FDA/MCERSI Workshop
Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?
May 16, 2019, Natcher Conference Center, Bethesda, MD

U.S. FOOD & DRUG ADMINISTRATION

Ontogeny of Renal Function: Applications in Population-Based Modeling for Drug Development

Jian Wang, PhD, FCP
Associate Director for Regulatory Science
Office of Drug Evaluation IV
Office of New Drugs
Center for Drug Evaluation and Research

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

Renal Function and Glomerular Filtration Rate

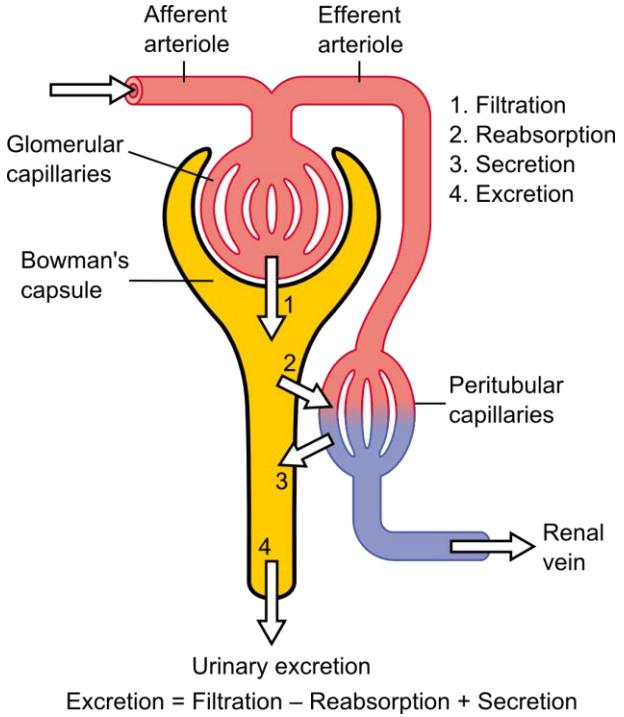
- Normal Level of GFR Varies by Age

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

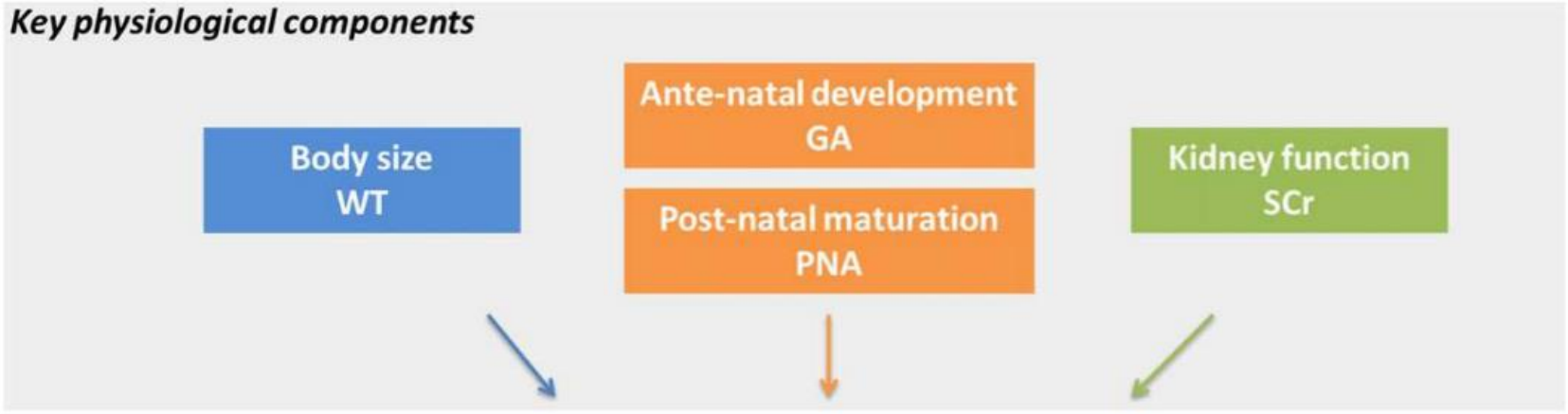
Stage	GFR (mL/min/1.73 m²)	Description
1	≥90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–29	Severe reduction of GFR
5	<15 (or dialysis)	Kidney failure



Hogg et Al. *Pediatrics* 2003

Current Population PK Modeling Approach

- A review based on 101 articles reporting PopPK models from 23 renally eliminated drugs
- Intention: to separate the effects of body size, age and renal diseases on drug clearance

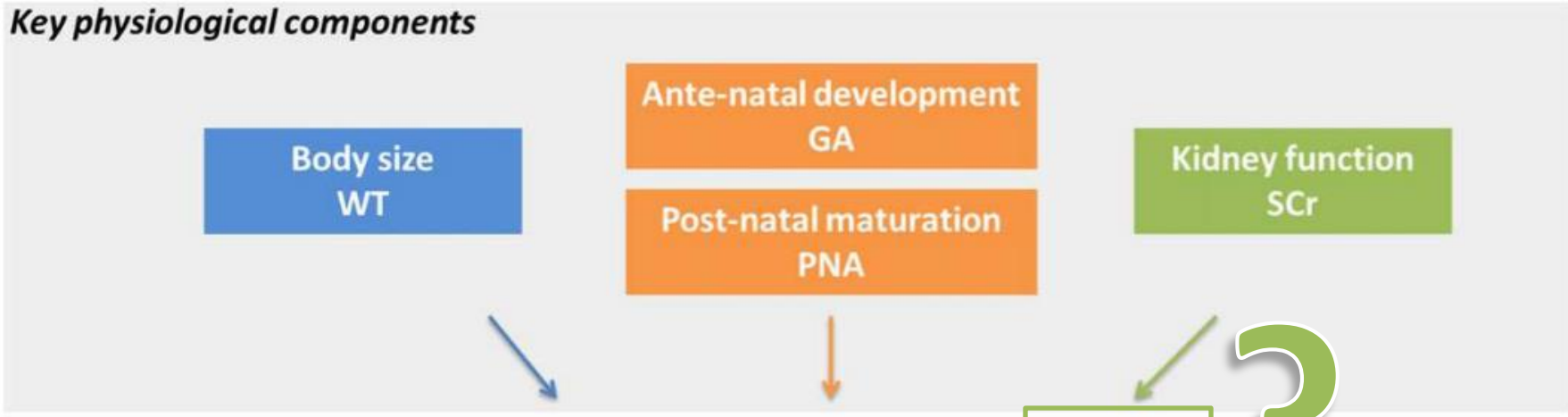


Note: F_{kidney} accounts for deviation from normal kidney function, eg, due to inflammatory disease or drug-related nephrotoxicity.

