal GFR
Dashed line: mean ± 2SD of normal GFR

Dots: eGFR calculated by Schwartz equation
eGFR(mL/min*1.73) = k*HT/SCR

Each color represents different data source of each drug

eGFR was calculated by Schwartz equations with k=0.33, 0.45, 0.55 and 0.70 (FDA Guidance)

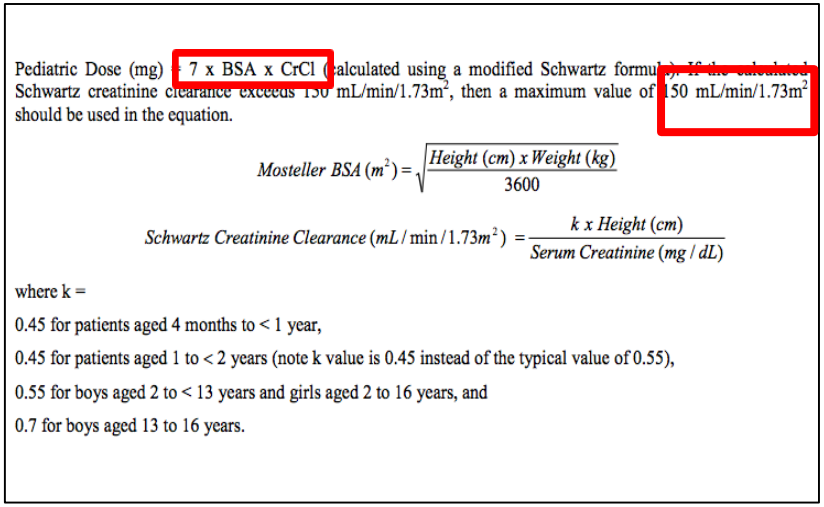
Use of Schwartz Equation or SCR in Pediatric Product Labeling: Examples

Therapeutic Area	Drug Name	Product Labeling	Age	Renal equations
Anti-infection	Avycaz (ceftazidime and avibactam)	Dosage adjustment required if eGFR < = 50 mL/min/1.73 m^2	> = 2 y	k=0.413
	Cefdinir	Lower dose is given to pediatric patients with CrCL <30 mL/min/1.73m^2	6 m – 12 y	k=0.55 for pediatric patients >1 y/o, k=0.45 for <=1y/o
	Ceftaroline fosamil	CrCL < 50 mL/min/1.73 m^2: Insufficient information to recommend dose for peds.	> 2 m	N/A
Partial-onset seizures	Lacosamide	For patients with CrCL < 30 mL/min/1.73 m^2 or ESRD, a reduction of 25% of the maximum dosage is recommended.	4 - <17 y	N/A
Chronic iron overload	Deferasirox	Do not use if baseline eGFR < 40 mL/min/1.73m^2. Exercise caution if baseline eGFR is 40-60 mL/min/1.73m^2. Reduce the dose by 10 mg/ kg/day if eGFR decreases by > 33%. Discontinue therapy for eGFR < 40 mL/min/1.73m^2	> = 2 y	N/A
Heart failure	Digoxin	Pediatric Patients Over 10 Years Old: Total Maintenance Dose = Loading Dose (i.e., Peak Body Stores) x % Daily Loss/100 (% Daily Loss = 14 + Creatinine clearance/5) Pediatric patients 5-10 y/o: average daily maintenance dose requirements is based on estimated CrCL.	> 5 y	k=0.33 for preterm babies, 0.45 for term infants, 0.55 for pediatric patients and adolescent girls, 0.7 for adolescent boys)
Anti-virus	Valganciclovir	Pediatric Dose (mg) = 7 x BSA x CrCL. Use the value of 150 if CrCL > 150 mL/min/1.73 m^2	1 m – 16 y	K=0.33 for LBW Infants <1 y/o, k=0.45 for non-LBW Infants <1 y/o, and 1 - <2 y/o children, k=0.55 for boys 2 - < 13 y/o and girls 2 - < 16 y/o, k=0.7 for boys 13-16 y/o.
Angiocardiography Computed Tomography	Iopamidol, Iohexol, Ioversol iopromide, iodixanol	Pediatric pts with serum creatinine > 1.5 mg/dL may have higher risk of adverse events	Varies from after birth to > 2 y	N/A

Implications of Schwartz Equation for Dose Selection in Pediatric Patients: Case Example

