Glomerular Filtration Rate

Estimations and Measurements

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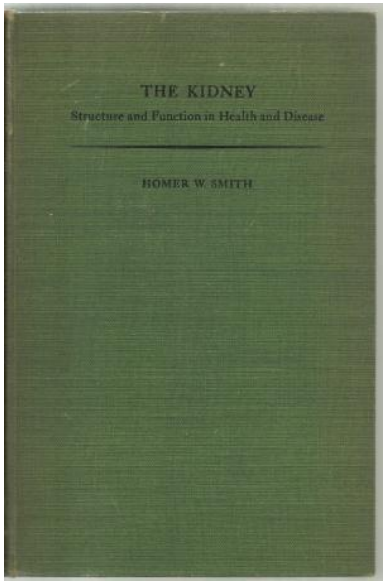
Summary

- Estimating GFR (creatinine, eGFR, cystatin C)
- USI
- Measuring GFR

The Glomerular Filtration Rate is usually the best parameter to assess the global kidney function.

So, how to measure (or estimate GFR)?



Renal function: concept of clearance

- Clearance of a solute (ml/min):

  volume of plasma cleared (« purified ») of this substance per time

  $$Cl = [U] \times [V] / [P]$$

- Ideal marker for GFR:
  - Constant production
  - No effect on GFR, non toxic
  - Not bound to protein, freely filtrated through glomerulus
  - No secretion, no absorption in the tubules
  - No extra renal clearance
  - Easy to measure, not too costly

Serum creatinine

- One of the most prescribed analyte in clinical chemistry
- …but the most important is to know its limitations
- Physiological limitations
- Analytical limitations

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Measurements of serum creatinine

- Jaffe methods
- Enzymatic methods
- Jaffe and enzymatic methods gives slightly different results

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Analytical limitations

- Jaffe: Pseudochromogen: glucose, fructose, ascorbate, proteins, urate, acetoacetate, acetone, pyruvate => false « high »
- Bilirubins: false « low »
- Few (fewer) interferences with enzymatic methods

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Analytical limitations

- Different Jaffe-Enzymatic methods, different calibration by different manufacturers

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Physiological limitations

- Production (relatively) constant but muscular production => serum creatinine is dependent of muscualr mass, not only GFR
    - gender
    - age
    - ethnicity
    - Muscular mass(creatine)
- Extra-renal production (bacterial)

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Physiological limitations

Tubular secretion of creatinine

- 10 to 40%
- Increase with decreased GFR
- Unpredictable at the individual level !