Outline

- **Ontogeny of 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



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

$$F_{size} = \frac{WT}{WT_{std}}^{0.75}$$

$$F_{maturation} = \frac{PMA^{Hill}}{TM50^{Hill} + PMA^{Hill}}$$

Pre-term (GA < 37 weeks): TM50=35, Hill=4.7
Full-term (GA > 37 weeks): TM50=40, Hill=14.5

$$F_{kidney} = \frac{GFR_{actual}}{GFR_{std}}^{PWR}$$

$$F_{kidney} = \frac{1}{Scr_{actual}}^{PWR}$$

$$F_{kidney} = \frac{Scr_{actual}}{Scr_{std}}^{PWR}$$

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

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

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

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

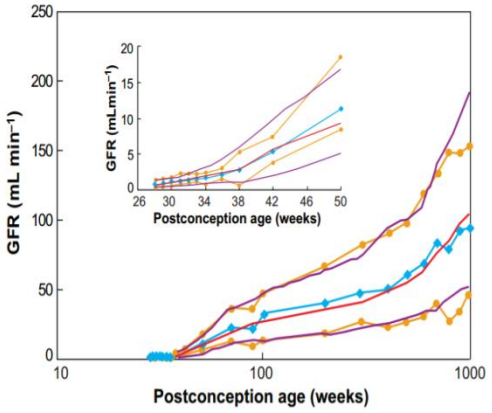
where GFRmat is the mature value for GFR (mL/min).

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



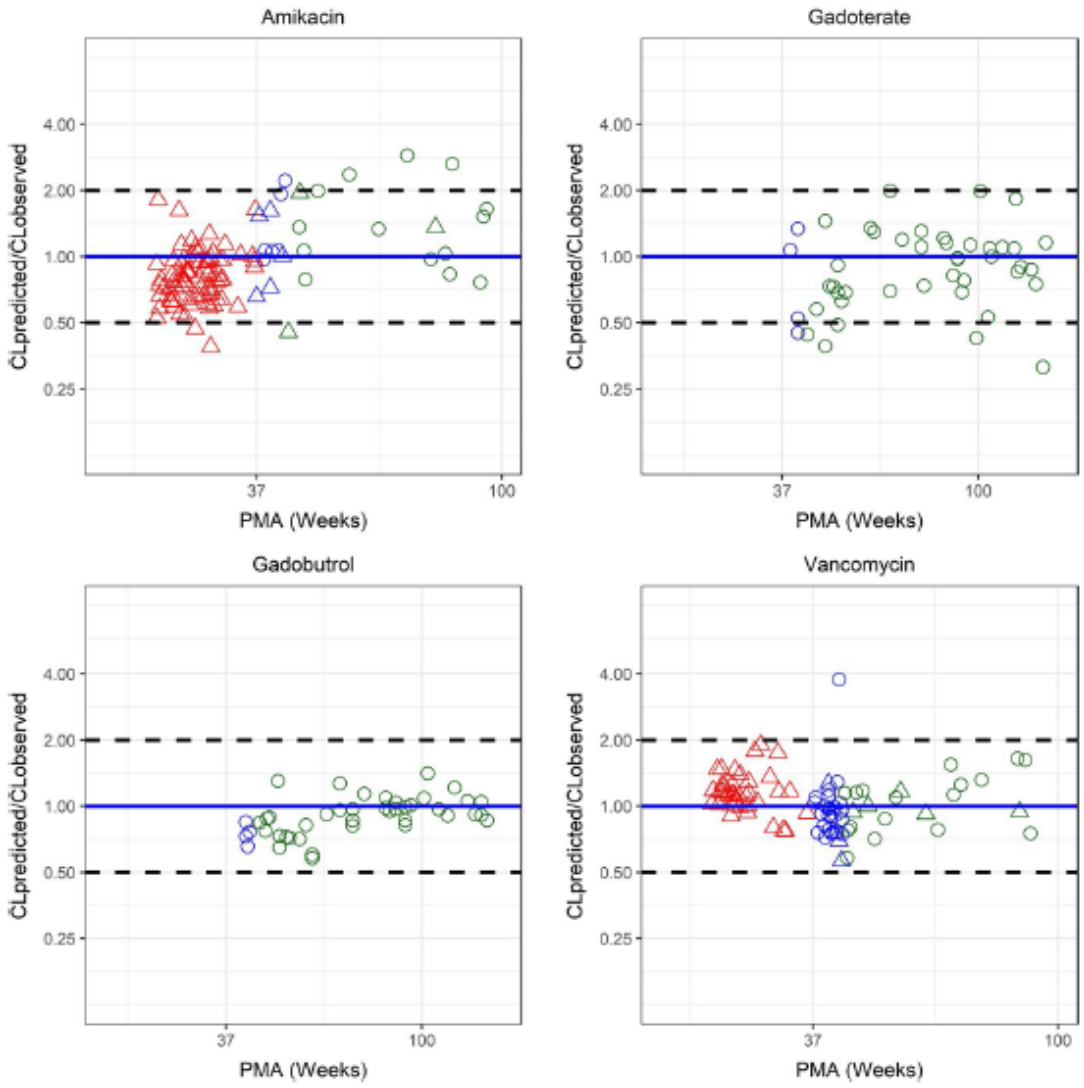
Collected PK Data from Renally Eliminated Drugs

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

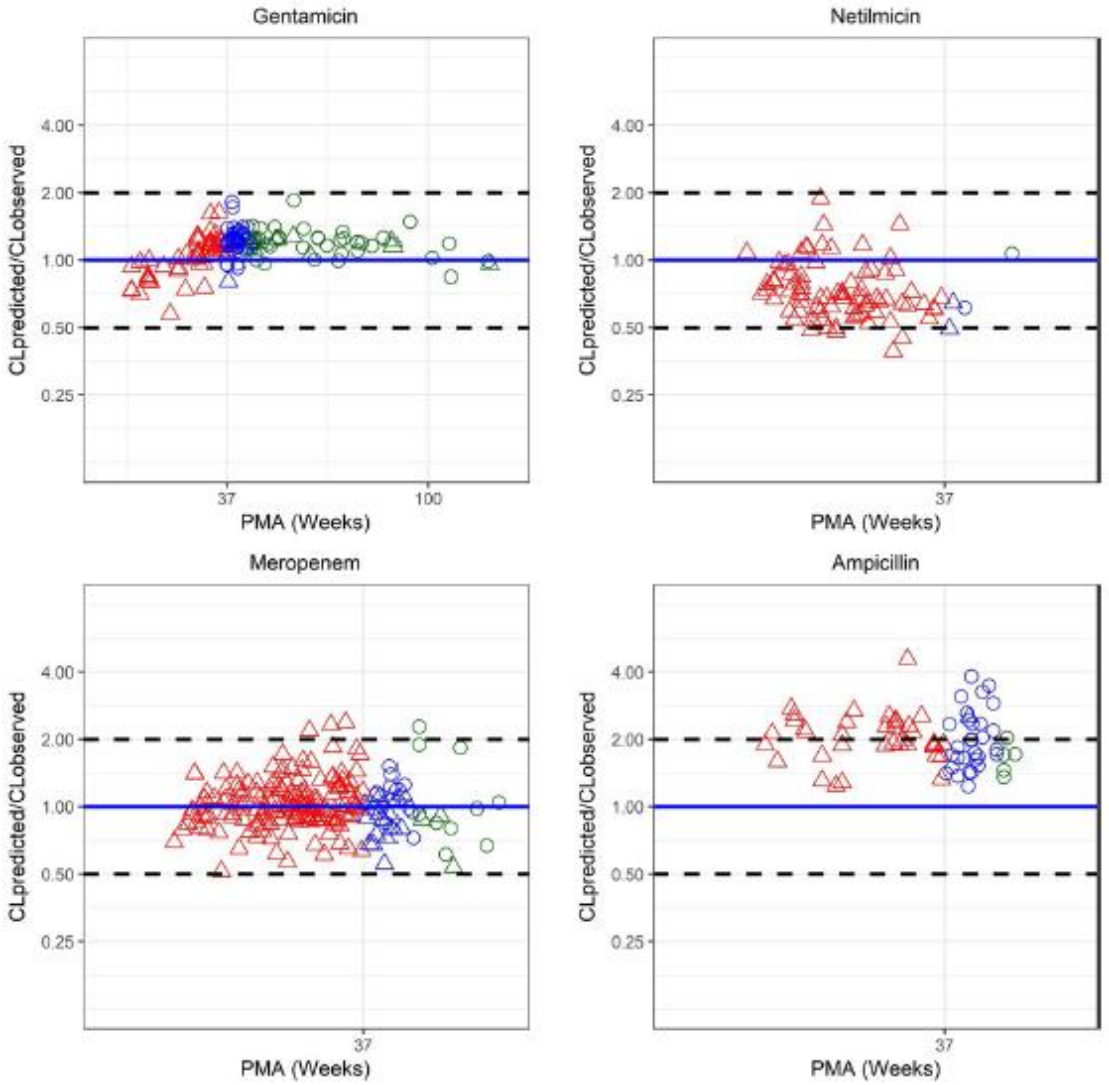
Distribution of Newborns and Infants in Age Categories

