Strengths and Limitations of Existing Estimation Methods and Applications to Specific Populations

George J. Schwartz, MD

Emeritus Professor of Pediatrics

Division of Pediatric Nephrology

University of Rochester Medical Center

Golisano Children's Hospital

Glomerular Filtration Rate (GFR)

- Best overall index of kidney function in health and disease
  - Affected by physiologic, pharmacologic, and pathologic conditions
  - GFR decline is correlated with decline in other renal functions (tubular reabsorption, secretion, metabolic function, etc)
- GFR cannot be directly measured in humans, and so true GFR cannot be known with certainty
  - GFR can be assessed from clearance measurements and estimated from serum renal biomarkers (creatinine, cystatin C)
  - Urinary inulin clearance (Cin) is considered the gold standard for measuring GFR
    - Cin has many problems including
      - Difficulty performing test, cumbersome
      - Availability of the inulin
      - Assay of the inulin
      - Expensive
    - Current markers include iothalamate, iohexol, and DTPA

Concept of Renal Clearance

- Concept of clearance: describes the functional capacity of a diseased versus normal kidney
- Clearance is a quantitative description of the rate at which the kidney excretes various substances relative to their concentration in plasma (Homer Smith, The Kidney, 1951)
  - Clearance = volume of plasma that 1 minute's excretion of urine suffices to remove of urea or creatinine (UV/P)
  - This is a virtual volume because all the blood is **partially** cleared
  - These volumes do not say how the substances are removed from plasma into the urine (filtration, secretion, partial reabsorption)
  - **Thus the need for a substance that is completely ultrafiltered through the glomeruli and neither reabsorbed, secreted nor metabolized by the tubules**
    - **In this case the renal clearance is identical with GFR**
      - **Inulin,** a polysaccharide fulfills these criteria
      - Creatinine, a muscle waste product, is filtered and some secreted

Clearance of X

- In the steady state, for any substance, the rate of its excretion = rate of its filtration
  - Therefore:
- $U_xV = GFR\ P_x$ or $GFR = U_XV/P_X$

U_X is concentration of X in urine, P_X is concentration of X in plasma (or serum), and V is urine flow (mL/min

- Basis for comparison of GFR between adults and children: **kidney weight** (Homer Smith 1951)
  - Kidney weight is directly related to body surface area
  - Glomerular number is proportional to kidney weight
  - BSA has been validated as a size comparator for GFR in children and adults (of varying sizes)
  - GFR is corrected to BSA by: x 1.73/BSA