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

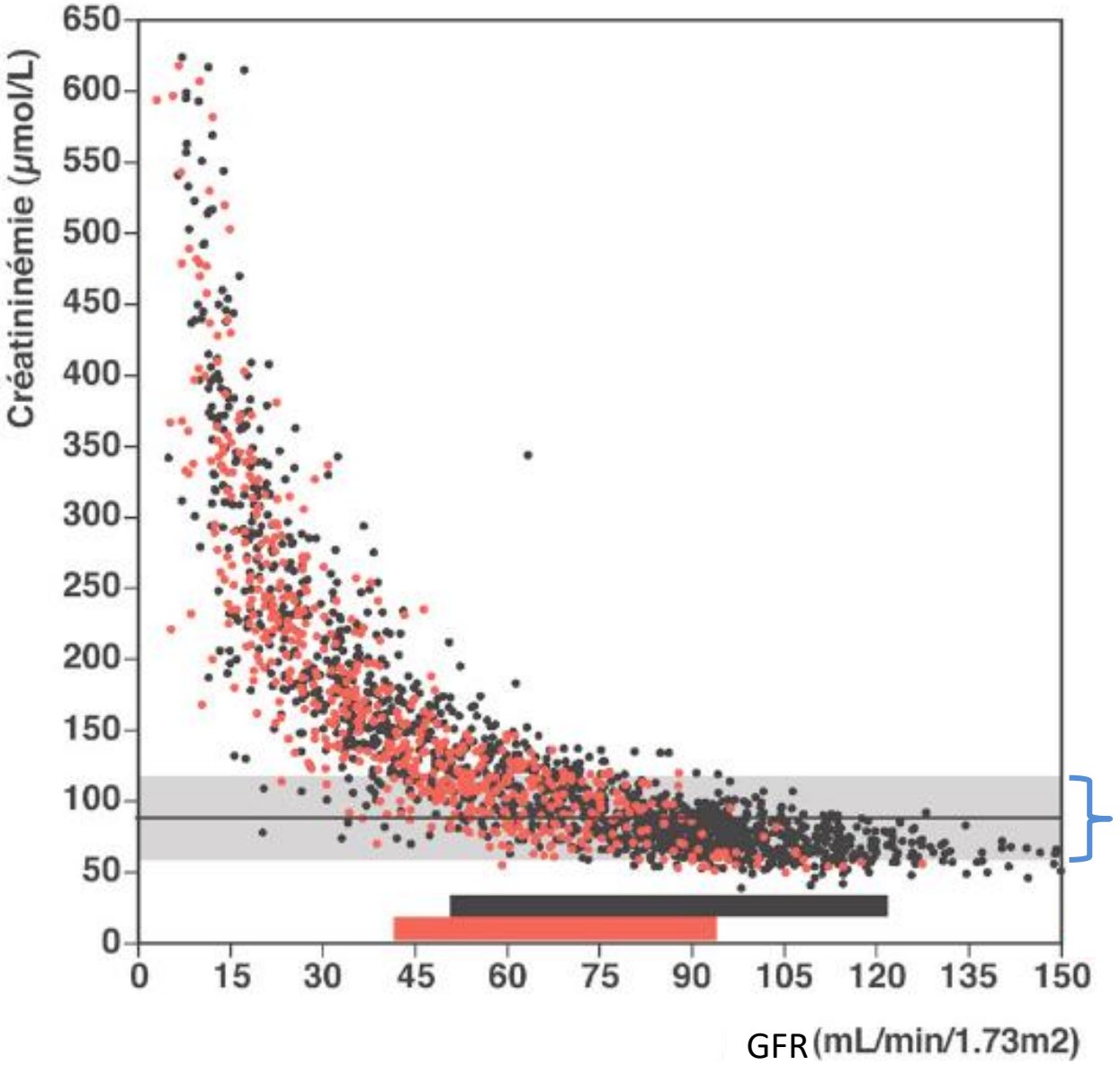
Drugs interaction with creatinine

- tubular secretion inhibitor
  cimetidin, trimethoprim, dolutegravir
- fibrates
- « high concentrations » interactions
  acetylcystein, dobutamin, lidocain, ascorbate

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531
Delanaye P, Nephron Clin Pract, 2011, 119, c187

Creatinine: to the trash?

- Very cheap (0.04€ /Jaffe)
- Good specificty
- Good analytical CV
- Favor for enzymatic methods



NephroTest Cohort (France)
Which GFR for patients with serum creatinine measured at 80 µmol/L (0.9 mg/dL)?

IC 95% for subjects<65 years old
IC 95% for subjects>65 years old

S. Creatinine lab normality range

With the kind permission of Marc Froissart

Serum Creatinine

- Exponential relationship between serum creatinine and GFR!!!

  In a given patient,

  if serum creatinine increased from 0.6 to 1.2 mg/dl
  => decrease in GFR of 50%

  if serum creatinine increased from 2.0 to 3.0 mg/dl
  => decrease in GFR of 25%

Creatinine clearance

- Not recommended by guidelines
- Creatinine tubular secretion
- Lack of precision:

errors in urine collection

22 to 27% for « trained » patients
50 to 70 % for others

large intra-individual variability for creatinine excretion

KDIGO, Kidney Int, 2012, 3
Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Creatinine clearance

- The Cockcroft original study
- Final sample n=236
- But the starting sample was 534 with 2 available creatinine clearance in medical wards
- Exclusion of 56% (!) because :

1. Variability of serum creatinine > 20%: n=29
2. Creatinine excretion/24 h < 10 mg/d: n=31
3. Inadequate (?) data: n=65
4. Variability of creatinine excretion > 20%: n=173 (32%)

Cockcroft DW, Nephron, 1976, 16, p31

Creatinine-based equations

- MDRD, Cockcroft
- CKD-EPI
- Others (FAS, Lund-Malmö)
- Other biomarkers (Cystatin)

Table 1. MDRD study equations and Cockcroft equation commonly used for GFR estimation

Cockcroft and Gault

$$\text{GFR (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{7.2 \times \text{SCr (mg/dl)}} \times 0.85 \text{ if woman}$$