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)

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



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



Model Application in Drug Development

- **Case Example:**
  - Gadobenate dimeglumine; gadolinium-based contrast agent with ~95% renal elimination
  - Pharmacokinetic simulations based on the maturation model was 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.

Renal Maturation Model in Drug Development

- Opportunities:
  - PMA based sigmoidal Emax model, in combination with body weight- based scaling and kidney function assessment, can be used in population PK modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants with normal renal function in clinical trials.

- Challenges:
  - The current models do not incorporation renal ontogeny of **reabsorption and secretion**. Better understanding of the ontogeny of drug transporters and metabolisms in kidney are needed.
  - The model does not account in the **renal impairment** (e.g. *kidney disease or drug-related nephrotoxicity).*

Outline

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

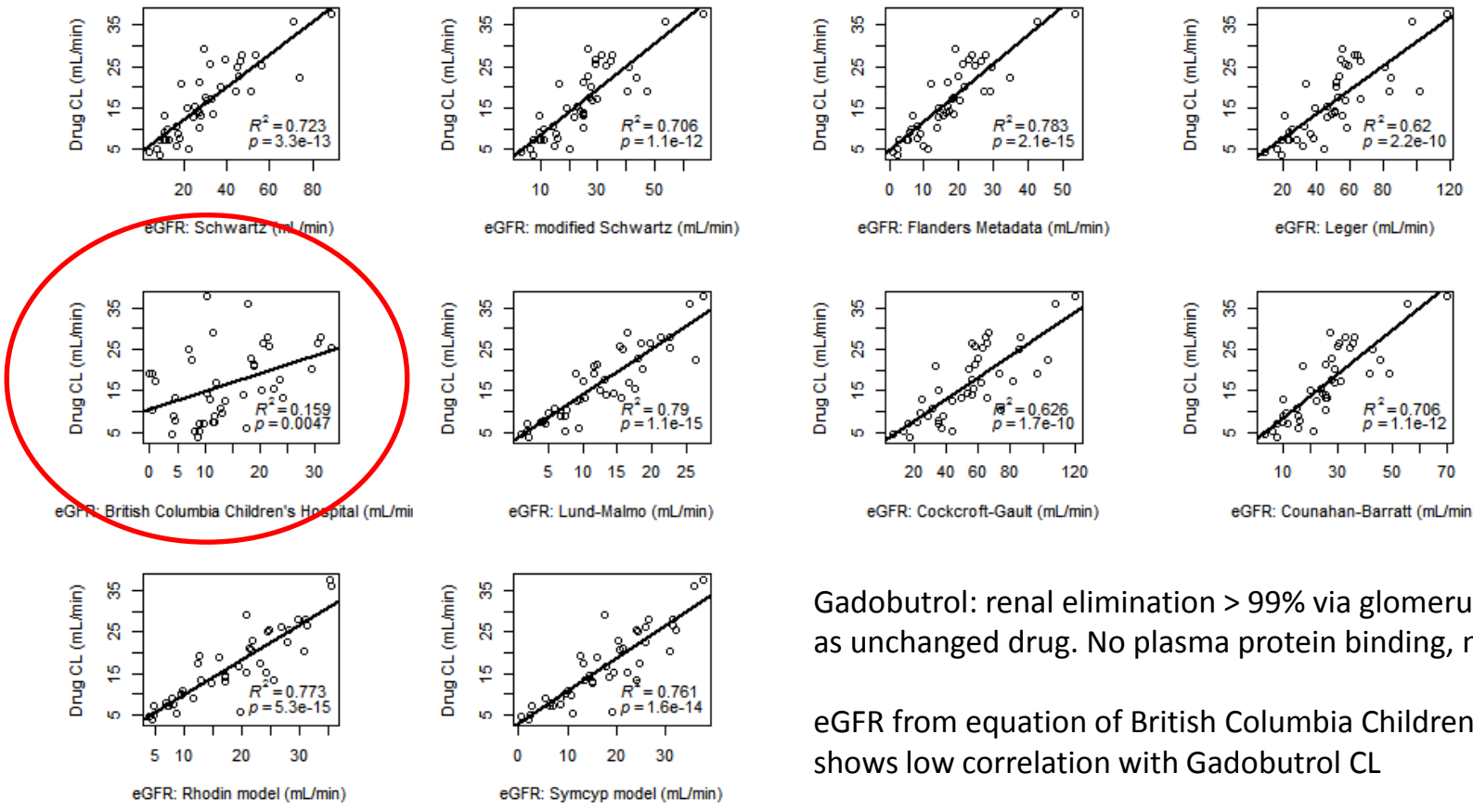
- **Bedside Renal function Models**
  - Overview
  - Evaluation with drug PK data
  - Challenges and opportunities

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

- **Schwartz**
  - 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
  - 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