GFR Reaches Adult Levels by 1.5 y/o

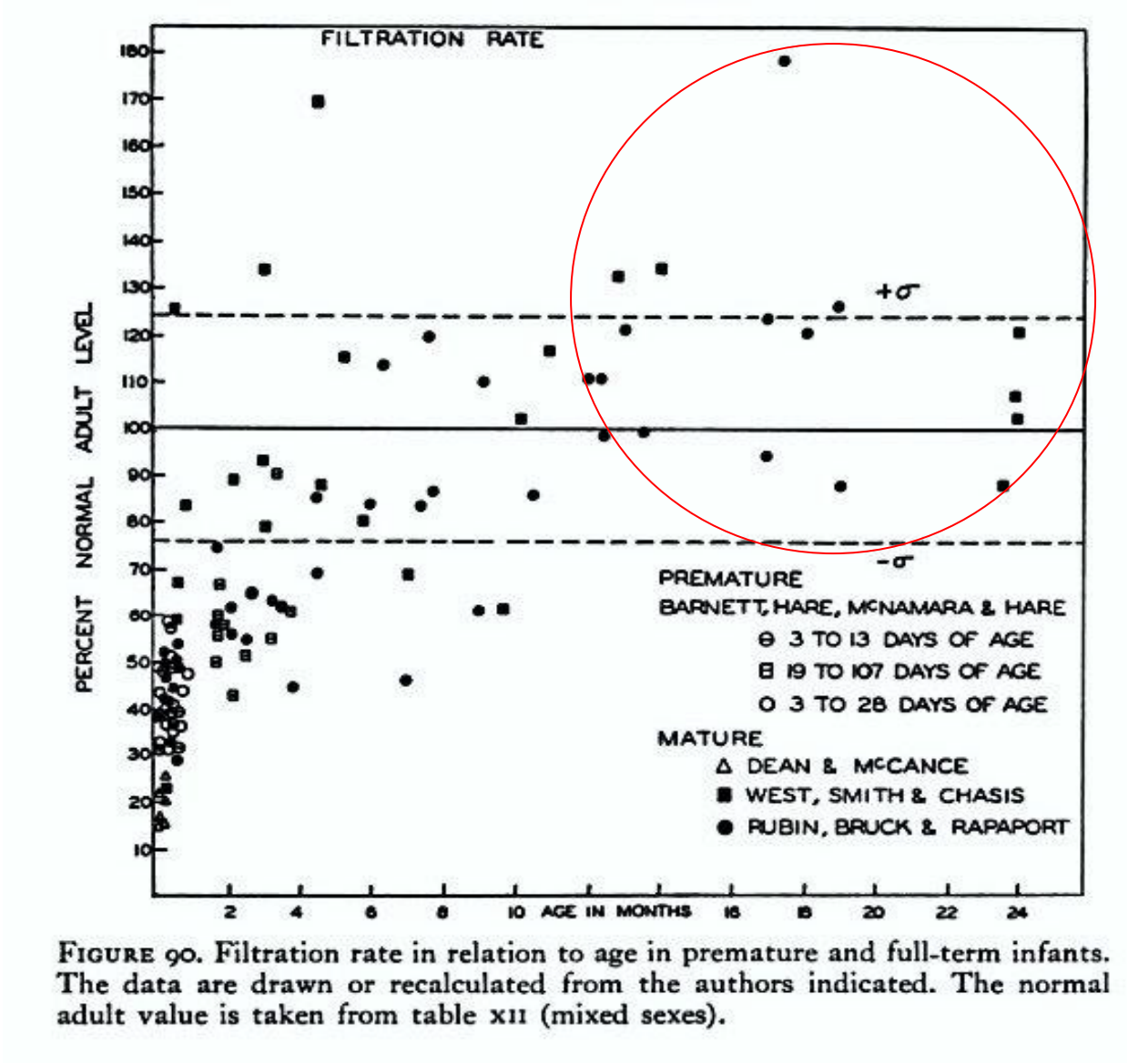
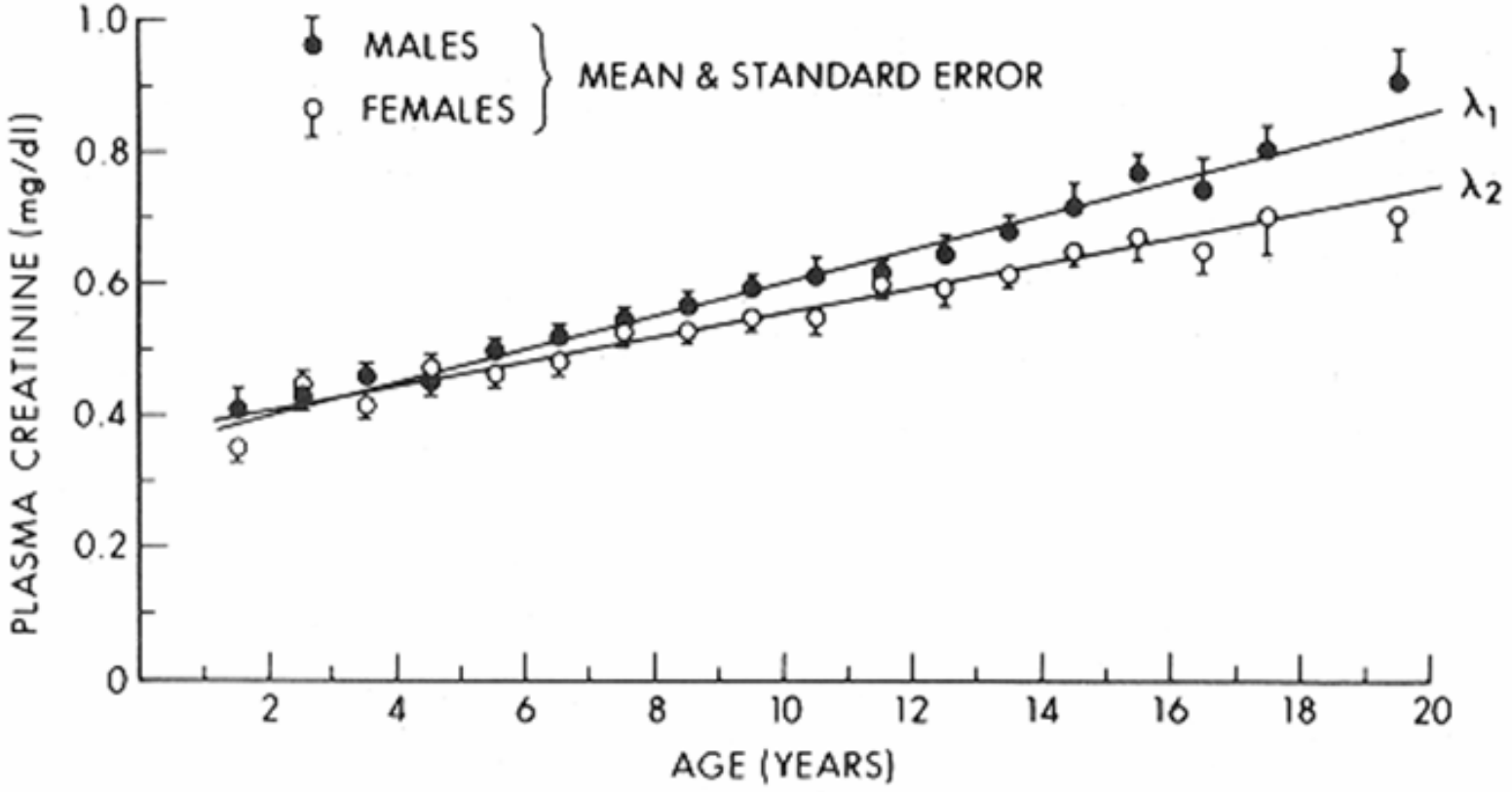


FIGURE 90. Filtration rate in relation to age in premature and full-term infants. The data are drawn or recalculated from the authors indicated. The normal adult value is taken from table XII (mixed sexes).

H. Smith, The Kidney

Serum Creatinine Rises with Age in Children



Schwartz J Ped 88:828,1976

Creatinine Coefficient in Children
Talbot AJDC 55:42, 1938

Group	24 h Cr mg/kg	Est %Musc Wt/Body Wt
Obese	14.0	25
NL	20.5	37
Lean	30.7	55
Emaciated	9.0	16

- Muscle mass is highly correlated with urinary creatinine excretion
- 1 gm urinary creatinine corresponds to 17.8 kg in infants and 17.9 in man

Derivation of k
eGFR = k*L/Scr

- **Ccr (ml/min/1.73 m^2) = UcrV/Scr * 1.73/SA**

- Assumptions:
  - SA proportional to L^2
  - UcrV = creatinine production rate
  - Creatinine production rate proportional to muscle mass
  - Muscle mass proportional to L^3
  - So, UcrV proportional to L^3 and:

- **Ccr** = k'* (L^3/Scr) * (1.73/L^2) = **k * L/Scr**
  - k = 1.73 * k' (mg creatinine per 100 min * cm * 1.73 m^2)

Schwartz Pediatrics 58:259, 1976

Original “k” values for Jaffe Creatinine
First update for Enzymatic Creatinine

- Preterm: 0.33
- Term: 0.45
- Children: 0.55
- Pub. Girls 0.55
- Pub. Boys 0.7

to 30 d: k=0.31 (Smeets et al, JASN 2022)