4-Variable MDRD study equation (IDMS traceable)

$$\text{GFR (ml/min/1.73 m}^2) = 175 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if woman)} \times 1.21 \text{ for Black-American}$$

Cockcroft DW, Nephron, 1976, 16, p31
Levey AS, Ann Intern Med, 1999, 130, p461

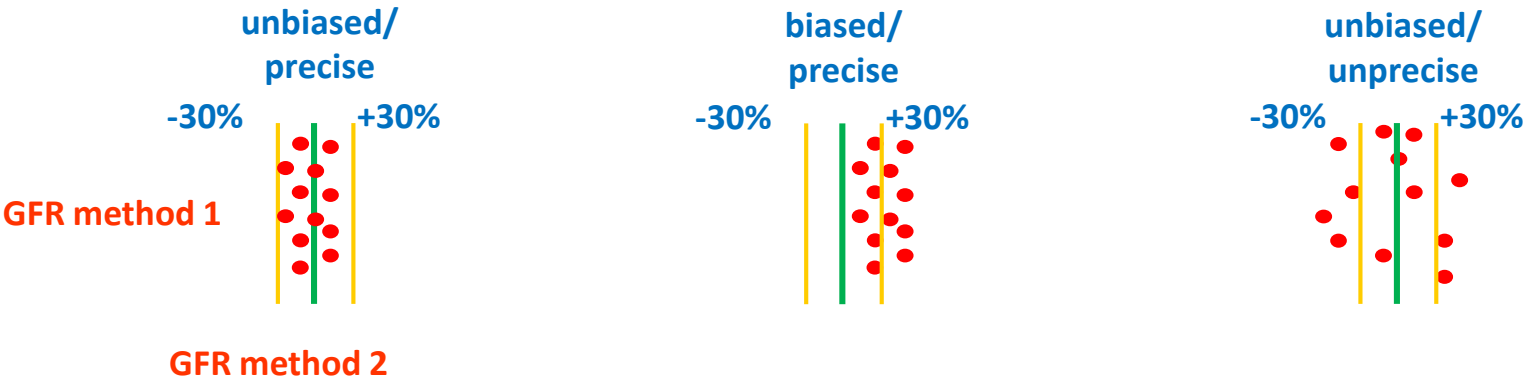
Cockcroft versus MDRD

	Cockcroft	MDRD
Population	Canada 1976	USA 1999
N	249	1628
Mean GFR	73	40
Measured GFR	Creatinine Clearance	Iothalamate
Assay	Jaffe	Jaffe
% women	4	40
% black	0 (?)	12
Mean age	18-92	51
Mean weight	72	79.6
Indexation for BSA	No	yes
Internal validation	no	yes

Cockcroft DW, Nephron, 1976, 16, p31
Levey AS, Ann Intern Med, 1999, 130, p461

Statistics

- Good correlation: a *"sine qua non"* condition but insufficient
- Bias: mean difference between two values = the systematic error
- Precision: SD around the bias = the random error
- Accuracy 30% = % of eGFR between ± 30% of measured GFR



Predictive Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations for Estimating Renal Function

Marc Froissart,*†§ Jerome Rossert,†‖ Christian Jacquot,‡§ Michel Paillard,*†§ and Pascal Houillier*†§

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Recent recommendations emphasize the need to assess kidney function using creatinine-based predictive equations to optimize the care of patients with chronic kidney disease. The most widely used equations are the Cockcroft-Gault (CG) and the simplified Modification of Diet in Renal Disease (MDRD) formulas. However, they still need to be validated in large samples of subjects, including large non-U.S. cohorts. Renal clearance of ^{51}Cr-EDTA was compared with GFR estimated using either the CG equation or the MDRD formula in a cohort of 2095 adult Europeans (863 female and 1232 male; median age, 53.2 yr; median measured GFR, 59.8 ml/min per 1.73 m^2). When the entire study population was considered, the CG and MDRD equations showed very limited bias. They overestimated measured GFR by 1.94 ml/min per 1.73 m^2 and underestimated it by 0.99 ml/min per 1.73 m^2, respectively. However, analysis of subgroups defined by age, gender, body mass index, and GFR level showed that the biases of the two formulas could be much larger in selected populations. Furthermore, analysis of the SD of the mean difference between estimated and measured GFR showed that both formulas lacked precision; the CG formula was less precise than the MDRD one in most cases. In the whole study population, the SD was 15.1 and 13.5 ml/min per 1.73 m^2 for the CG and MDRD formulas, respectively. Finally, 29.2 and 32.4% of subjects were misclassified when the CG and MDRD formulas were used to categorize subjects according to the Kidney Disease Outcomes Quality Initiative chronic kidney disease classification, respectively.