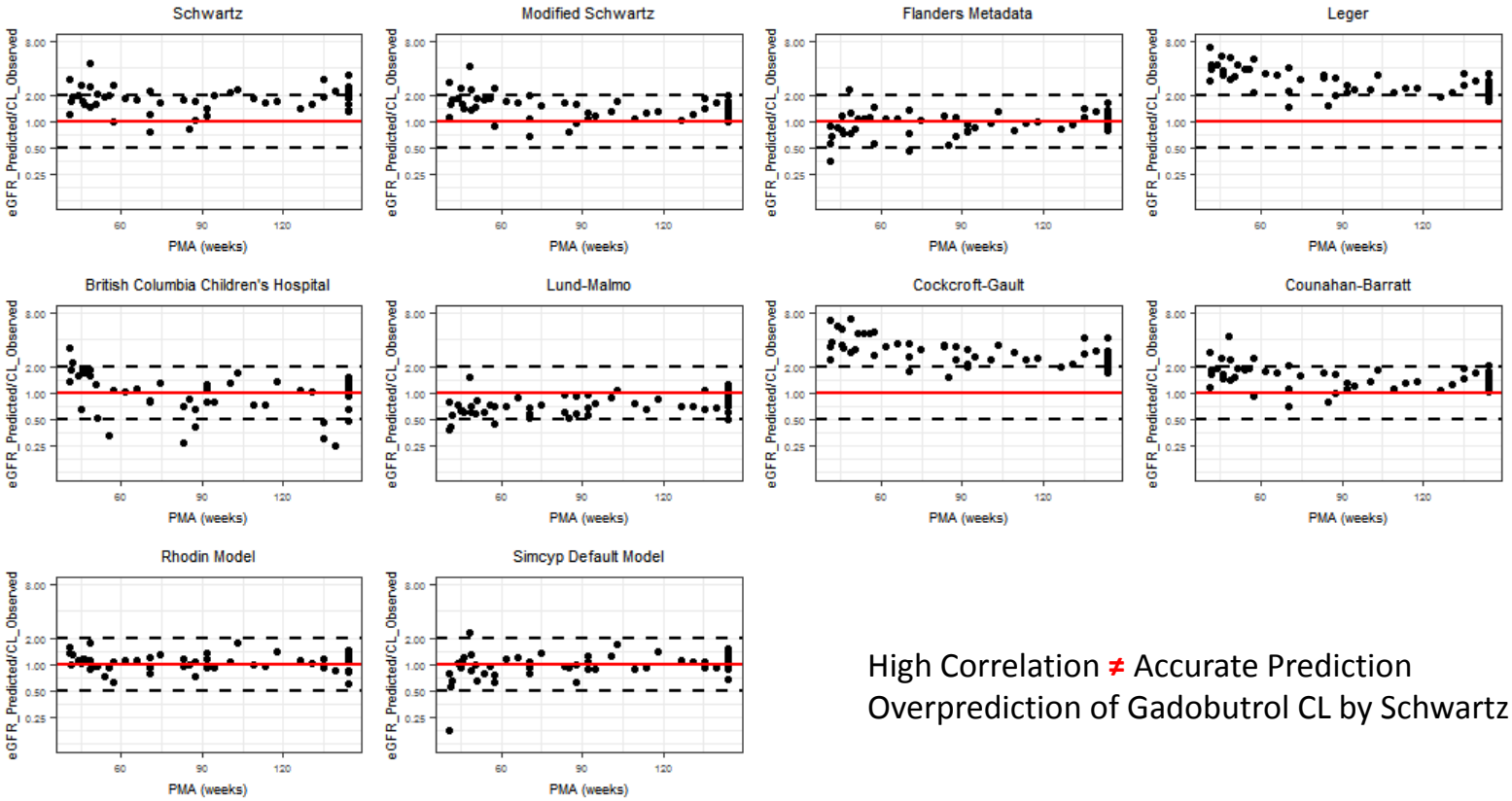
Does eGFR Well-Predict Gadobutrol CL?



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

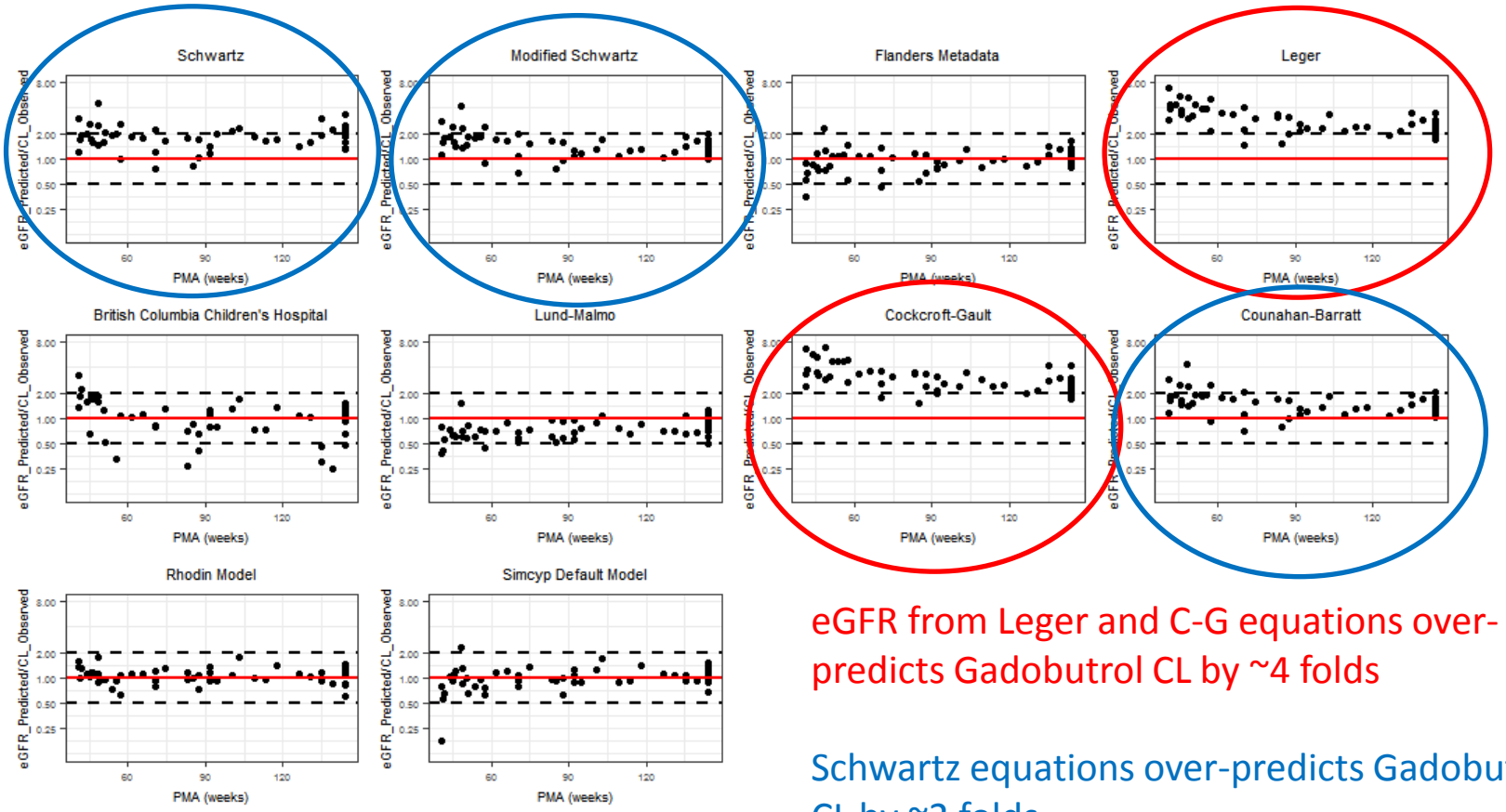
eGFR from equation of British Columbia Children's Hospital shows low correlation with Gadobutrol CL

Does eGFR Well-Predict Gadobutrol CL?