0.41 CKiD 2009
but see Pierce et al,
KI 2021

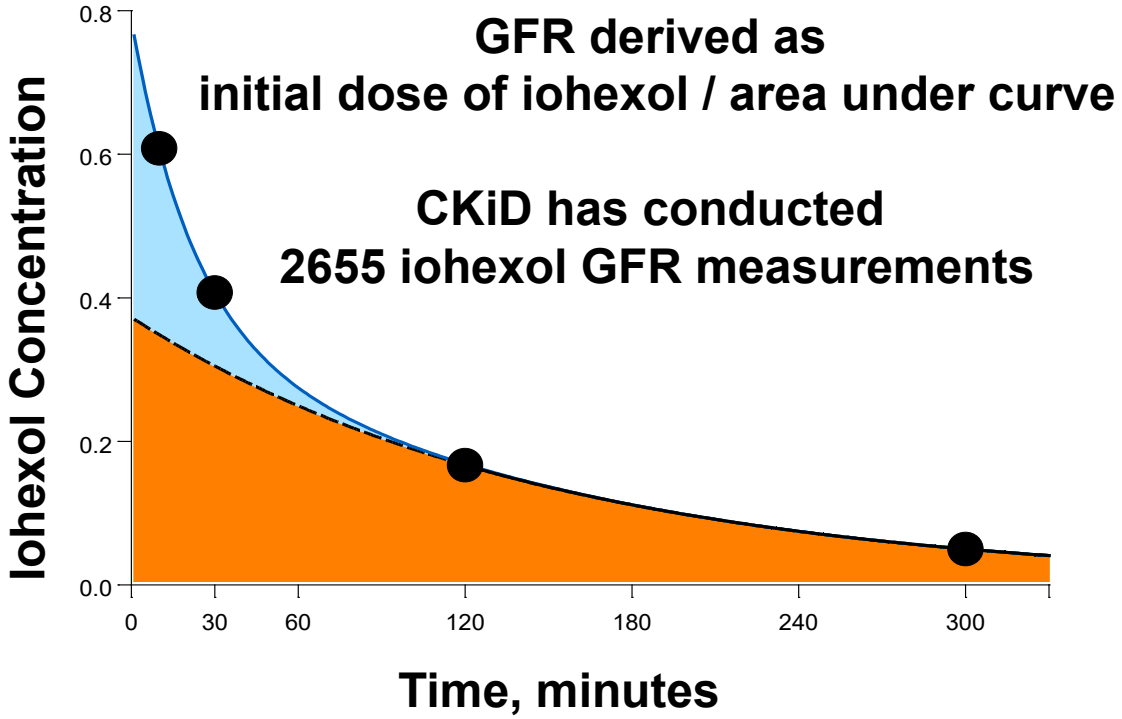
Schwartz et al, Ped Clin North America 1987
Schwartz et al, JASN 2009

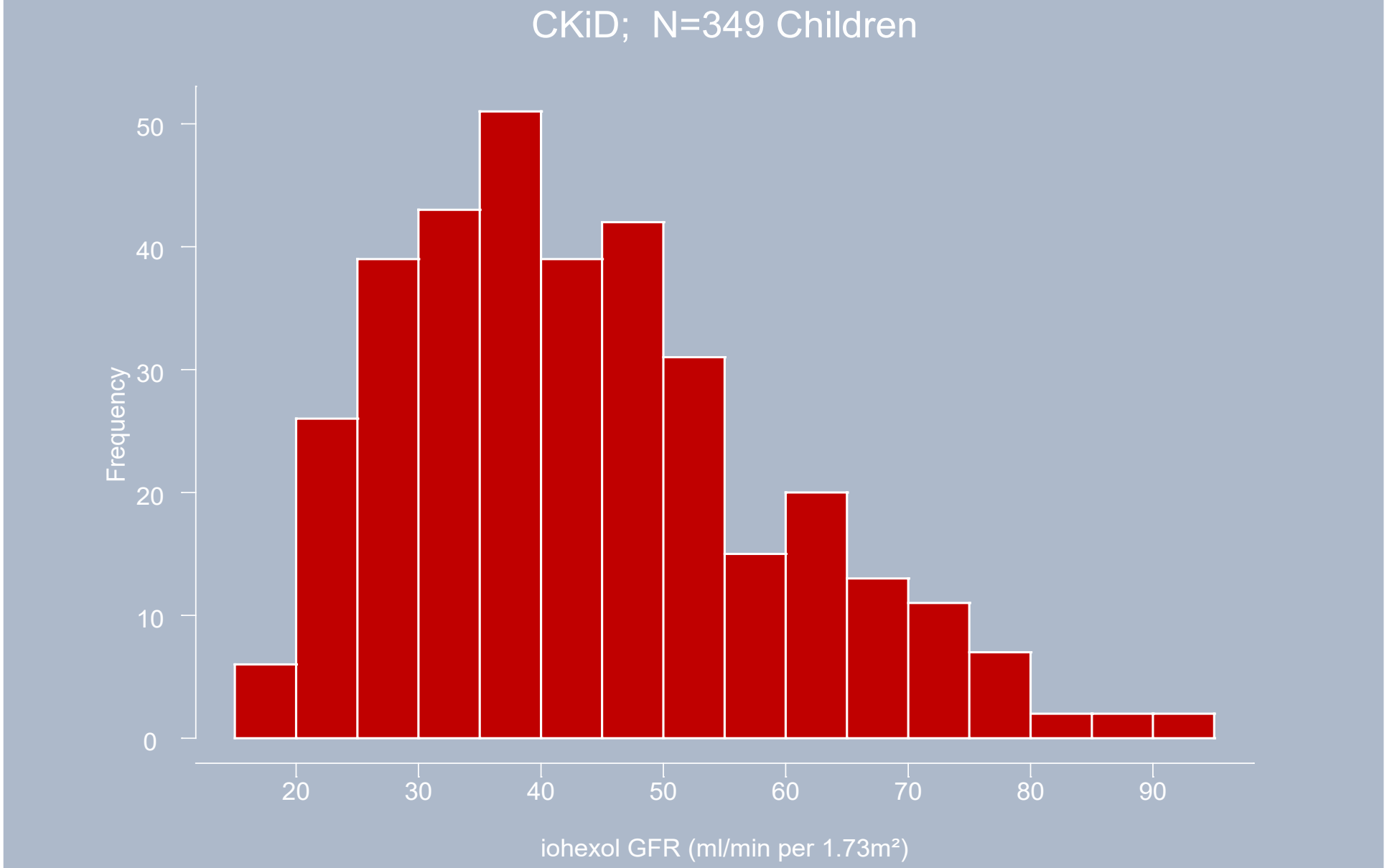
The Chronic Kidney Disease in Children Study: ckidstudy.org

- **2003 - Present**
- **Longitudinal observational study with annual follow-up**
- **1100 Participants enrolled with mild to moderate CKD**
- **Multicenter: >50 clinical sites in United States and Canada**
- **Scientific areas of focus: CKD progression, cardiovascular comorbidities, growth, neurocognitive development**