J Am Soc Nephrol 16: 763–773, 2005. doi: 10.1681/ASN.2004070549

Table 3. Bias, precision, and accuracy of the MDRD and CG formulas[a]

	N	Bland and Altman (ml/min per 1.73 m^2)		Accuracy within (% of Subjects)			CRMSE (ml/min per 1.73 m^2)
		Bias	Precision	15%	30%	50%	
MDRD formula							
high GFR[b]	1044	−3.3	17.2	61.3	92.4	98.8	17.5
low GFR[c]	1051	1.3	8.5	54.8	82.9	93.3	8.6
overall	2095	−1.0	13.7	58.0	87.2	96.0	13.8
CG formula							
high GFR[b]	1044	0.4	19.4	56.1	88.0	97.4	19.4
low GFR[c]	1051	3.5	9.7	41.2	69.0	85.2	10.3
overall	2095	1.9	15.4	48.7	78.5	91.3	15.5

[a]Results obtained with these formulas were compared with GFR values obtained by measuring the renal clearance of ^{51}Cr EDTA. Bias is defined as the mean difference between estimated and measured GFR. Precision is 1 SD of bias. Accuracy was assessed by determining the percentage of subjects who did not deviate >15, 30, and 50% from measured GFR and by calculating the combined root mean square error (CRMSE).

[b]Measured GFR ≥60 ml/min per 1.73 m^2.

[c]Measured GFR <60 ml/min per 1.73 m^2.

CLINICAL EPIDEMIOLOGY www.jasn.org

Evaluation of the Modification of Diet in Renal Disease Study Equation in a Large Diverse Population

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*Tufts-New England Medical Center, Boston, Massachusetts; †Johns Hopkins University, Baltimore, Maryland; ‡University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; §University of Utah, Salt Lake City, Utah; ‖University of Illinois at Chicago, Chicago, Illinois; ¶National Institutes of Health, Phoenix, Arizona; and **Case Western Reserve University, Cleveland, Ohio

J Am Soc Nephrol 18: 2749–2757, 2007.

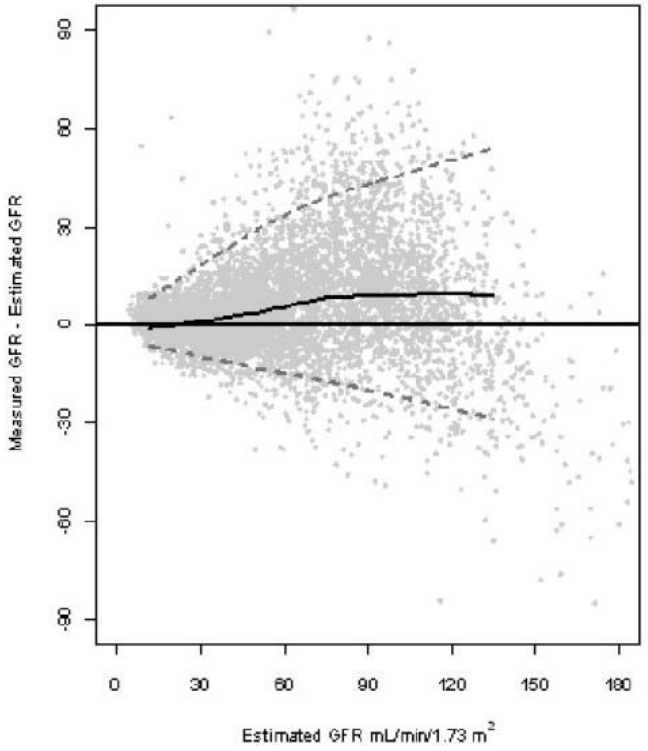


Figure 2. Difference of the MDRD Study equation by level of eGFR. Difference is calculated as (mGFR − eGFR). Solid horizontal

- Excellent accuracy, bias, precision in stage 3-4 CKD
- Best accuracy observed: 80-85%
- Better than Cockcroft especially in precision, in stage 3-4, in obese