Valcyte (valgancyclovir): A prodrug of ganciclovir, rapidly metabolized to ganciclovir, which is >90% renal eliminated through glomerular filtration and active tubular secretion

Pediatric dosage recommendation includes adjustment for renal impairment



Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using a modified Schwartz formula). If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation.

$$Mosteller\ BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (mL/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dL)}$$

where k =

0.45 for patients aged 4 months to < 1 year,

0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

- Initial dosing recommendation did not include a maximum value for CrCl in children

FDA Safety Announcement on 09-15-2010[1]:

- Be aware of possible valganciclovir overdose in pediatric patients with low body weight, low body surface area, or below normal serum creatinine.
- When calculating the pediatric dose of Valcyte with the modified Schwartz formula, a maximum value of 150 mL/min/1.73 m^2 should be used in the formula.
- When the calculated pediatric dose of Valcyte exceeds 900 mg, a dose of 900 mg should be administered to the child.

[1]http://www.fda.gov/Drugs/DrugSafety/ucm225727.htm

SCR-based Models in Drug Development

- BSA-adjusted eGFR correlates but is often higher than observed clearance of renally-eliminated drugs.

- eGFR calculated from Schwartz equation significantly exceeds upper limit of normal ranges, possible reasons include:
  - Assay variations
  - Biological variations

- Dose selection in pediatric patients with renal impairment
  - Requires actual pediatric patient data (possible overdosing using SCR-based prediction)
  - Serum creatinine data should be incorporated into population modeling
  - For drugs with altered dosage guidelines for adults with renal impairment, pediatric guidelines should be developed also

Renal Impairment in Pediatrics

Challenges

- Lack of markers for assessing renal impairment
- Lack of large PK, biomarker and clinical outcome data
- Lack of consensus, rationale on dosing strategies
- Lack of specific drug labels

Opportunities

- Identify new renal biomarkers for pediatric renal impairment
- Collect and share PK and clinical data to create large clinical database
- Optimize and standardize dosing strategies
- Enhance drug labels for neonates and infants.

Collaboration between clinicians and scientists in academia, industry and regulatory agencies is the key.

Adapted from Rodieux, Clinical pharmacokinetics, 2015

Summary

- Age based renal maturation models are used in population PK modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants in clinical trials.
- SCR-based eGFR correlates but is often higher than observed clearance of renally-eliminated drugs.
- Different renal function models were built from different data sources, and significant differences exist between these models.
- More high-quality data are needed to support an optimal model, especially for pre-term infants and patients with renal impairment.
- However, we should start to apply what we know to current pediatric drug development.

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ADMINISTRATION

PBPK of Renally Cleared Drugs

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 475–483; doi:10.1002/psp4.12101

ORIGINAL ARTICLE

Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children

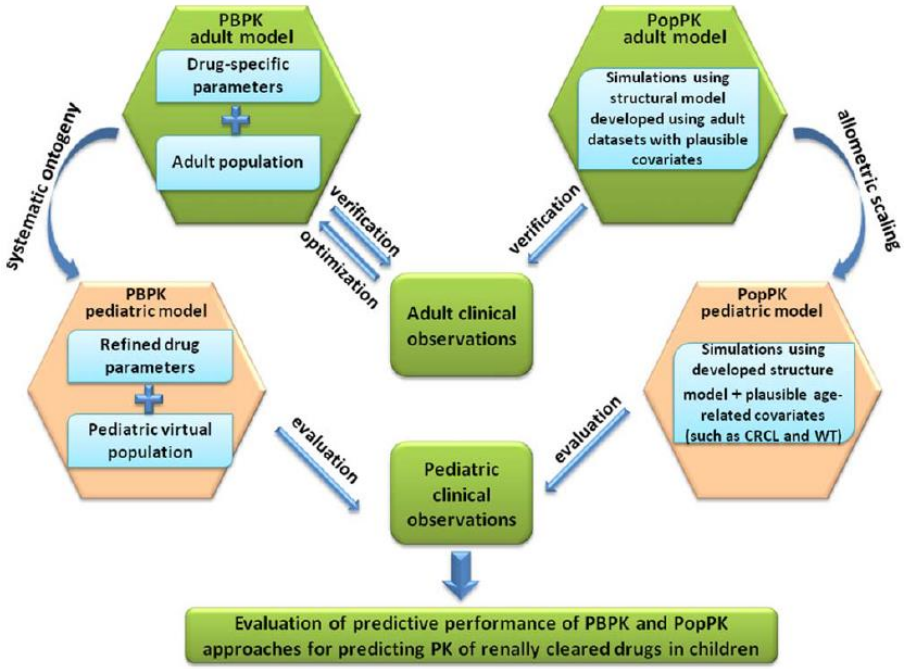
W Zhou[1], TN Johnson[2], H Xu[1], SYA Cheung[3], KH Bui[1], J Li[1], N Al-Huniti[1] and D

