ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

Comparison of Various Renal Function Models in Neonates

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OTS/CDER/OMTP/FDA

Disclaimer: My remarks today are my own personal views and do not represent those of the FDA

Highlights

- Target population: neonatal or child
- Specific population issues prime for PBPK as a tool: rapidly changing GFR in neonates and children <2 years old
- Why PBPK may out-perform other pharmacometric tools: both PBPK models and traditional compartment models with covariates rely on empirical equations to fit observed data

Outline

- Overview of various models for renal function quantification in neonates
- Evaluation of models with new data
- Summary

Available Models for GFR Quantification in Neonates

- Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 1987, 34: 571-90 (Schwartz model)
- Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children, Clin Pharmacokinet. 2006;45(9):931-56 (Simcyp default model)
- Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH. Human renal function maturation: a quantitative description using weight and postmenstrual age, Pediatr Nephrol. 2009 Jan;24(1):67-76. (Rhodin model)
- GastroPlus model

Equations

- Schwartz model
  - eGFR (mL/min/1.73m2)=k*HT (cm)/Scr (mg/dL) (k=0.45 for <1 yr or 0.55)
- Simcyp default model
  - eGFR (L/hr) = ((-6.616*BSA^2) + (99.054*BSA) - 17.74)/1000*60
- Rhodin model
  - eGFR (L/hr) =(WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*7.26
- Gastroplus model (Confidential)
  - Simulated by providing age (full term infant)
- Modified Rhodin model
  - eGFR (L/hr) =(WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*CL_{adult}
- PNA+GA model*
  - eGFR (L/hr) =(WT/70)^0.75 (1-(1-0.404*(GA/37)^3.3)*exp(-PNA*0.693/20.8)) *7.2

*:Wang J, et al., Renal Clearance in Newborns and Infants: Predictive Performance of Population-Based Modeling for Drug Development, Clin Pharmacol Ther. 2018 Dec 19

Data Source for Schwartz Model

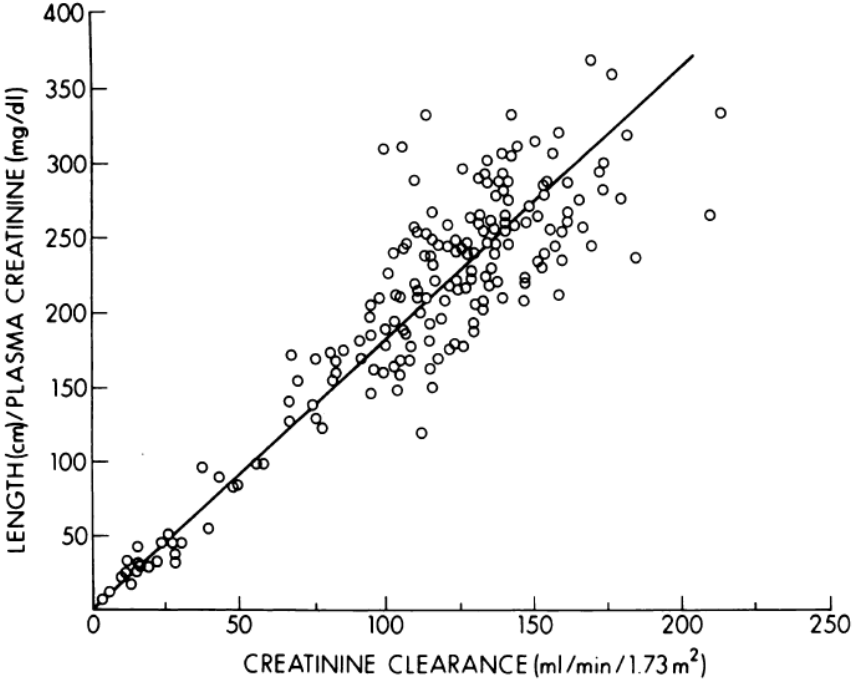


FIG. 2. Relationship between Ccr and length (cm)/Pcr (mg/dl) in the 1973 study sample. The line represents the regression coefficient of the equation Ccr = 0.55 L/Pcr (No. = 186; r = .893).

Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976 Aug;58(2):259-63

Model Validation for Schwartz Model

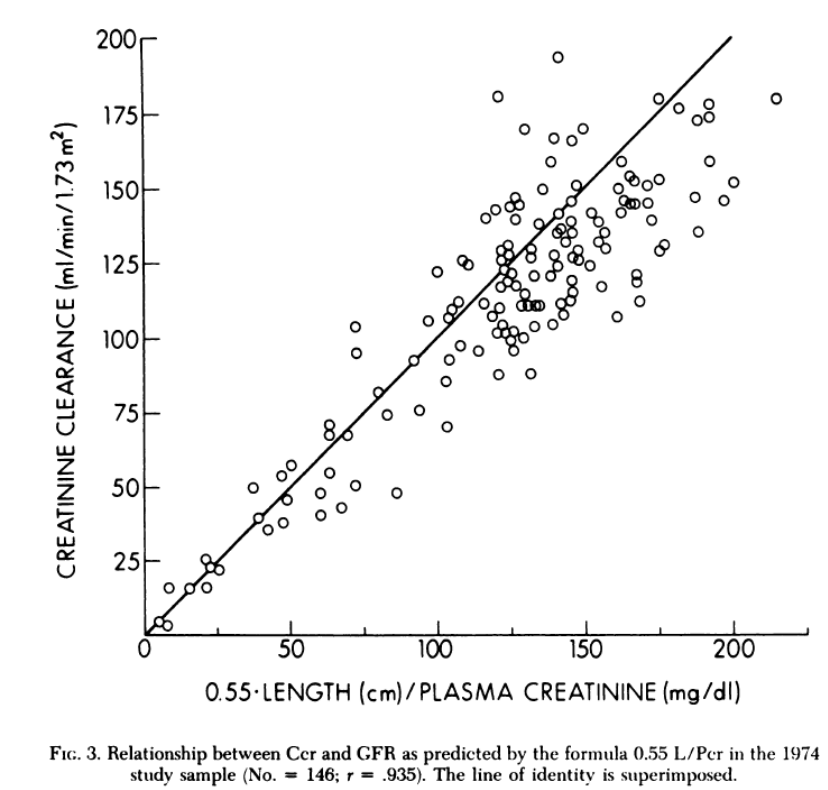


FIG. 3. Relationship between Ccr and GFR as predicted by the formula 0.55 L/Pcr in the 1974 study sample (No. = 146; r = .935). The line of identity is superimposed.

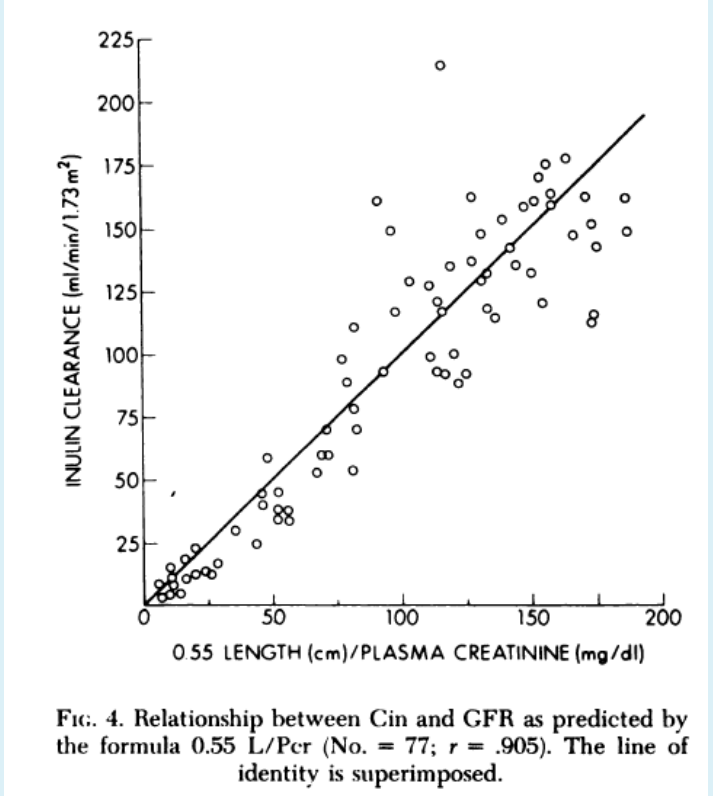


FIG. 4. Relationship between Cin and GFR as predicted by the formula 0.55 L/Pcr (No. = 77; r = .905). The line of identity is superimposed.

Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976 Aug;58(2):259-63

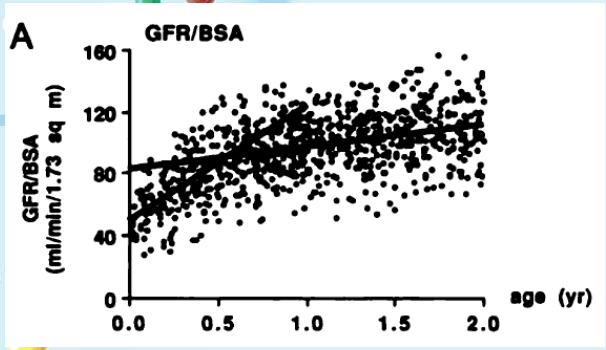
Data Source for Simcyp Model

Table II. Studies measuring glomerular filtration rate (mL/min/1.73m^2) with age in children used to define renal drug clearance with age in the Simcyp® Paediatric model

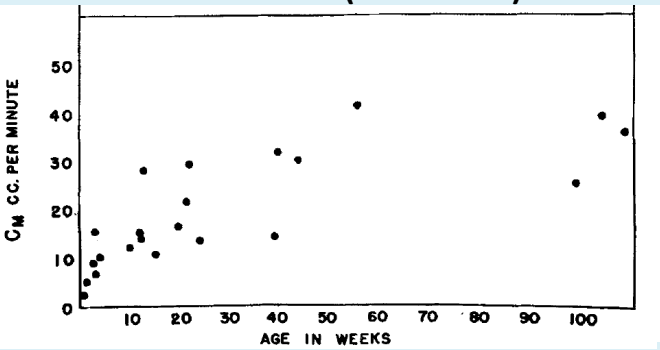
Probe	Neonate			Infant		Child		Adult	Reference
	<24h	1–7d	8–28d	1–3mo	3–12mo	1–5y	5–15y		
^{51}Cr-EDTA	45				90 (6mo)	105 (2y)			46
Mannitol	40	43	45	75	98 (6mo)	120y)			47
Inulin	18.6 ± 6.7	19.6 ± 4.7	38.5 ± 11.7						48
Inulin	20.1		37.5						49
Inulin	31.8								50
Inulin	29.3								51
Mannitol	43	45	48 ± 9.7	67.8 ± 8.7	90.6 ± 27	117 ± 26	131 ± 11		26
Inulin		39	47	58	103	120	127	127	52
Inulin		38.5		70.2	110	121	127	127	53

Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children, Clin Pharmacokinet. 2006;45(9):931-56

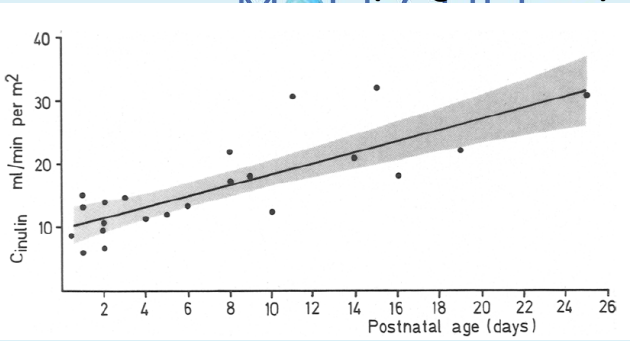
Ref 46 (Peters 1994)



Ref 47 (West 1948)



Ref 48 (Guignard 1975)



Ref 49 (Fawer 1979)

The development of renal function was studied in neonates with gestational ages ranging from 28 to 43 weeks. The effect of gestational age on the maturation of renal function was assessed in newborn infants studied during the first 72 h of life.

Ref 50 (Coulthard 1983, preterm babies)

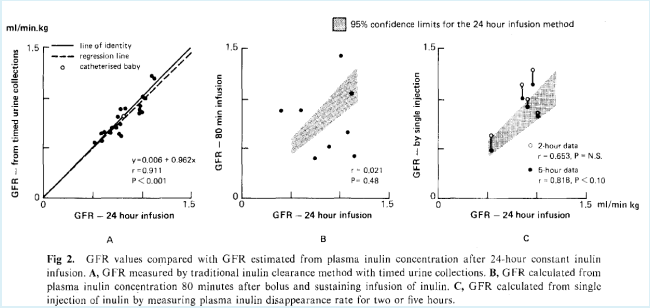


Fig 2. GFR values compared with GFR estimated from plasma inulin concentration after 24-hour constant inulin infusion. A, GFR measured by traditional inulin clearance method with timed urine collections. B, GFR calculated from plasma inulin concentration 80 minutes after bolus and sustaining infusion of inulin. C, GFR calculated from single injection of inulin by measuring plasma inulin disappearance rate for two or five hours.

Ref 26 (Rubin 1949)

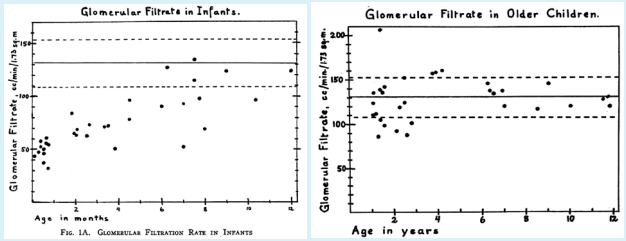


FIG. 1A. GLOMERULAR FILTRATION RATE IN INFANTS

Ref 52 (Heilbron 1991)

We have reviewed the studies that provide the current standards of reference for glomerular filtration rate (GFR) in normal children from 14 days to 12 years of postnatal age.

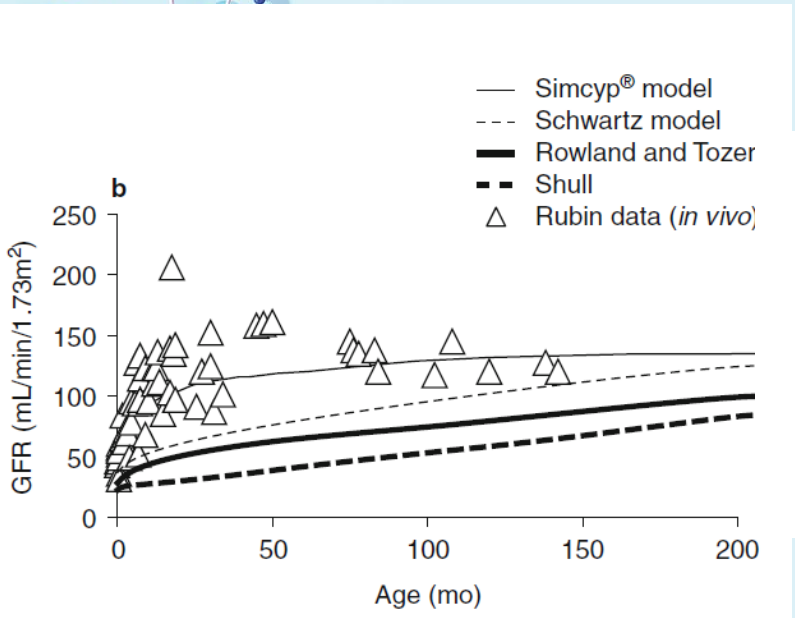
Ref 51 (Strauss 1981)