MDRD: the limitations

- MDRD more bias (absolute) and less precision in high GFR
- Non negligible proportion of subjects with stage 2 classified as stage 3 CKD
- Trend to underestimate GFR especially in young women

MDRD: limitations = creatinine (exp -1.154)
1) analytical limitation

- MDRD study equation: Cleveland Laboratory

  Modified Kinetic Jaffe (Beckman Astra CX3)

- NHANES study :

  Modified Kinetic Jaffe (Hitachi 737)

difference of 0.23 mg/dl between two methods

(higher results with Hitachi)

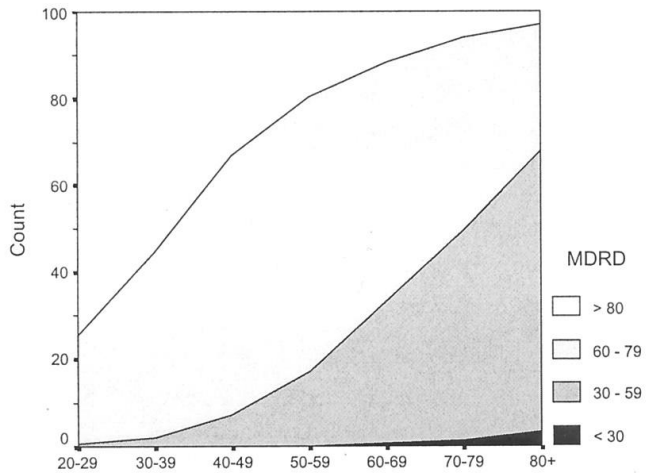
If creatinine is 1 mg/dL: difference in eGFR will be 21 ml/min/1.73m² with MDRD

If creatinine is 2 mg/dL: difference in eGFR will be 6 ml/min/1.73m² with MDRD

Coresh, J. et al. J Am Soc Nephrol 2002;13:2811-2816

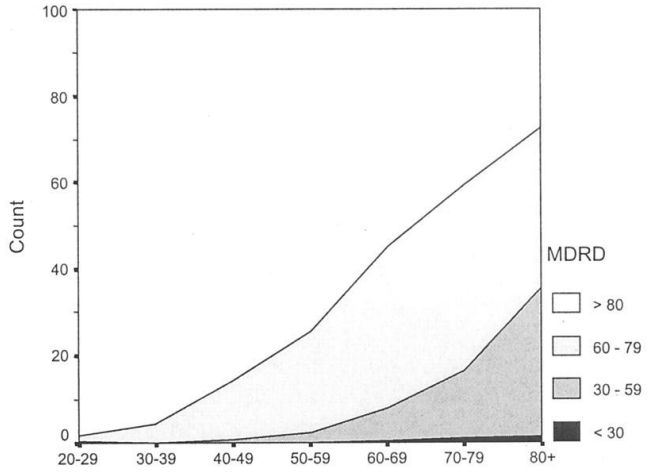
MDRD: limitations = creatinine
1) analytical limitation

UNCALIBRATED



N	3037	2827	2138	1422	1670	1241	916	Total 13251
≥ 80	74.6%	55.2%	33.0%	19.5%	11.7%	6.1%	2.8%	41.8%
60-79	24.8%	42.7%	59.7%	63.3%	54.9%	44.2%	29.4%	45.4%
30-59	0.6%	2.0%	7.2%	17.2%	32.7%	48.5%	64.6%	12.5%
< 30	<0.1%	<0.1%	<0.1%	<0.1%	0.7%	1.2%	3.2%	0.3%

CALIBRATED



3037	2827	2138	1422	1670	1241	916	Total 13251
98.3%	95.7%	85.7%	74.4%	55.1%	40.7%	27.5%	82.1%
1.5%	4.2%	13.5%	23.3%	36.9%	42.7%	37.0%	14.5%
0.2%	<0.1%	0.8%	2.4%	7.6%	15.7%	34.3%	3.2%
<0.1%	<0.1%	<0.1%	<0.1%	0.5%	0.9%	1.2%	0.2%