Clin Pharmacokinet (2017) 56:383–394
DOI 10.1007/s40262-016-0445-9

ORIGINAL RESEARCH ARTICLE

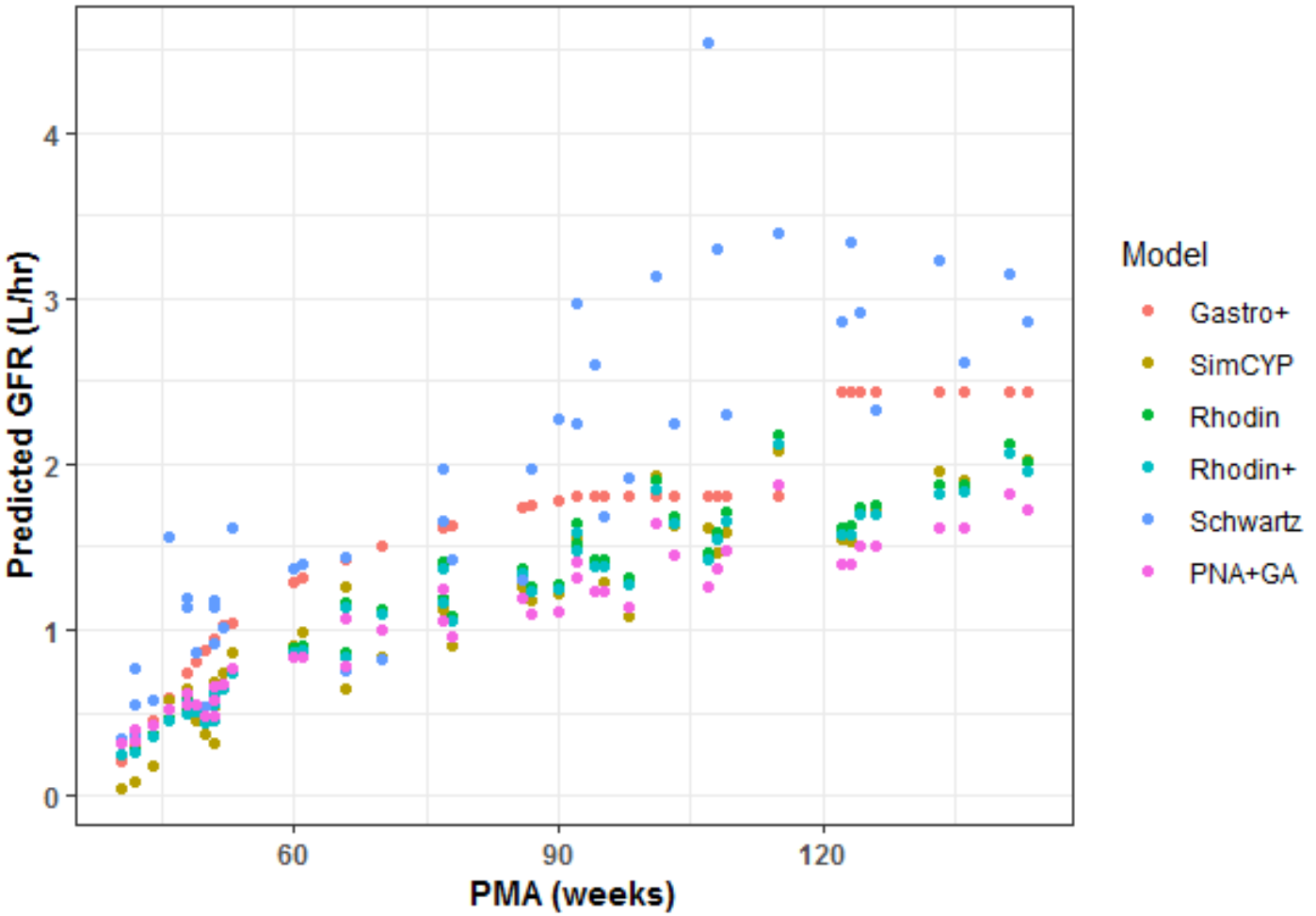
Physiologically Based Pharmacokinetic P and Emtricitabine in Neonates and Infan