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

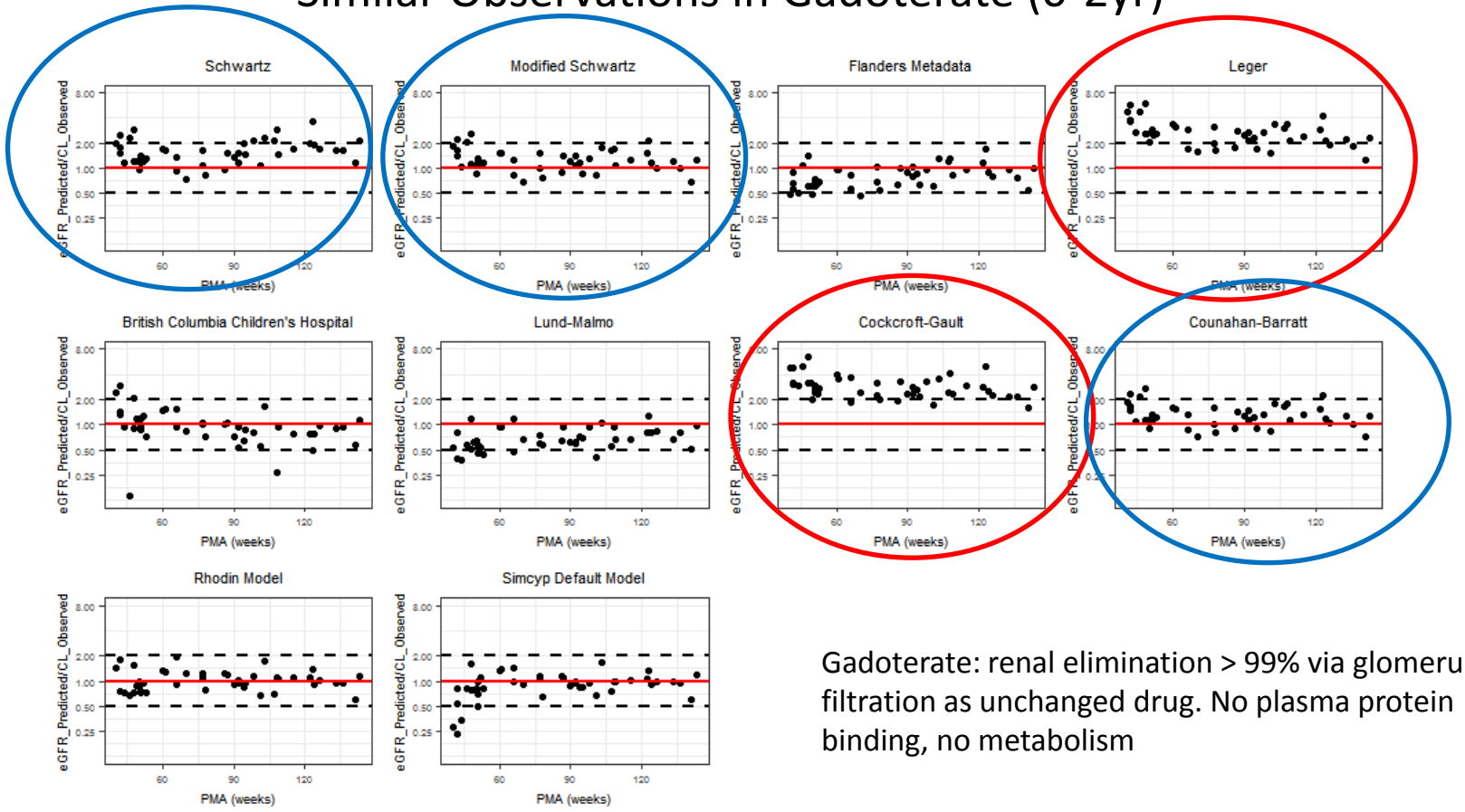
Does eGFR Well-Predict Gadobutrol CL?



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

Schwartz equations over-predicts Gadobutrol CL by ~2 folds

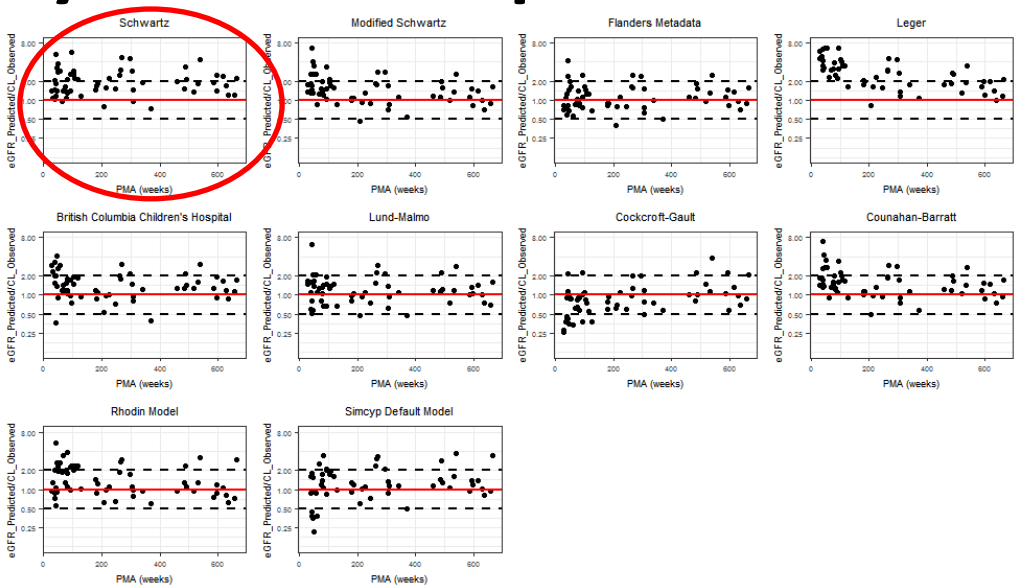
Similar Observations in Gadoterate (0-2yr)



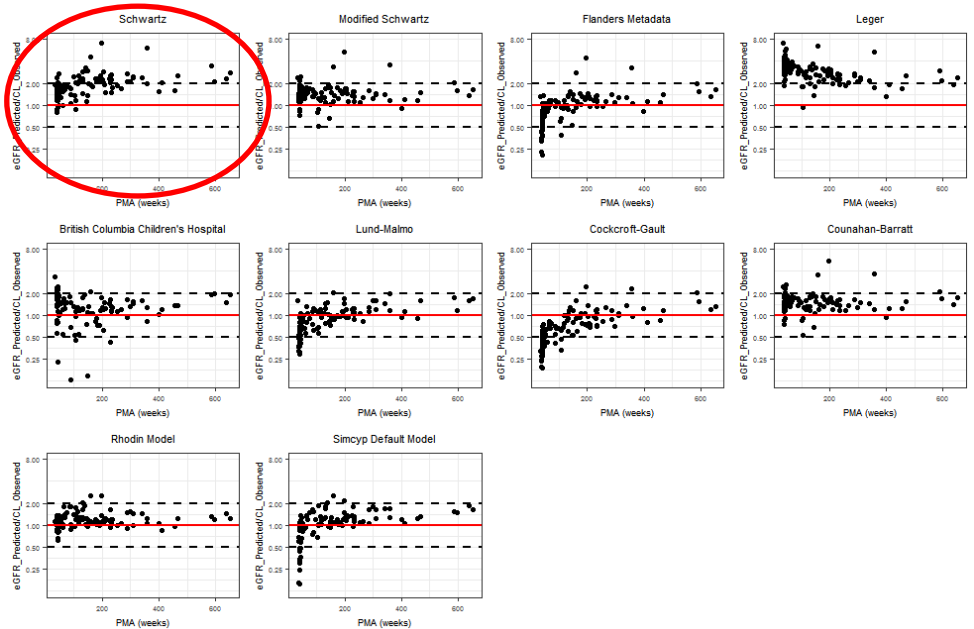
Gadoterate: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism

Comparison of Drug CL with eGFR Calculated by Schwartz Equation

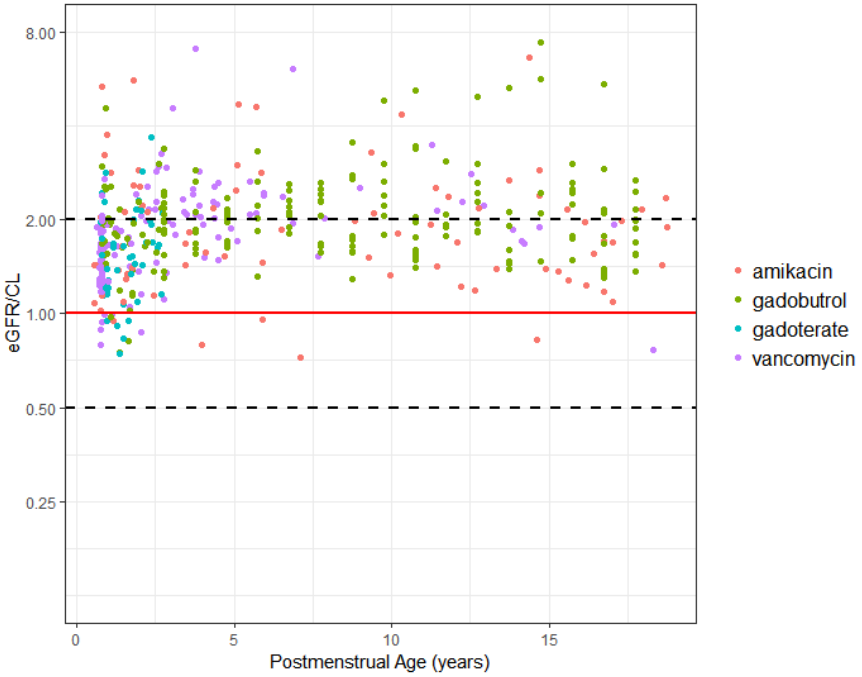
Amikacin



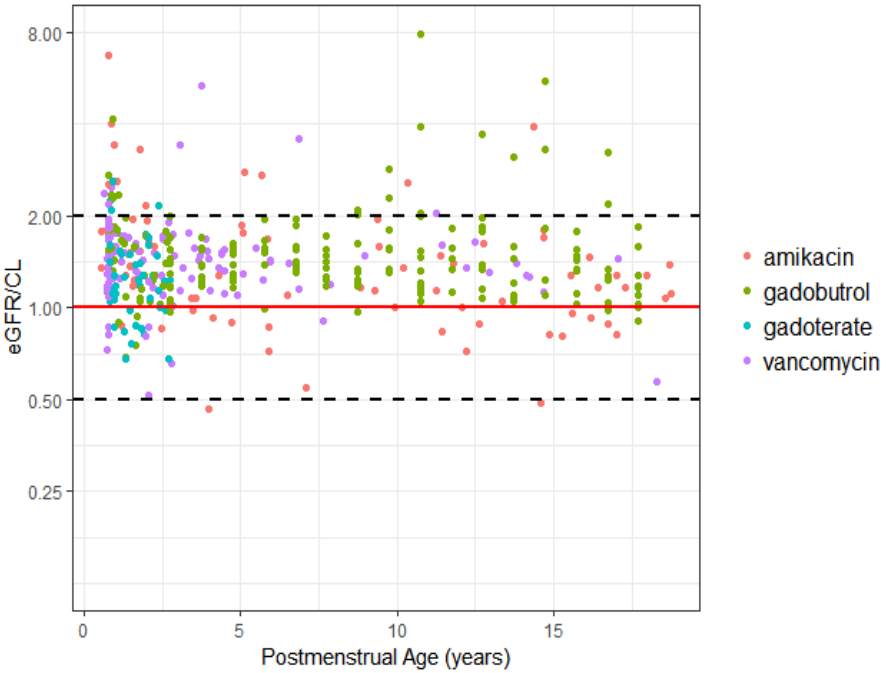
Vancomycin



Over-Estimating Drug Clearance Using Schwartz Equations



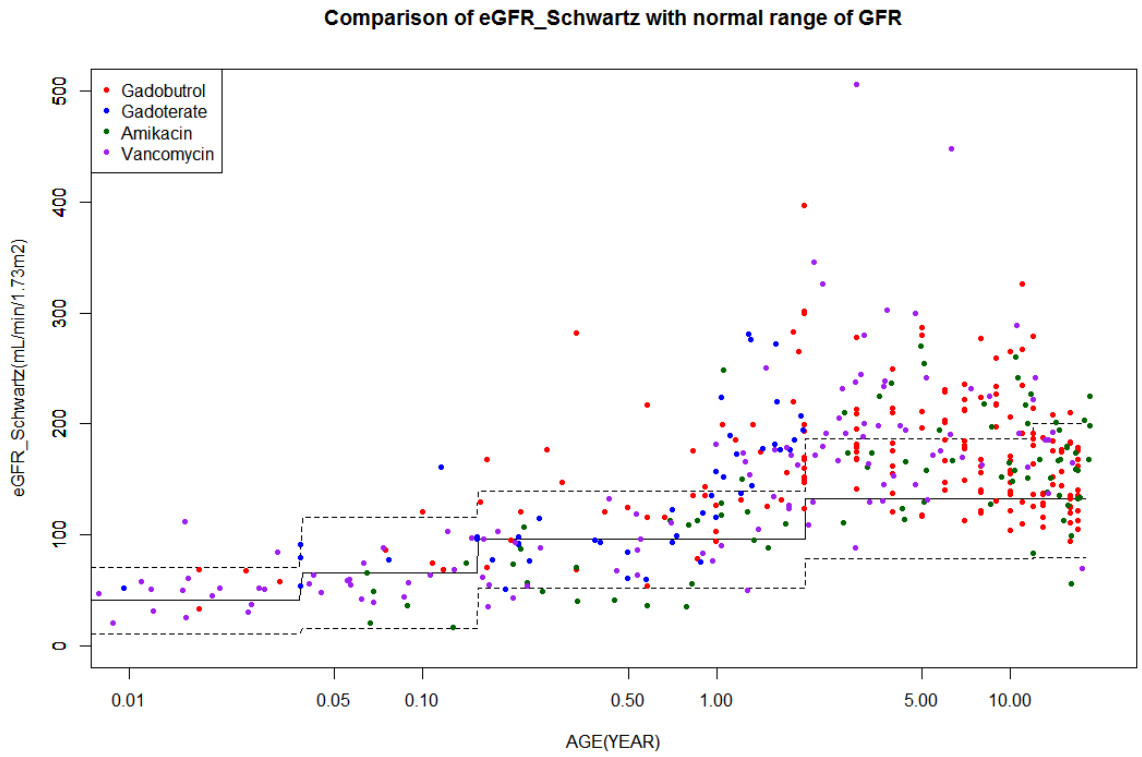
(k=0.33 for LBW<1yr, 0.45 for Term <1 yr, 0.55 for >= 1 yr female, 0.70 for >= 1 yr male)



(k=0.413)

Schwartz equation adopted by FDA 2014 Clin Pharm Guidance

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
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

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)

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.