Coresh, J. et al. J Am Soc Nephrol 2002;13:2811-2816

IDMS traceability

A multicentric evaluation of IDMS-traceable creatinine enzymatic assays

Laurence Piéroni [a], Pierre Delanaye [b,*], Anne Boutten [c], Anne-Sophie Bargnoux [d], Eric Rozet [e], Vincent Delatour [f], Marie-Christine Carlier [g], Anne-Marie Hanser [h], Etienne Cavalier [i], Marc Froissart [j], and Jean-Paul Cristol [d]
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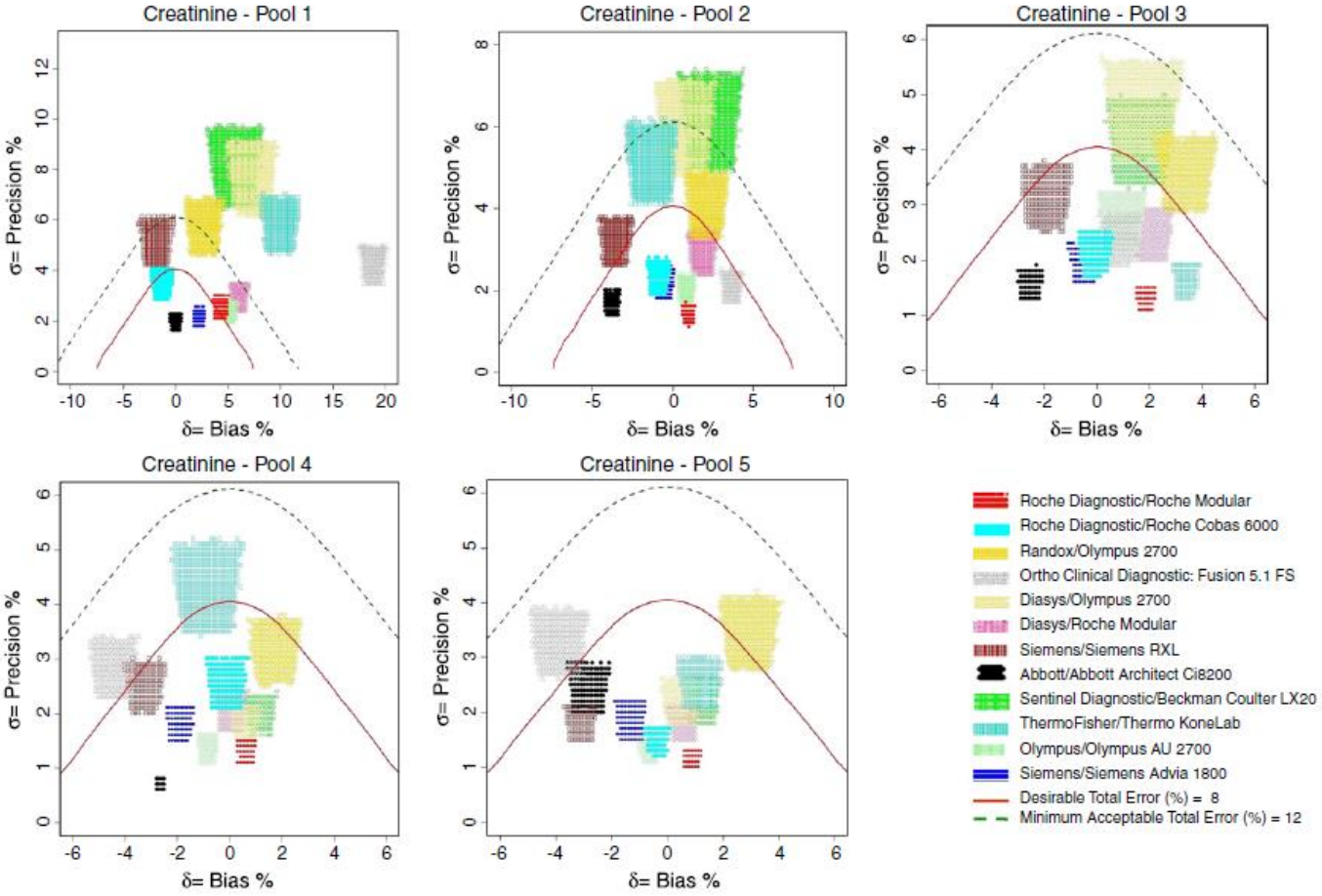
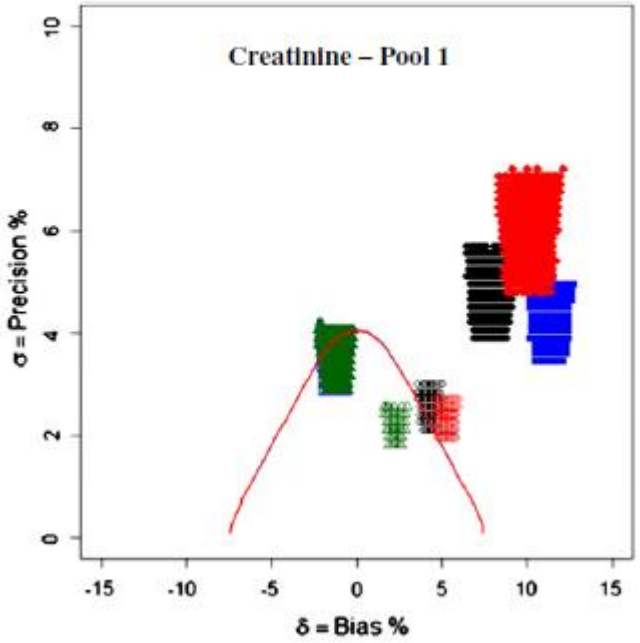
Clinica Chimica Acta 412 (2011) 2070–2075