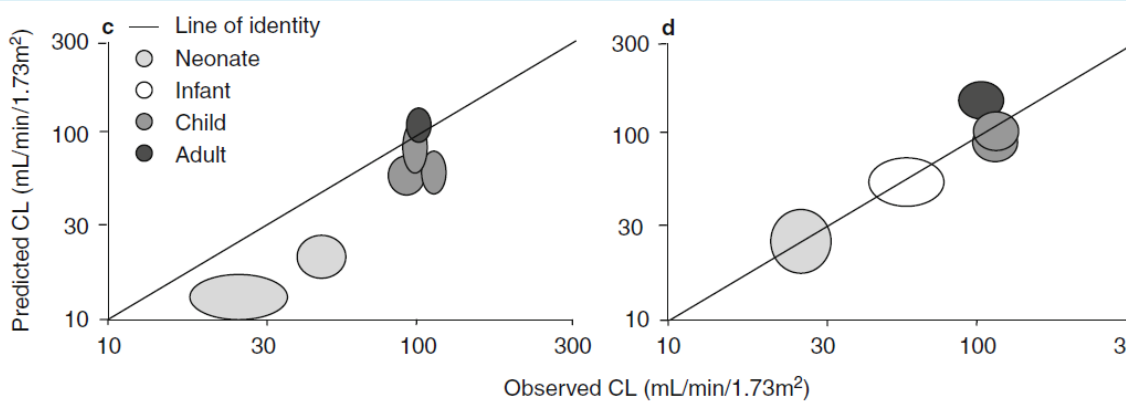
Renal function was studied serially in 17 healthy term infants during the hours immediately following birth.

Ref 53 (Stewart 1987)

The kidneys of neonates are inefficient at drug elimination, leading initially to prolonged elimination half-lives of many drugs.

Model Validation for Simcyp Model





(c) gentamicin; (d) vancomycin.

Rubin MI, Bruck E, Rapoport M, et al. Maturation of renal function in childhood: clearance studies. J Clin Invest 1949; 28: 1144-62 (Mannitol clearance for GFR)

Data Source for Rhodin Model

FROM MOLECULE TO PATIENT

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

(Bird 2003) (Cole 2004) (Rubin 1949) (Coulthard 1985) (Coulthard 1985) (Bouvet 2006) (Grubb 2005) (Wilkins 1992)

Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH. Human renal function maturation: a quantitative description using weight and postmenstrual age, Pediatr Nephrol. 2009 Jan;24(1):67-76

Model Validation for Rhodin Model

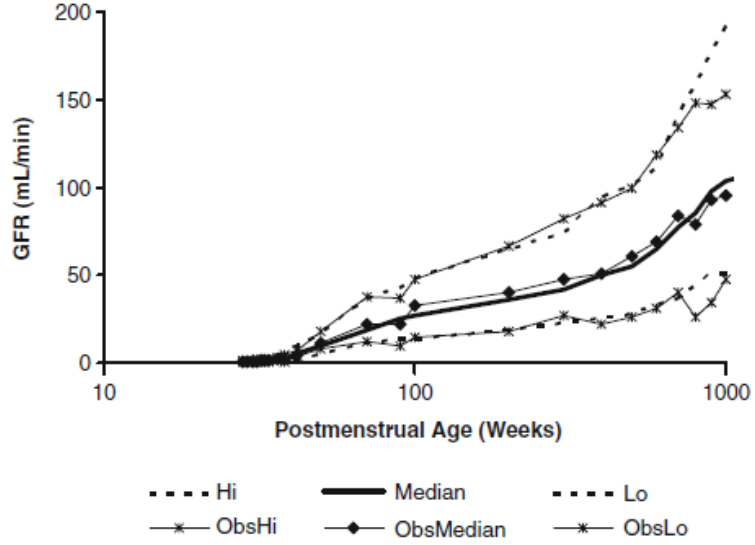


Fig. 1 VPC for the full population (different age groups), based on the theoretical allometric size model with a sigmoid hyperbolic maturation function of postmenstrual age (PMA). The median and 90% intervals are shown for the observed (*Obs*) values and for the model predictions. *Thick solid line* Median prediction, *dashed lines* prediction intervals. *Hi* High, *Lo* low, *GFR* glomerular filtration rate

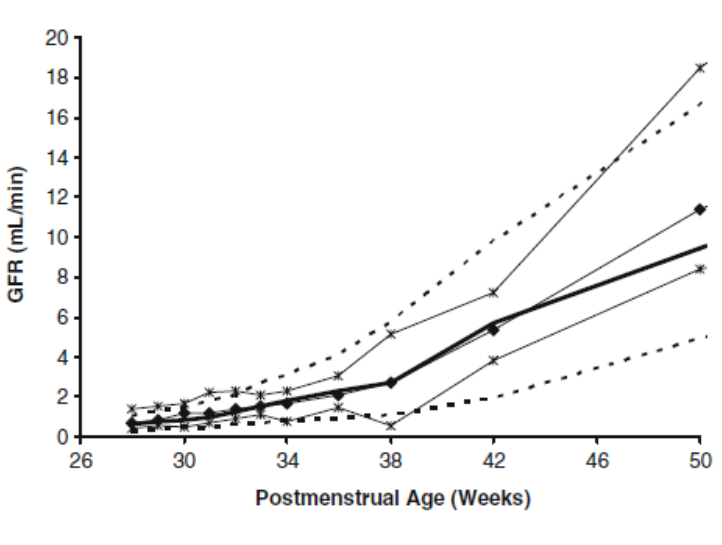


Fig. 2 VPC for children (different age groups), based on the theoretical allometric size model with a sigmoid hyperbolic maturation function of PMA. The median and 90% intervals are shown for the observed (*Obs*) values and for the model predictions. *Thick solid line* Median prediction, *dashed lines* prediction intervals. *Hi* High, *Lo* low

Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH. Human renal function maturation: a quantitative description using weight and postmenstrual age, Pediatr Nephrol. 2009 Jan;24(1):67-76

Data Source and Model Validation for Gastroplus Model

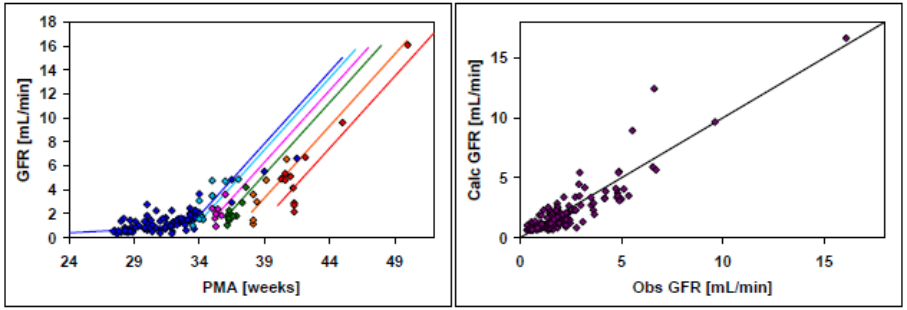


Figure 4-28: Plot of GFR vs post-menstrual age (PMA) for neonates up to 12 weeks old (left) and born after 27-33 (dark blue), 34 (light blue), 35(magenta), 36 (green), 38 (orange) and 40 (red) weeks of gestation (left) and plot of calculated vs observed GFR for the same data (right). Points represent experimental data (Arant 1978, Coulthard 1985, DeWoskin 2008, Fawer 1979) lines show GFR calculated in GastroPlus.

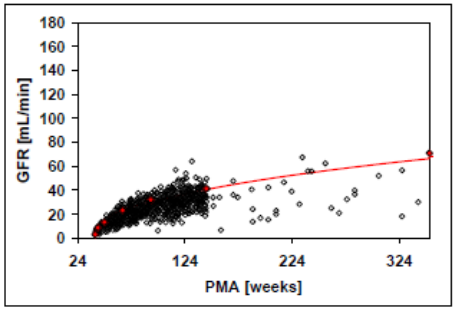


Figure 4-29: Plot of GFR vs post-menstrual age (PMA) for infants and children up to 6 years old. Points represent experimental data (Bird 2003, Kearns 2003, Peters 1994, Rubin 1949, Stevens 2007) line shows GFR calculated in GastroPlus for infants and children from 12 weeks to 6 years.

GastroPlus manual, version 9.0

Data Source for PNA+GA Model

FROM MOLECULE TO PATIENT

Table 1 Drug clearance and renal clearance in adults

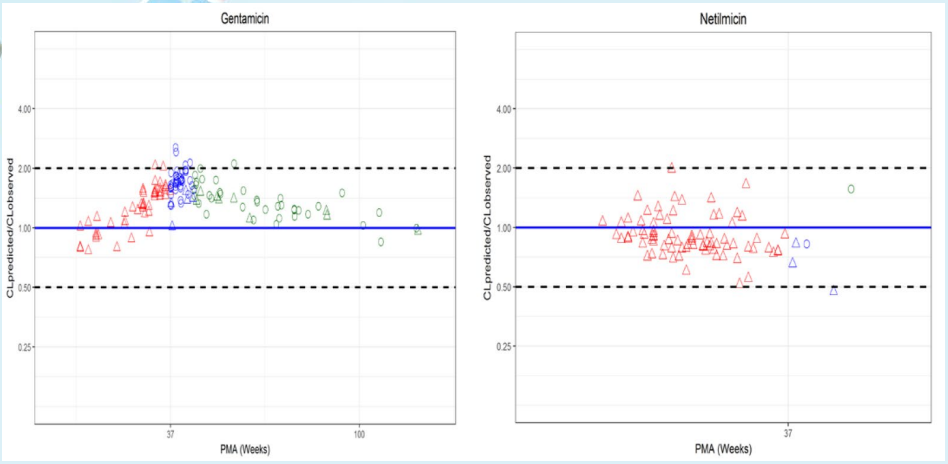
Drug	Total clearance (L/hour)	Renal clearance (L/hour)	% Renal clearance	Contribution of nonrenal elimination pathways
Amikacin[25]	6.0 ± 0.5	5.0 ± 0.9	94	< 5% metabolism
Gadobutrol[26]	6.2	6.2	> 99	No metabolism
Gadoterate[27]	7.1	7.1	> 99	No metabolism
Vancomycin[28]	5.9 ± 1.5	5.3 ± 2.0	~ 90	~ 10% metabolism

Table 2 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)

*:Wang J, et al., Renal Clearance in Newborns and Infants: Predictive Performance of Population-Based Modeling for Drug Development, Clin Pharmacol Ther. 2018 Dec 19