http://www.fda.gov/Drugs/DrugSafety/ucm225727.htm

Adapted from slides "Dose Adjustments for Renal Impairment in Pediatric Patients" by Fenan Solomon, Dec 2014

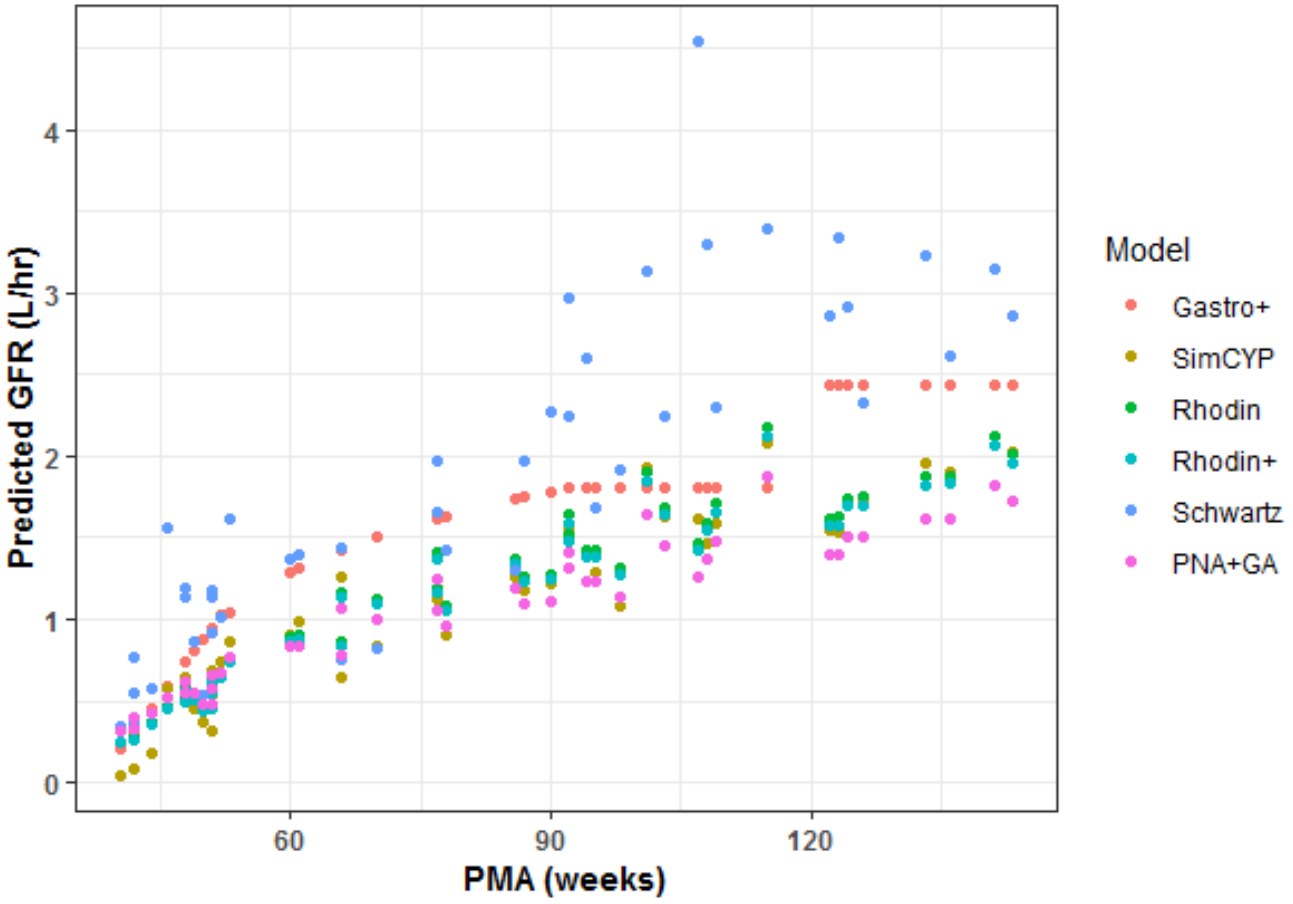
Application of SCR-based Models in Drug Development

- BSA-adjusted eGFR correlates but often higher than observed CL of predominantly renal-eliminated drugs

- eGFR calculated from Schwartz equation significantly exceeds upper limit of normal range, possible reasons include
  - Variations of SCR measurement at low concentration
  - Sub-optimal k values in Schwartz equation which varies by age

- Implications for pediatric dose selection
  - Selecting dose for initial clinical trial in pediatric patients
    - Potential use of eGFR to predict drug CL and dose for predominantly renal-eliminated drugs
  - Approval of dose for labeling
    - Establish an drug-specific equation based on observed data and pop-PK
    - Apply a upper limit on eGFR if using it to calculate dose
    - More data is needed to study dosing in renal-impaired pediatric patients

A Direct Comparison of All Models



Wang Y, ASCPT 2019 Annual meeting

Use of Pediatric Renal Function in Drug Development - Current Status

- For drugs with altered dosage guidelines for adults with renal impairment, pediatric guidelines should be developed also.
  - Requires some actual pediatric patient data, but M&S may be able to extend those dosage guidelines
  - Serum creatinine and some appropriate model should be acceptable for now
  - Additional experience may allow us to make better predictions in premature infants in the future

Summary

- **Different renal function models were built from different data sources**
- **Significant differences exist between these models**
- **More high-quality data are needed to support an optimal model**
- **However, we should start to apply what we know to current pediatric drug development**

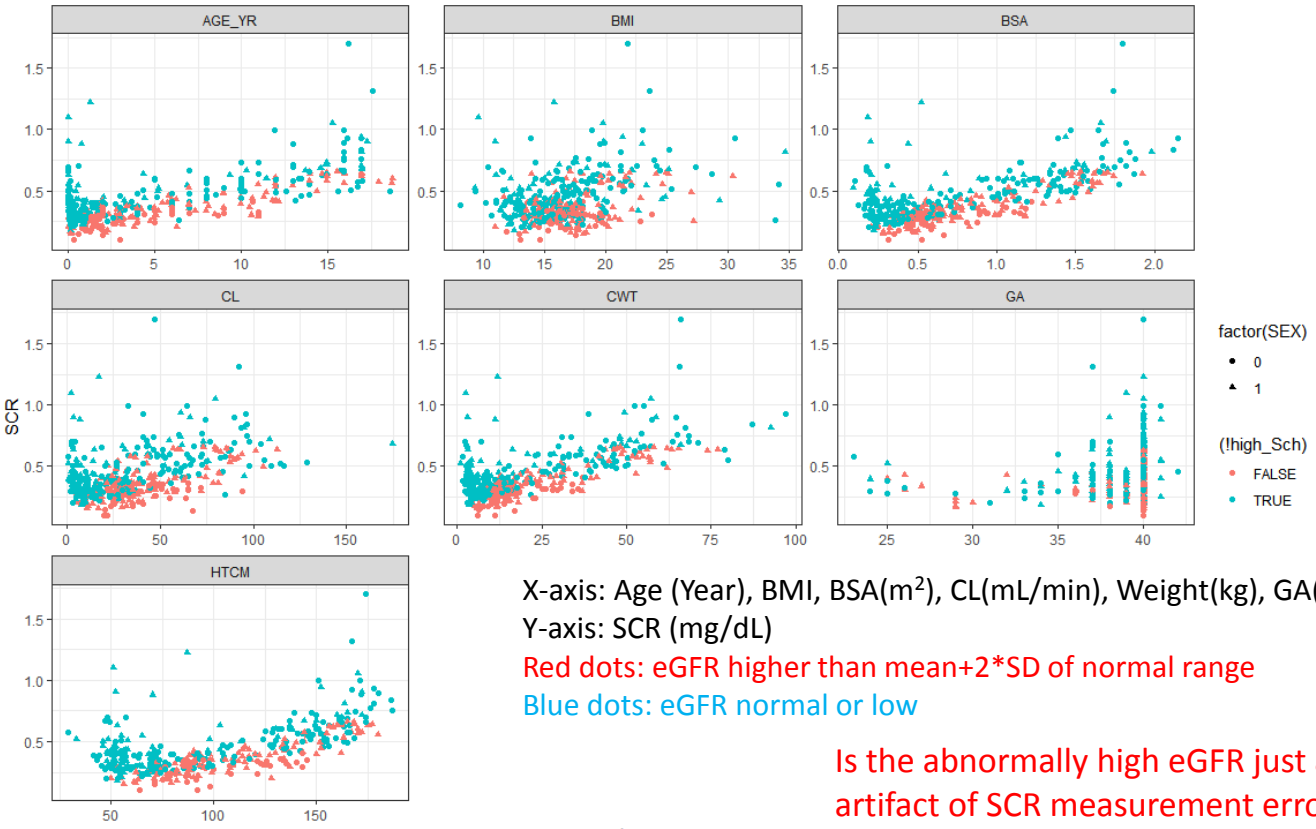
List of References about Equations to Calculate eGFR