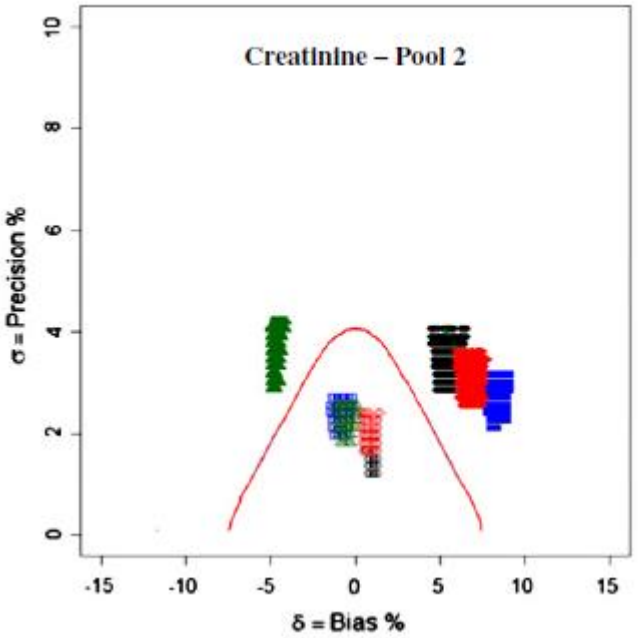
MDRD: 186 => 175

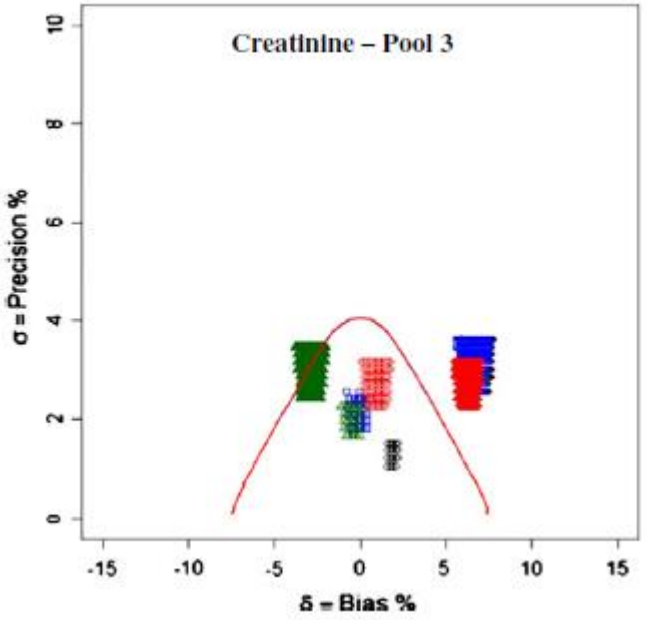
Results of GC-IDMS from LNE

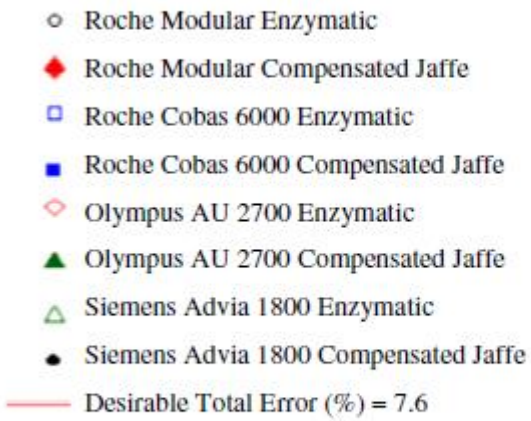
Pool 5: 174.5 +/-3.1 µmol/L
Pool 4: 149.7 +/-2.9 µmol/L
Pool 3: 97.9 +/-1.7 µmol/L
Pool 2: 74.4 +/-1.4 µmol/L
Pool 1 : 35.9 +/-0.9 µmol/L











Boutten A, Clin Chim Acta, 2013, 419, p132

MDRD: limitations = creatinine analytical limitations

CRITICAL DIFFERENCE = f(CVa, CVi)

= 19% (Jaffe)

Male, Caucasian, 60 y:

If MDRD higher than 60 ml/min/1,73m² => just use >60 mL/min/1.73 m²

Creat = 1.00 mg/dL

≈ GFR_{MDRD}=76 ml/min/1.73m²

Creatinine= 0.81 mg/dL

GFR_{MDRD}= 97 ml/min/1,73m²

Creatinine= 1.19 mg/dL

GFR_{MDRD}= 62 ml/min/1,73m²

Kuster N, Clinica Chimica Acta, 2014, 428C, 89

Delanaye P, J Nephrol, 2014, 27, 467

MDRD: limitations = creatinine clinical limitations

Specific population: MDRD is not magic!!
Keep our clinical feeling!!

Anorexia Nervosa (Delanaye P, Clin Nephrol, 2009, 71, 482)

Cirrhotic (Skluzacek PA, Am J Kidney Dis, 2003, 42, 1169)

Intensive Care (Delanaye P, BMC Nephrology, 2014, 15, 9)

Severely ill (Poggio ED, Am J Kidney Dis, 2005, 46, 242)

Heart transplanted (Delanaye P, Clin Transplant, 2006, 20, 596)

Kidney transplantation (Masson I, Transplantation, 2013, 95, 1211)