Model Validation for PNA+GA Model



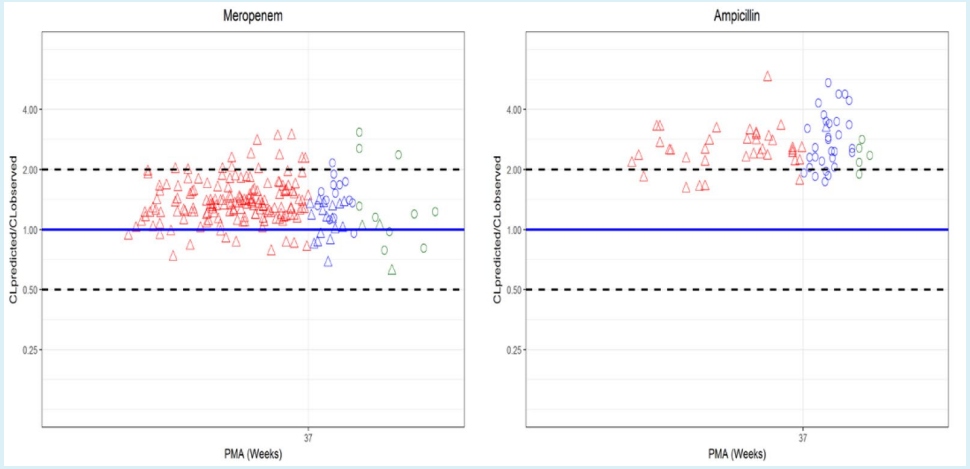


Figure S2. Overall performance of clearance prediction for drugs 60 - 80% renally- eliminated in newborns and infants using GA+PNA based model. The circles represent patients with gestational age >= 37 weeks and the triangles represent patients with gestational age < 37 weeks. The colors of red, blue, dark-green represent < 37 weeks PMA, 37 to < 42 weeks PMA, ≥ 42 weeks PMA, respectively. The dotted lines represent 0.5 and 2-fold for the ratio of model predicted clearance relative to the observed value (population PK estimated CL).

Wang J, et al., Renal Clearance in Newborns and Infants: Predictive Performance of Population-Based Modeling for Drug Development, Clin Pharmacol Ther. 2018 Dec 19