- Schwartz 1976 (k=0.55 for 6 month to 20 years old): Pediatrics. 1976 Aug;58(2):259-63. https://www.ncbi.nlm.nih.gov/pubmed/951142
- Schwartz 1984 (k=0.45 for 1 week – 12 month old): J Pediatr. 1984 Jun;104(6):849-54. https://www.ncbi.nlm.nih.gov/pubmed/6726515
- Modified Schwartz (k=0.413): J Am Soc Nephrol. 2009 Mar;20(3):629-37. https://www.ncbi.nlm.nih.gov/pubmed/19158356
- Counahan-Barratt (k=0.43): Arch Dis Child. 1976 Nov;51(11):875-8. https://www.ncbi.nlm.nih.gov/pubmed/1008594
- Flanders Metadata: Pediatr Nephrol. 2010 May;25(5):927-34. https://www.ncbi.nlm.nih.gov/pubmed/20012996
- Leger: Pediatr Nephrol (2002) 17: 903. https://doi.org/10.1007/s00467-002-0964-5
- British Columbia Children's Hospital: J Am Soc Nephrol. 2006 Feb;17(2):487-96 https://www.ncbi.nlm.nih.gov/pubmed/16371435
- Lund-Malmo: Scand J Clin Lab Invest. 2007;67(7):678-95, https://www.ncbi.nlm.nih.gov/pubmed/17852799
- Cockcroft-Gault: Nephron. 1976;16(1):31-41. https://www.ncbi.nlm.nih.gov/pubmed/1244564
- Simcyp default model: Clin Pharmacokinet. 2006;45(9):931-56 https://www.ncbi.nlm.nih.gov/pubmed/16928154
- Rhodin model: Pediatr Nephrol. 2009 Jan;24(1):67-76 https://www.ncbi.nlm.nih.gov/pubmed/18846389

Acknowledgments

- FDA
  - Yaning Wang
  - Yifei Zhang
  - Mona Khurana
  - Yu Jiang
  - Gilbert Burckart
  - Lynne P. Yao
  - Charles J. Ganley
- University of Utah
  - Shaun S. Kumar
  - Catherine Sherwin
  - Bob Ward

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

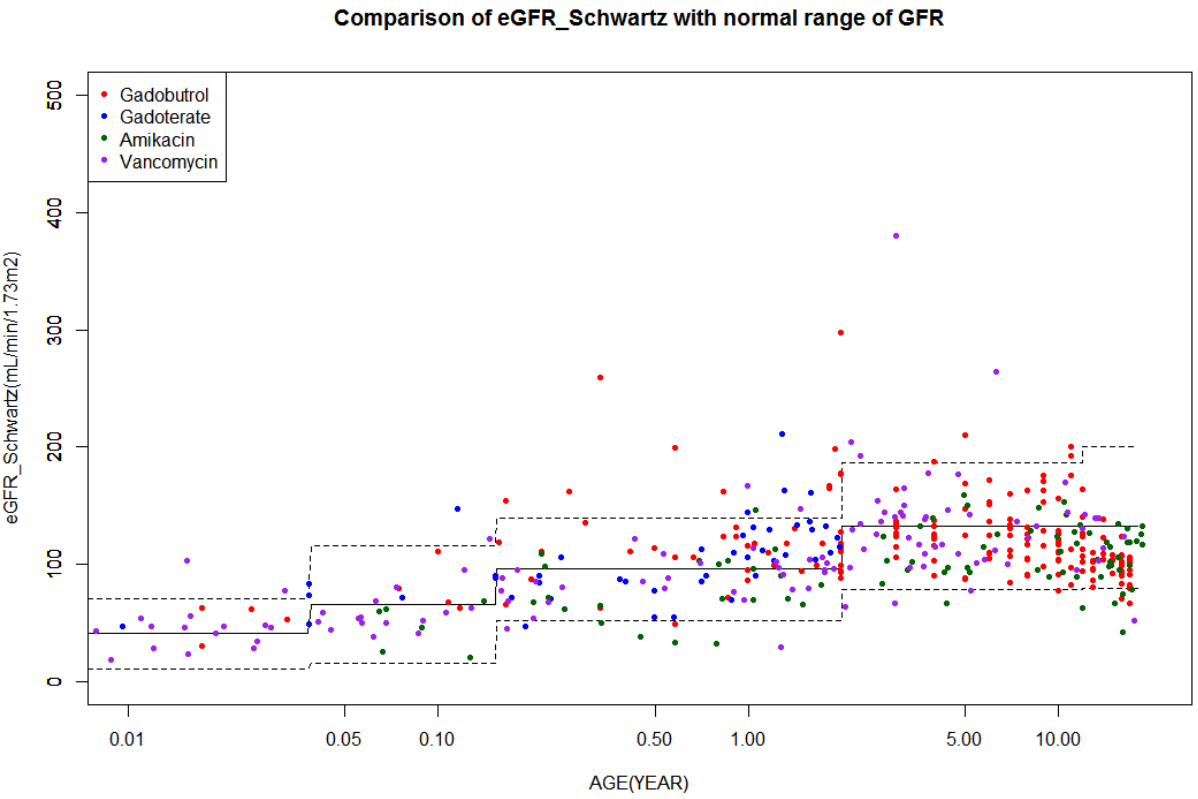


X-axis: Age (Year), BMI, BSA(m^2), CL(mL/min), Weight(kg), GA(weeks), Height(cm)
Y-axis: SCR (mg/dL)
Red dots: eGFR higher than mean+2*SD of normal range
Blue dots: eGFR normal or low

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)

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
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

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=0.413


FDA
U.S. FOOD & DRUG
ADMINISTRATION