GFR measurement by plasma iohexol clearance

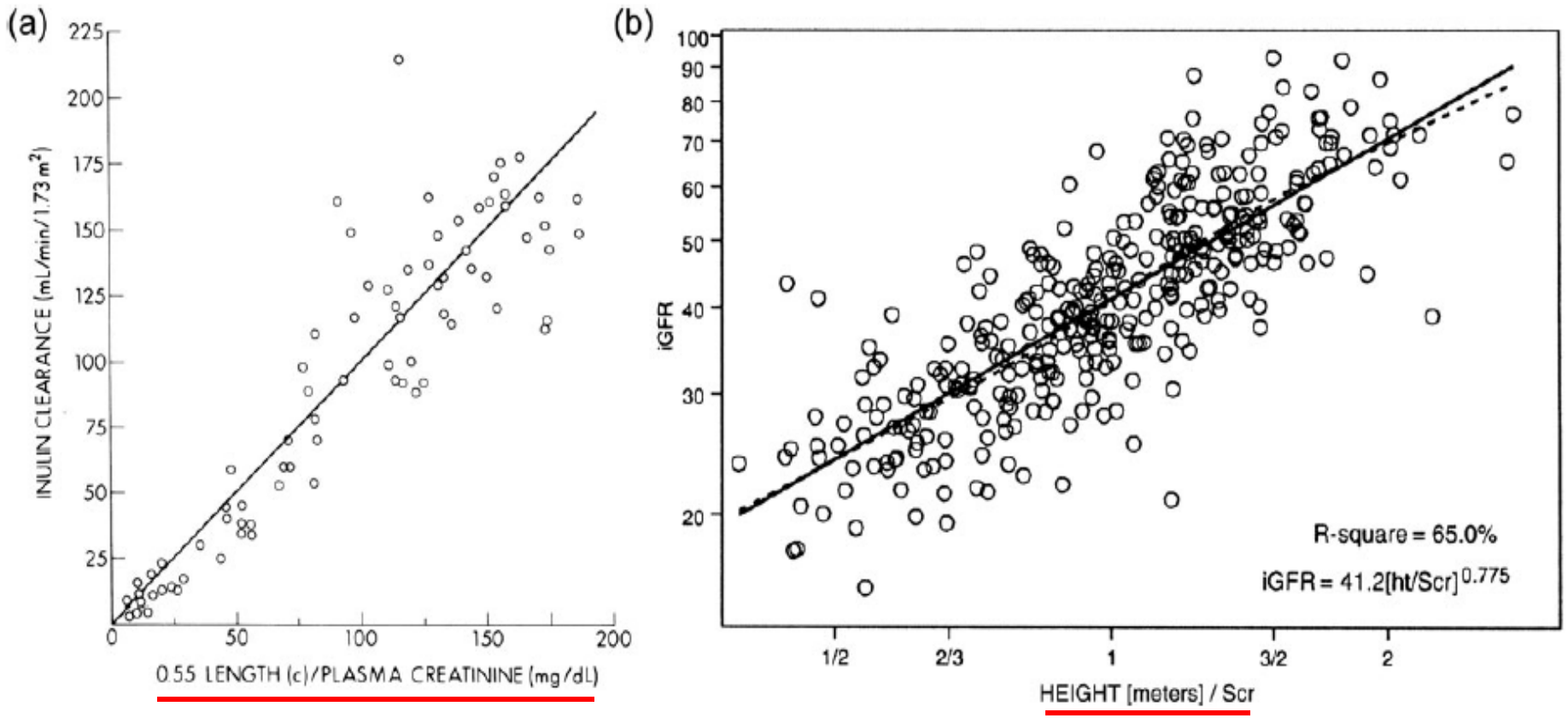
- Injection of iohexol
- Non-ionic contrast agent (Omnipaque™)
- No protein binding
- Rare side effects
- Not secreted, metabolized or reabsorbed by kidney
- Extrarenal elimination negligible





Schwartz et al, JASN 2009

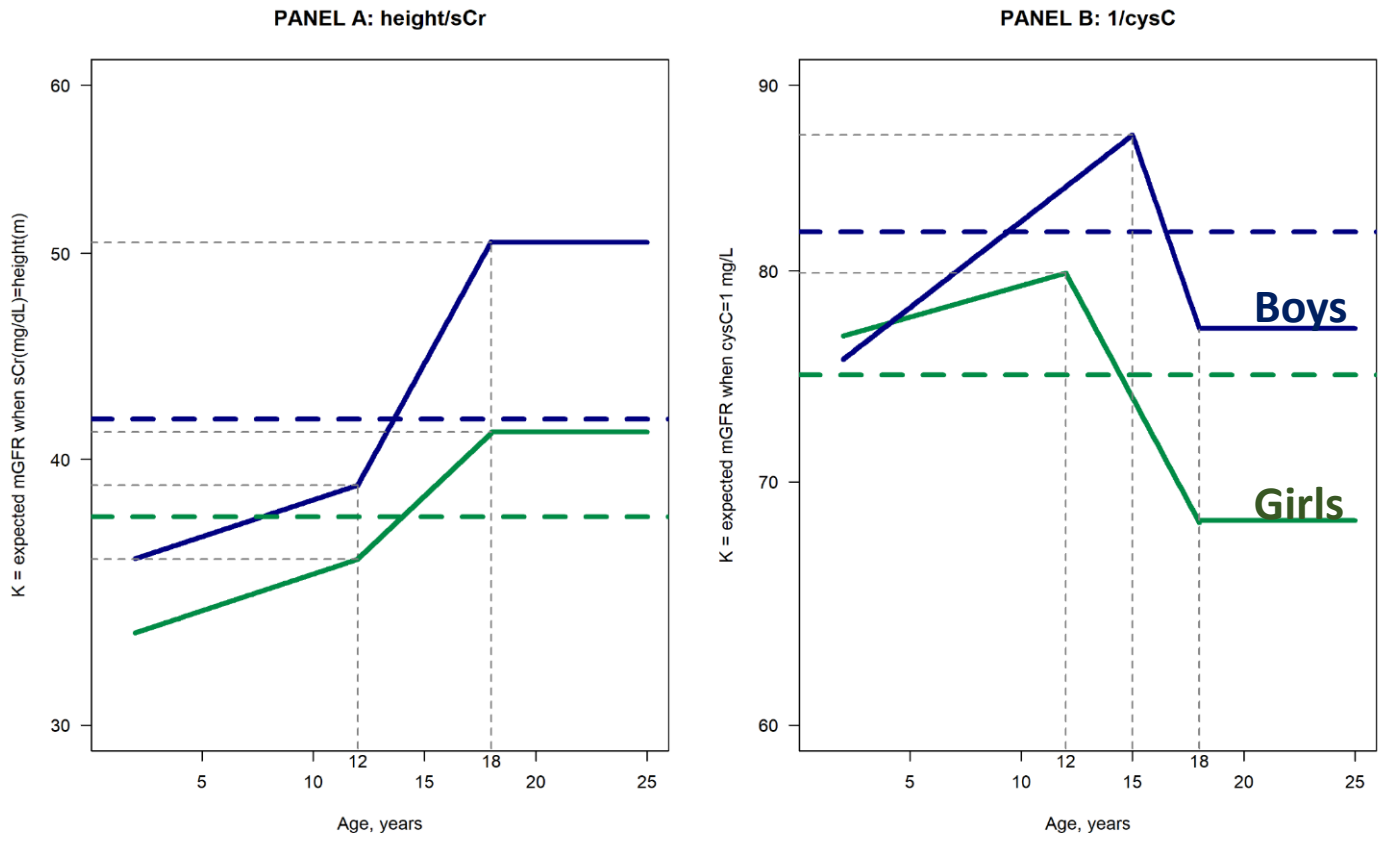
Height and Scr are important for eGFR
Height is a surrogate for muscle mass