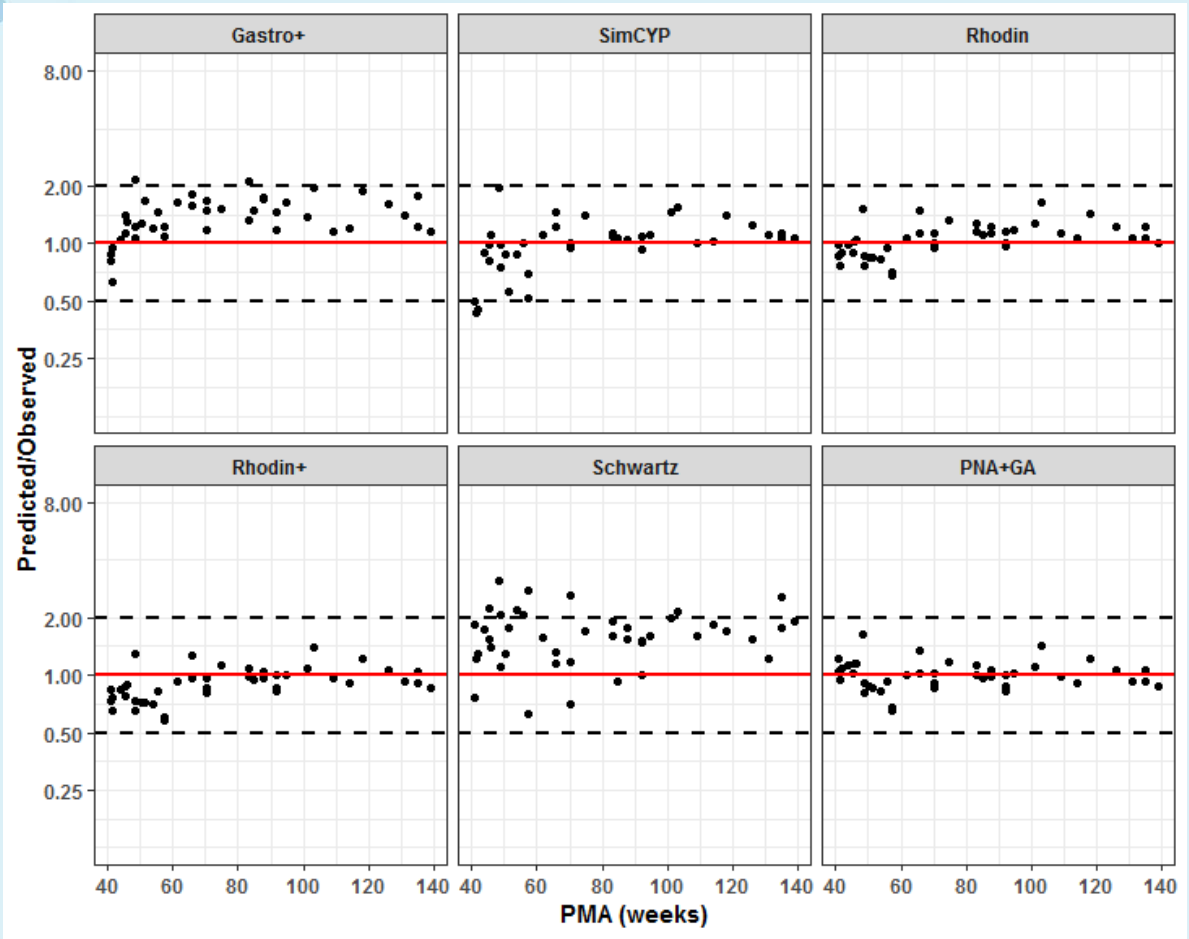
Data: Gadovist® and Dotarem®

- Macrocyclic, gadolinium-based contrast agent (GBCA)
- Complete GFR elimination, ideal compounds for estimating renal maturation function. (CL: 6.2 L/hr and 7.07 L/hr in 70 kg adults)
- Approved Indication: for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

Study Design in Pediatric Patients < 2 yo

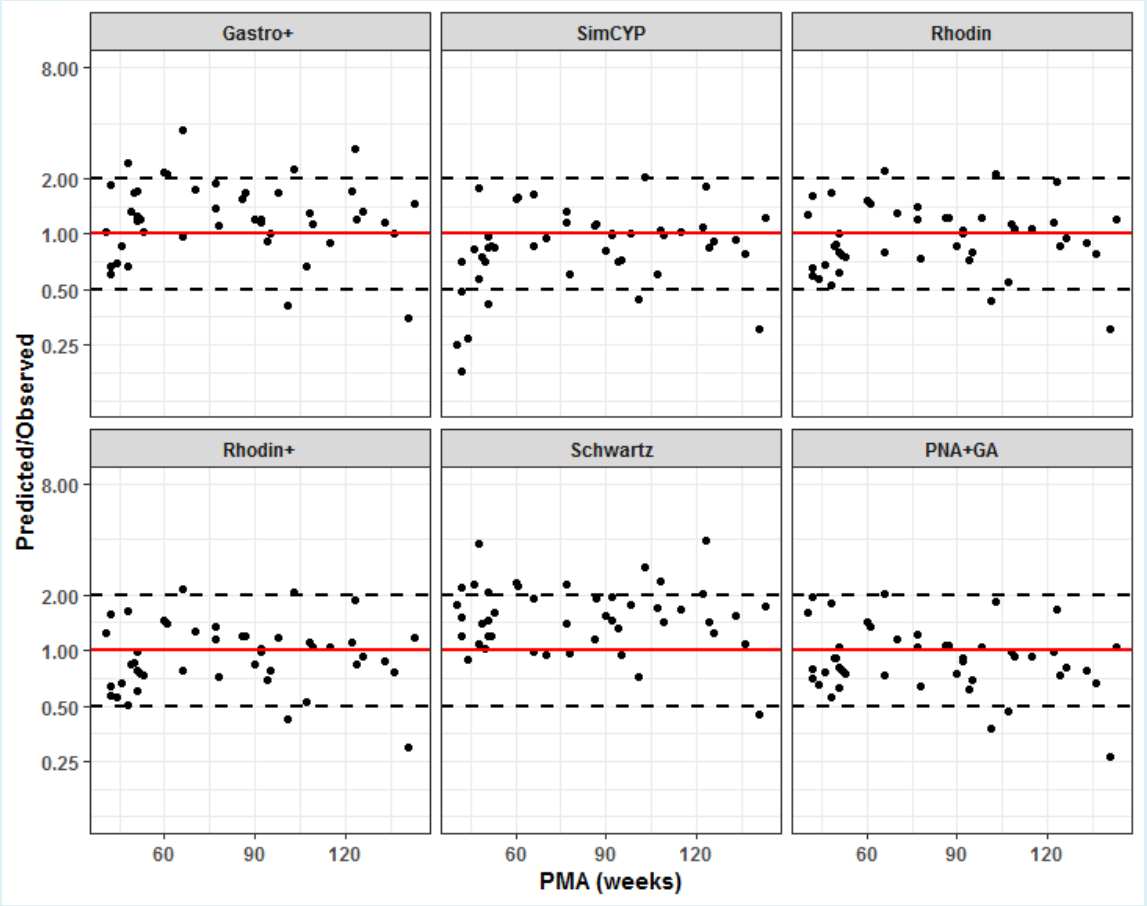
- **Gadavist :**
  - **term newborns.**
  - **N=43 (38 subjects >1 months, 5 subjects < 1 months)**
  - **Sparse Sampling scheme: 3 blood samples per subject; one during each time window (15 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection)**
- **Dotarem:**
  - **term newborns.**
  - **N=45 (40 subjects >1 months, 5 subjects < 1 months)**
  - **Sparse Sampling scheme: 3 blood samples per subject; one during each time window (10 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection)**