Peng Duan[1] · Jeffrey W. Fisher[2] · Kenta Yoshida[3] · Lei Zhang[3] · Gilbert J. Burckart[3] · Jian Wang[3]



Ontogeny of renal function captured in the Simcyp pediatric module was used in both studies

A Direct Comparison of All Models



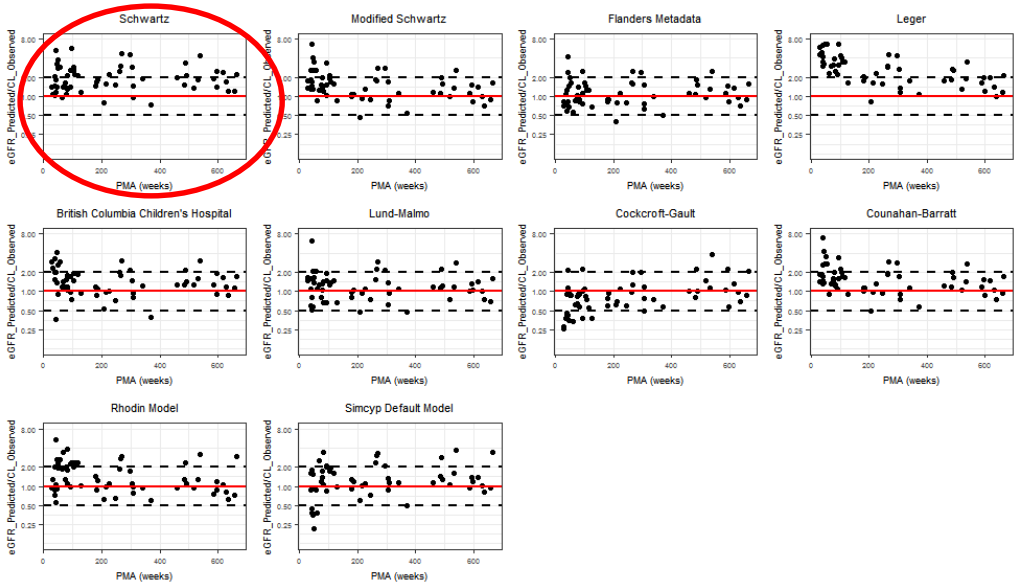
Estimation of GFR

- Renal clearance
  - Equivalent volume of plasma from which a substance would have to be totally removed to account for its excretion in urine (per unit of time)

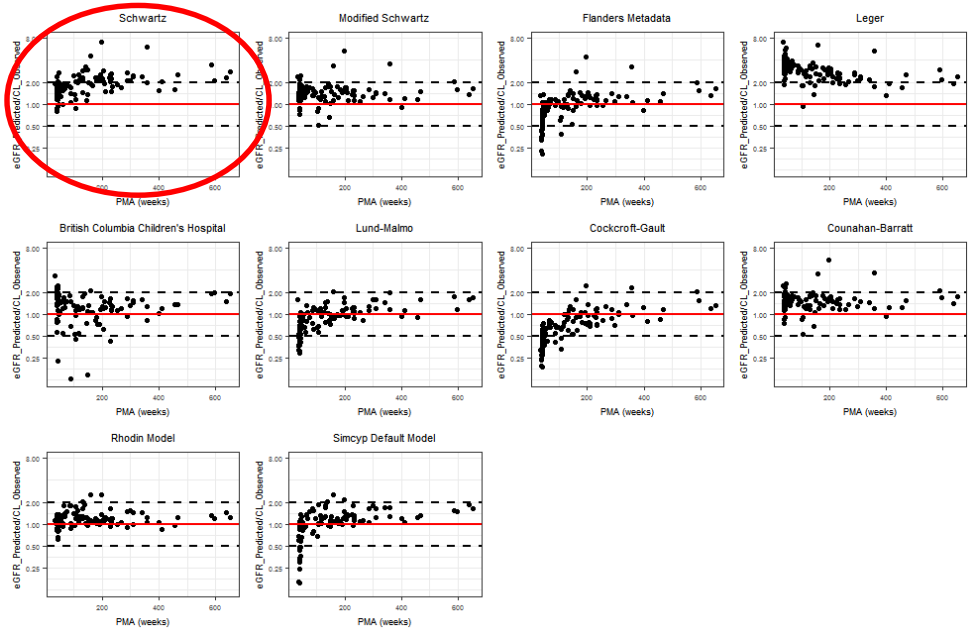
- Clearance of a substance can be used to estimate GFR if:
  - Substance is filtered to the same extent as water
  - Not reabsorbed or secreted by the tubule
  - Not metabolized or synthesized by the kidney