Schwartz J Peds 58:259, 1976 & JASN 20:629, 2009

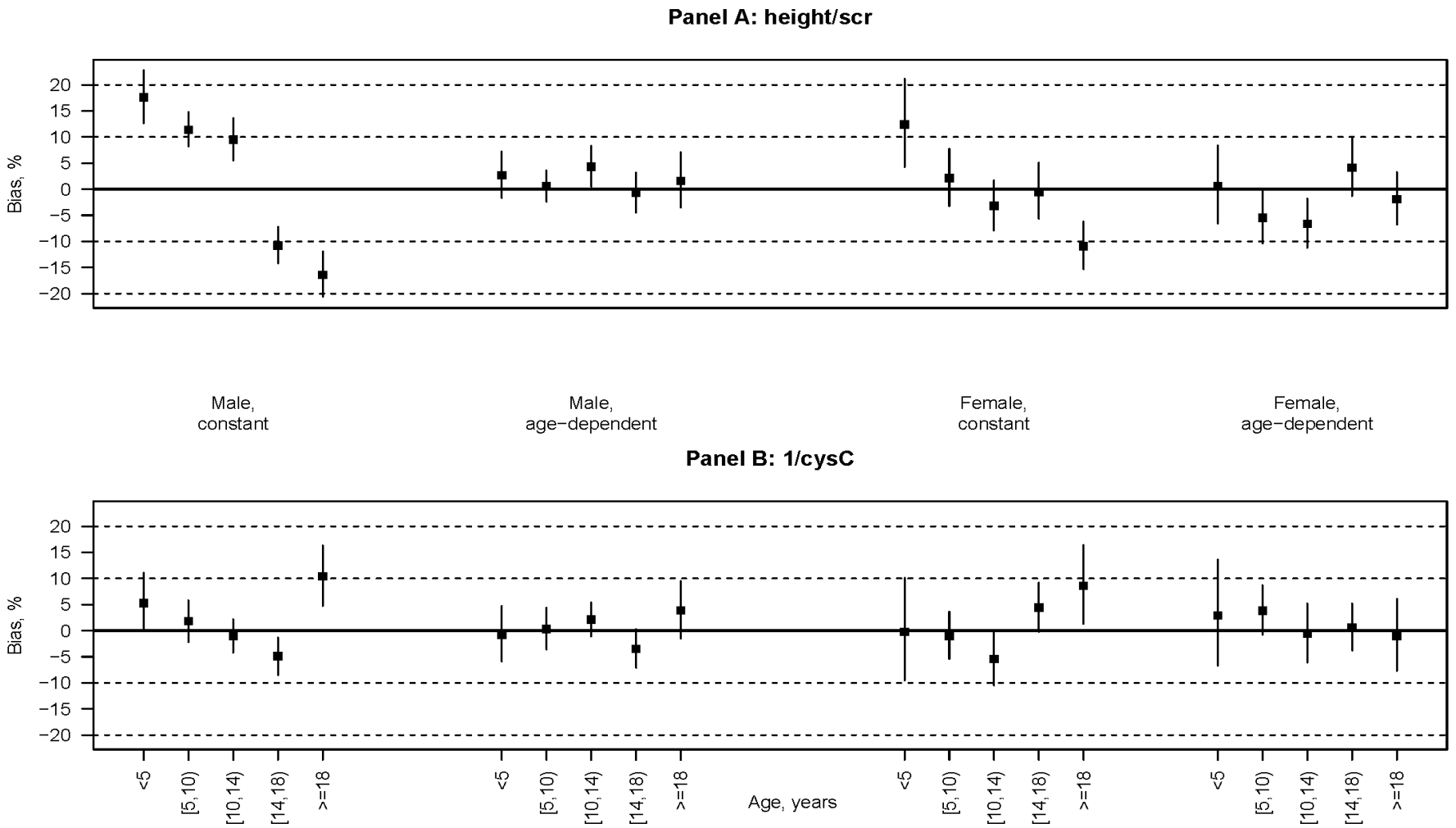
U25 eGFR (2nd CKiD update)

Figure 1: Sex-specific values of K by age for the CKID U25 constant (dashed line) and age–dependent (solid line)