Predicted GFR/Observed GFR Based on Gadovist Pediatric Data



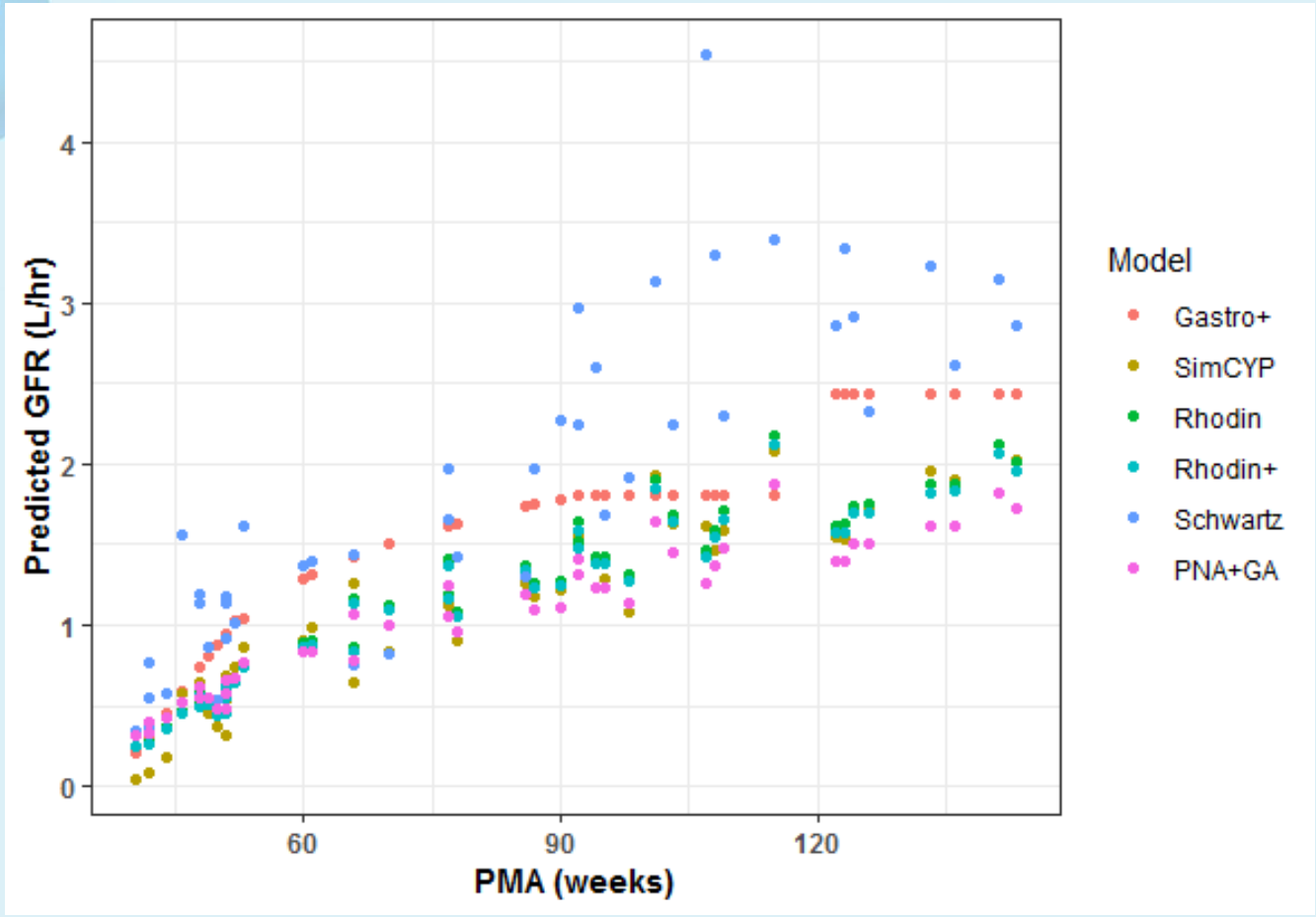
Observed GFR is individual CL estimate from neonate/infant popPK analysis

Predicted GFR/Observed GFR Based on Dotarem Pediatric Data



Observed GFR is individual CL estimate from neonate/infant popPK analysis

A Direct Comparison of All Models



Summary

- Different GFR models were built from different data sources
- Significant differences exist between these models
- More high quality data are needed to support an optimal model

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FROM MOLECULE TO PATIENT

Acknowledgments

- Jian Wang
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- Gilbert J. Burckart
- Lynne P. Yao

FROM MOLECULE TO PATIENT

THANK YOU

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Division of Pharmacometrics (DPM) /Office of Clinical Pharmacology (OCP) is Hiring!

- **Positions**
  - PBPK reviewer and Pharmacometrics reviewers
- **Responsibility**
  - Approve and label the drug product with particular attention to drug do sing at the individual and population levels.
  - Provide advice on trial design and development path decisions to sponsors.
  - Conduct research to create new knowledge based on the unique data available at the FDA (i.e. prior submissions) and literature to inform better regulatory decisions by the FDA and drug development decisions by sponsors
- **Minimum requirements**
  - An earned Ph.D. or other professional doctorate in PKPD, Statistics, Engineering, Clinical Pharmacology, or relevant fields
  - Hands-on experience with modeling and simulation software (e.g. NONMEM, SAS, Splus/R, Trial Simulator, WinBUGs, Phoenix, Monolix, GastroPlus, PKSIM, SimCYP, etc.)
  - Good knowledge of PK/PD modeling principles and statistics.
  - Good communication and interpersonal skills
  - Candidates should have continuous residence in the US for the last 3 years.
- **How to apply**
  - Send your CV to Yaning.Wang@fda.hhs.gov or Hao.Zhu@fda.hhs.gov