Comparison of Drug CL with eGFR

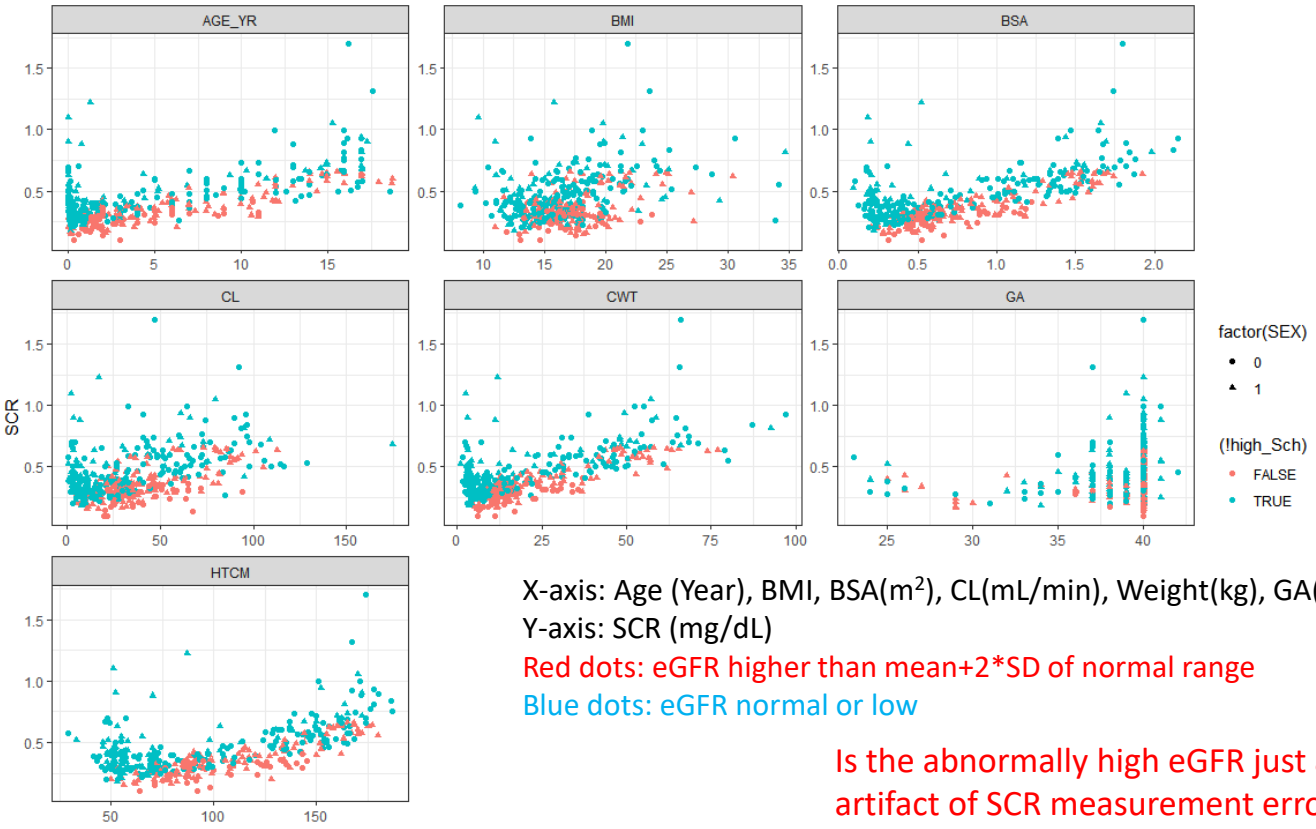
Amikacin



Vancomycin



The subjects who have abnormally high eGFR corresponds to low SCR measurement



X-axis: Age (Year), BMI, BSA(m^2), CL(mL/min), Weight(kg), GA(weeks), Height(cm)
Y-axis: SCR (mg/dL)
Red dots: eGFR higher than mean+2*SD of normal range
Blue dots: eGFR normal or low