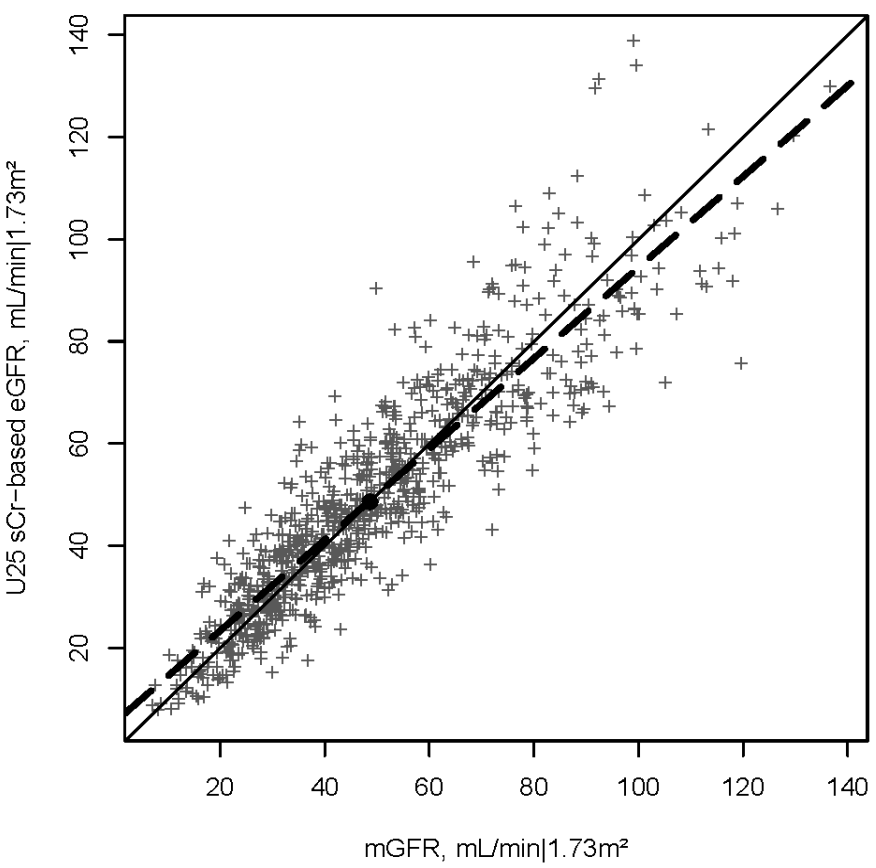


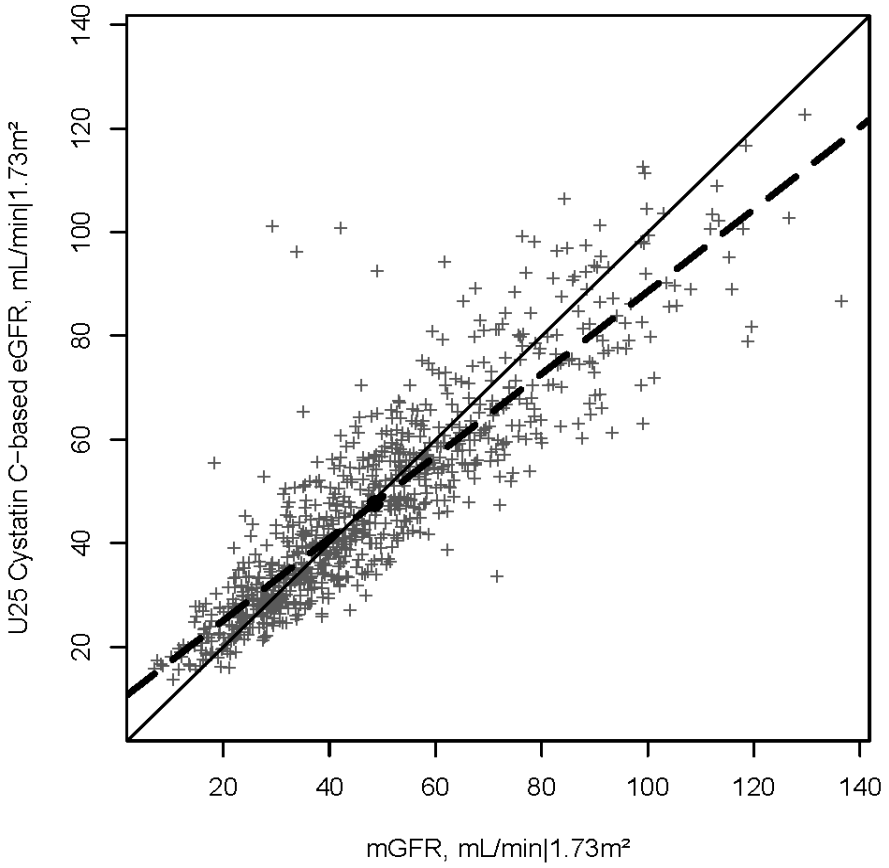
Pierce et al, KI 2021

Mean bias (percent) of CKiD U25 eGFR vs. iohexol mGFR by age and sex in the validation dataset (n=1764 obs., 618 participants)



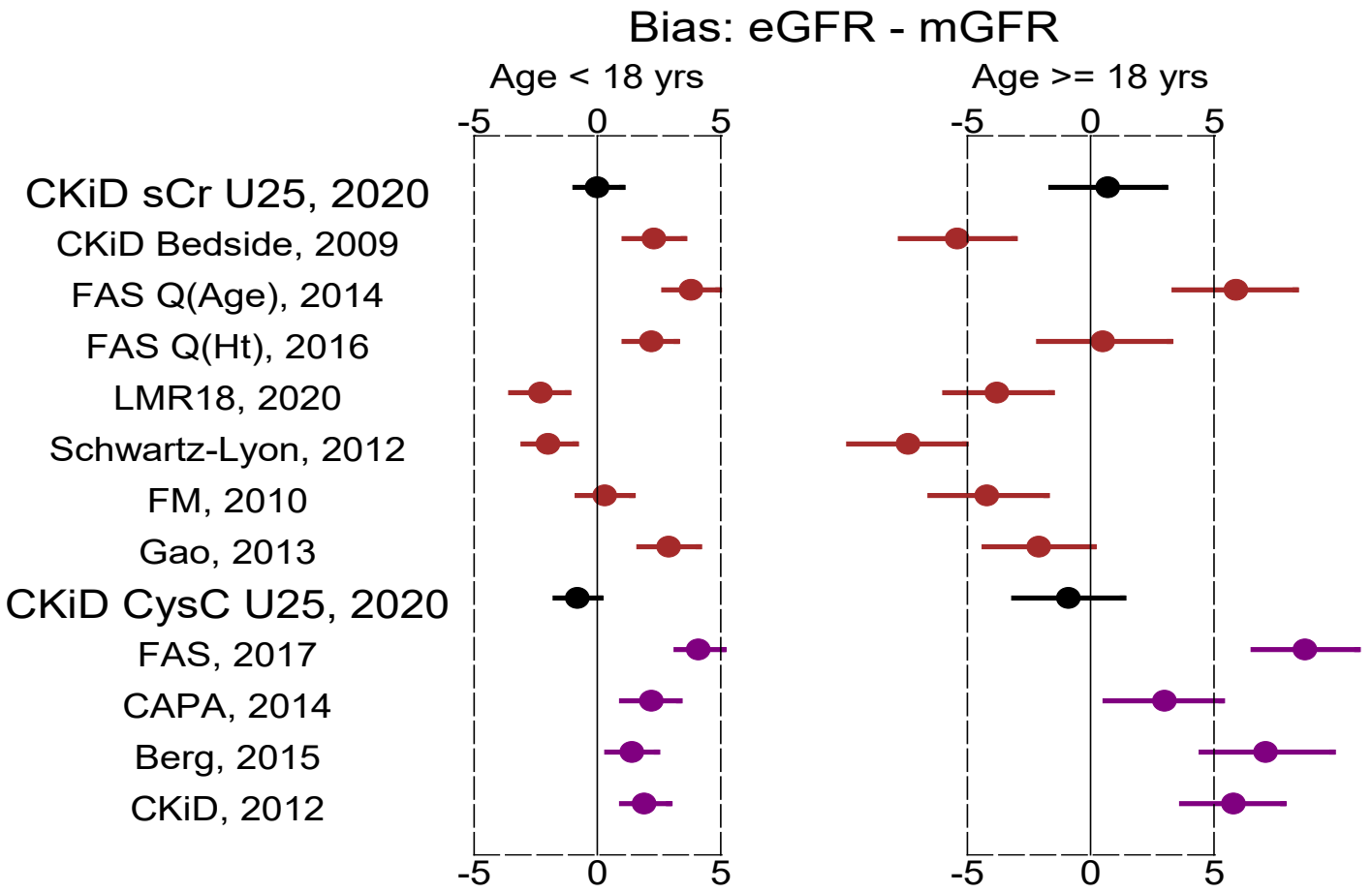
Iohexol GFR compared with U25-based Cr-GFR (L) and CysC (R)