Is the abnormally high eGFR just an artifact of SCR measurement error?

eGFR was calculated by Schwartz equations with k=0.33, 0.45, 0.55 and 0.70 (FDA Guidance)

Case study: Meropenem PK Highlights

- Administered as IV infusion in adults and children >3 months
- Protein binding is ~2%
- **~ 70%** excreted unchanged by the kidneys
- Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less
- $T_{1/2}$ ~1 hour

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050706s035lbl.pdf

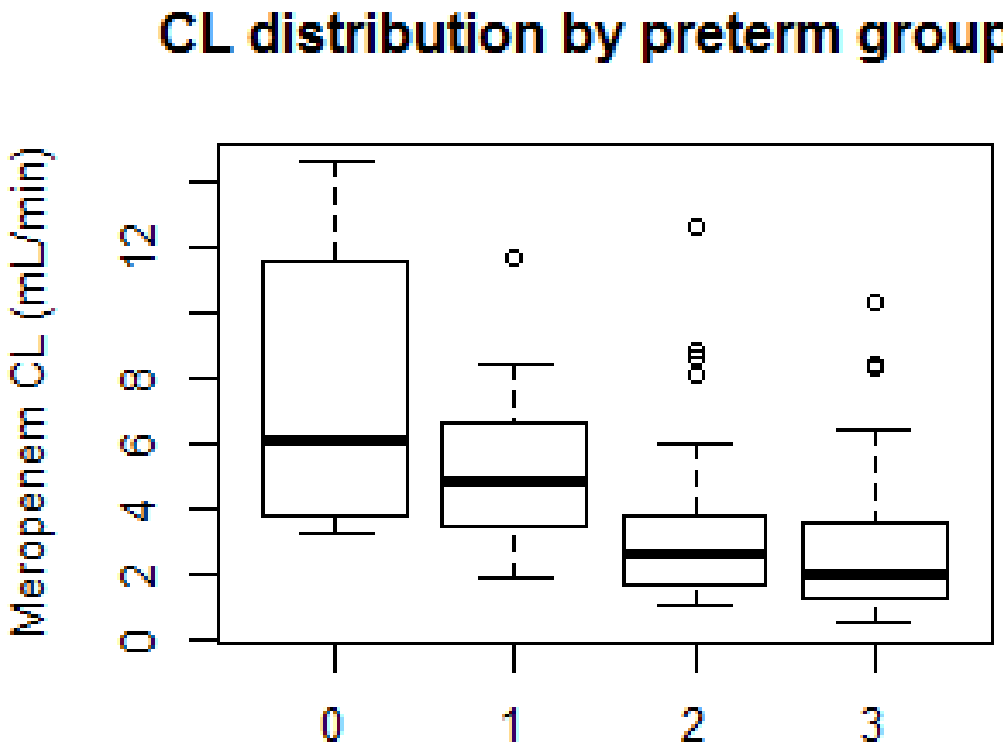
Meropenem Dosing Regimen

1. Cohort 1: 20 mg/kg every12 hours in infants <32 weeks GA and PNA <2 weeks
2. Cohort 2: 20 mg/kg every 8 hours in infants <32 weeks GA and PNA ≥2 weeks
3. Cohort 3: 20 mg/kg every 8 hours in infants ≥32 weeks GA and PNA <2 weeks
4. Cohort 4: 30 mg/kg every 8 hours in infants ≥32 weeks GA and PNA ≥2 weeks

- ✓ The rationale for dose selection was based on simulation studies performed from prior small meropenem PK studies in older infants.
- ✓ The simulation studies explored the likelihood of achieving a predefined therapeutic target by gestational and postnatal age.