Pierce et al, KI 2021

Absolute bias (eGFR-mGFR) for CKiD U25 sex- and age-dependent eGFR and 11 other published equations for children and young adults in validation data (891 obs. from 310 participants)



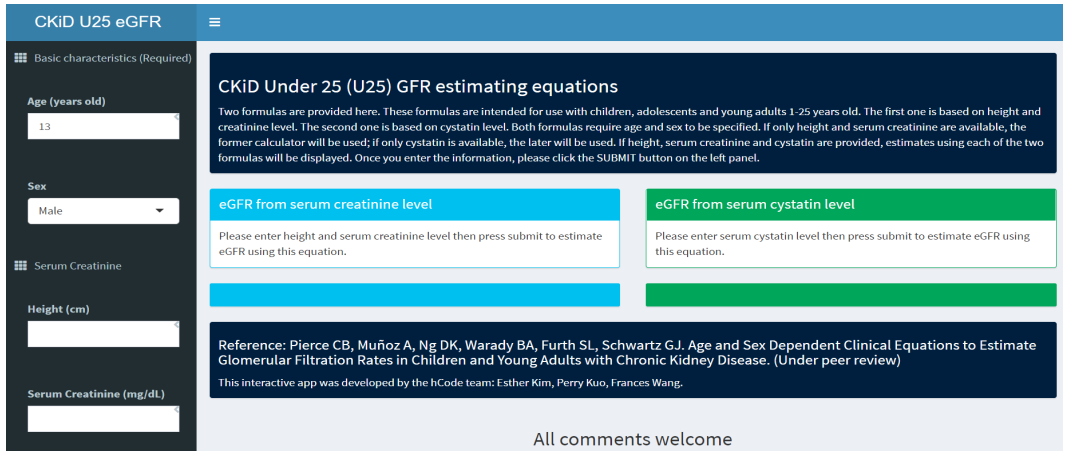
Brown for Ht/sCr
Purple for CysC

Pierce et al, KI 2021

Conclusions

- CKiD has provided simple formulas to estimate GFR by multiplying ht/sCr or the reciprocal of CysC by sex and age dependent constants from 1 to 25 years of age
- Estimates are continuous on age; no jumps.
  - U25 eGFR average based on Scr and CysC is more accurate and precise than either eGFR alone
- A calculator is available online and by mobile app (QxMD)

https://ckid-gfrcalculator.shinyapps.io/eGFR/



Examination of CKiD population using other eGFRs

Munoz, Roem, and Schwartz

- Apply U25, CKD-EPI, and EFKC to 105 studies from >= 18 years
- External validation of U25 in Normal Children (Nyman AJKD 2022)
- Analysis of Discordant cases of U25scr and UK25cysC eGFRs

U25, CKDEPI and EKFC on 105 studies from 69 children while they were >= 18 years (part of the testing data in Pierce, Muñoz, Ng, Warady, Furth, Schwartz. KI 2021)

- CKiD population with mild-moderate CKD, 38% female, 19% black

	Creatinine			Cystatin C			Combined		
	U25	**CKD-EPI**	**EKFC**	**U25**	**CKD-EPI**	**EKFC**	**U25**	**CKD-EPI**	**EKFC**
Bias ml/min	0.7	8.1	0.5	-0.9	3.6	4.8	-0.2	3.9	2.5
P10 %	46	32	44	46	37	31	52	44	51
P30 %	91	73	87	86	83	80	88	88	90
RMSE	9.7	13.6	9.5	10.8	13.4	12.2	8.5	10.8	8.9

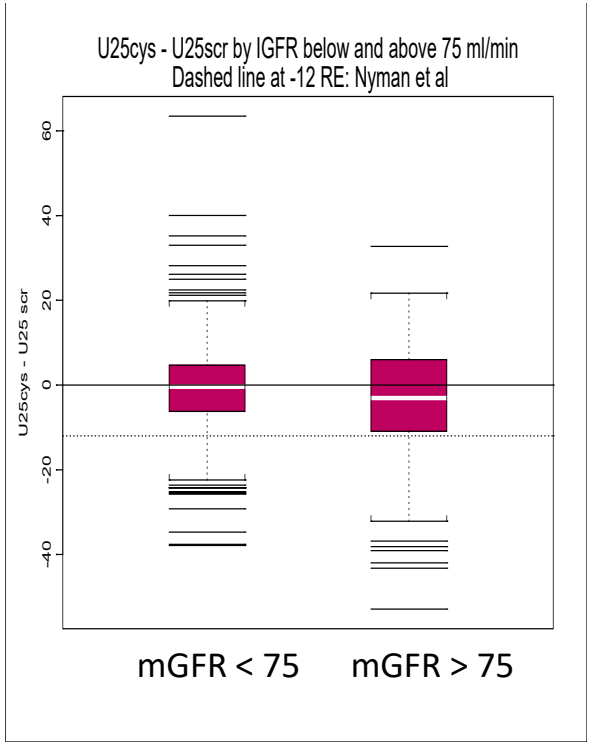
Summary

- **U25 outperformed CKDEPI and EKFC in testing data for measurements taken while children were 18 years of age or older. Specifically,**
  - **CKDEPI was upwardly biased and it overdispersed the iGFRs**
  - **EKFCscr had very good agreement with iGFR but it was slightly less accurate than U25scr**
  - **EKFCcys persistently overestimates the iGFRs by close to 5 ml/min.**
  - **The joint creatinine & cystatin equations for both CKDEPI and EKFC were upwardly biased.**
- **EKFC was closer to U25 than CKDEPI.**
- **The EKFC equations were not reproduced by the CKiD data and contrary to EKFC equations, they did not agree with each other.**

EXTERNAL VALIDATION OF U25 IN NORMAL CHILDREN:

The Modified CKiD Study Estimated GFR Equations for Children and Young Adults Under 25 Years of Age: Performance in a European Multicenter Cohort (Nyman, et al AJKD 2022)

	2 to <18		18 to 25	
N	2293		1816	
Median Age	12		20	
Median Creatinine	0.59		0.85	
Median CysC	0.96		0.96	
Median mGFR corr	97		92	
Median U25-mGFR	U25-Cr 1.3	U25-CysC -12.8	U25-Cr 2.1	U25-CysC -11.5
U25 within 30%	84%	83%	83%	84%



Conclusions/Comments

- **U25scr does very well in European children and young adults with normal GFRs**
- **U25cys underestimates normal GFRs but P_{30} is high because bias of -12 ml/min is 42% of the 30% of normal GFRs (= 28.5= 30% of 95 ml/min)**
- **In testing data set of U25 paper, it is the case that U25cys < U25scr for those with iGFR > 75 ml/min.**
- **CKiD ought to characterize the pitfalls of U25cys among those with high GFRs (i.e., capitalizing on good performance of U25scr for high GFRs, carry out iohexol studies on those with U25scr > 60 ml/min).**

CKiD ANALYSES OF DISCREPANT CASES OF U25scr and U25cys

Discrepancy Type	Magnitude	N	eGFR – iohexolGFR, mean ± SD U25scr	U25CysC	U25average
U25scr > U25cysC	>30%	312	+11.53 ± 11.84	-8.66 ± 10.73	+1.44 ± 10.19
U25cycC > U25scr	>30%	330	-7.45 ± 9.96	+8.66 ± 13.95	+0.60 ± 10.62
U25scr > U25cysC	>20% & <= 30%	218	+5.93 ± 9.11	-5.78 ± 9.17	+0.08 ± 8.88
U25cycC > U25scr	>20% & <= 30%	208	-4.71 ± 7.70	+4.82 ± 7.69	+0.06 ± 7.36
U25scr > U25cysC	>10% & <= 20%	407	+3.24 ± 8.75	-3.87 ± 9.10	-0.32 ± 8.80
U25cycC > U25scr	>10% & <= 20%	298	-4.67 ± 8.92	+1.99 ± 8.61	-1.34 ± 8.62
	within 10%	948	-0.63 ± 8.96	-0.72 ± 8.88	-0.67 ± 8.80

Summary: The average is an unbiased estimate of iohexol GFR even in the presence of discrepant results between the single-marker based U25 estimates.

Application of GFR estimating equations to children with normal, near-normal or discordant GFRs

Andrew L Schwaderer Paula Maier , Larry A. Greenbaum , Susan L. Furth , and George J Schwartz

Pediatric Nephrolology, December 2023

Table 1. Participant characteristics

	AGE	SEX	HT	WT	BMI	BSA	BUN	CREAT	CYS C
Mean	14.8	55% male	162.9	66.0	23.8	1.7	16.1	0.83	0.89
SD	3.6		18.7	28.7	7.1	0.5	6.6	0.25	0.2

N=29 iohexol plasma disappearance studies in children with CKD 1-2 with Cr- and CysC-based estimates

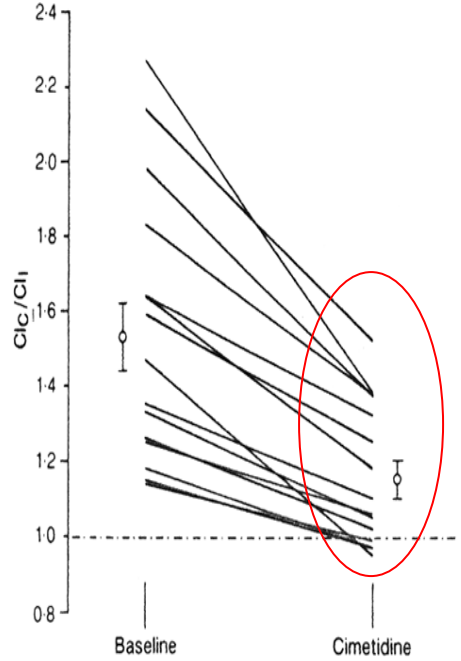
Cr-eGFR vs. CysC eGFR, application to discordant values

Discrepancy	n	Best GFR estimate
Cr-eGFR = CysC-eGFR	7	FAS-combined, U25-cysC, U25-combined
Cr-eGFR > CysC-eGFR by 15 ml/min	8	U25-cr, FAS-combined, U25-combined
CysC-eGFR > Cr-eGFR by 15 ml/min	14	U25-combined

Clearly, more studies of these biomarkers in estimating GFR must be performed in infants, children, and adolescents with near normal or normal kidney function

Limitations of Cr-eGFR

- Critical illness (ICU)
- Cr assay
- Rapidly changing Scr
- Body habitus: muscle wasting or
  weight training
- Nephrotic syndrome
  (↑ Cr secretion)



- So, if eGFR from Scr does not make sense:
  - Obtain eGFR from Cystatin C (10-20% agreement): take average
  - Perform classical clearance measurement via Cimetidine creatinine clearance (Van Acker Lancet 340:1326, 1992)
  - Iohexol or iothalamate mGFR

Questions?

MEDICINE *of* THE HIGHEST ORDER