Smith PB, Pediatric Infectious Disease Journal, 2011

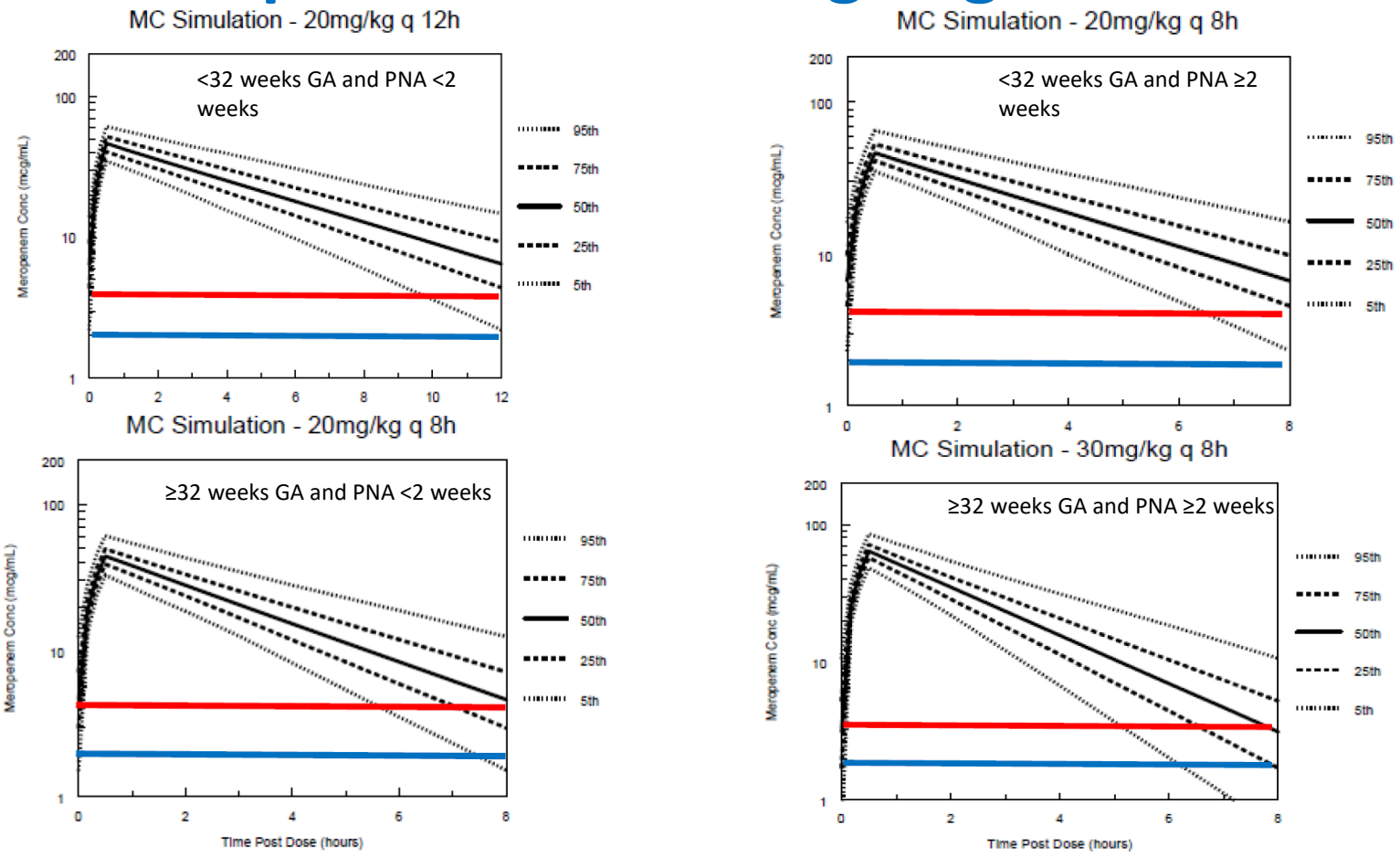
Meropenem CL Increases with Gestational Age



0 – GA >37 wks
1 – GA 32-37 wks
2 - GA 28-32 wks
3 – GA <28 wks

Maturational changes in meropenem CL were included through covariates of **PMA** and **Serum Creatinine** in the final PopPK model.

Monte-Carlo Simulations were Used to Optimize the Dosing Regimen



Simulations demonstrated that the systemic concentrations remained:

- > 4 mcg/mL for 50% of the dose interval in 96% of patients;
- > 2 mcg/mL for 75% of the dose interval in 92% of patients.

https://www.federalregister.gov/documents/2015/05/28/2015-12848/pediatric-studies-of-meropenem-conducted-in-accordance-with-the-public-health-service-act ; *Smith PB, Pediatric Infectious Disease Journal, 2011*