Obese (Bouquegneau A, NDT, 2013, 28, iv122)

Elderly (Schaeffner E, Ann Intern Med, 2012, 157, 471)

The new CKD-EPI equation

ARTICLE | Annals of Internal Medicine

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, MD, PhD, MHS, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)*

Ann Intern Med. 2009;150:604-612.

Table 2. The CKD-EPI Equation for Estimating GFR on the Natural Scale*

Race and Sex	Serum Creatinine Level, *μmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

- CKD-EPI
- Development dataset: n=5504
- Internal validation: n=2750
- External validation: n=3896
- Creatinine calibrated
- Median GFR in the development = 68 mL/min/1.73 m^2

Figure. Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.

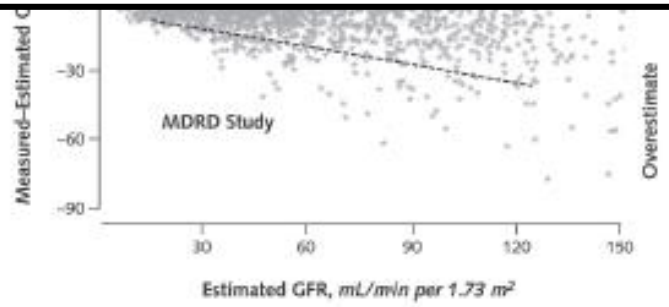


Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

Variable and Equation	All Patients	Patients With Estimated GFR <60 mL/min per 1.73 m²	Patients With Estimated GFR ≥60 mL/min per 1.73 m²
Median difference (95% CI), *mL/min per 1.73 m²*†			
CKD-EPI	2.5 (2.1–2.9)	2.1 (1.7–2.4)	3.5 (2.6–4.5)
MDRD Study	5.5 (5.0–5.9)	3.4 (2.9–4.0)	10.6 (9.8–11.3)
Interquartile range for differences (95% CI), *mL/min per 1.73 m²*‡			
CKD-EPI	16.6 (15.9–17.3)	11.3 (10.7–12.1)	24.2 (22.8–25.3)
MDRD Study	18.3 (17.4–19.3)	12.9 (12.0–13.6)	25.7 (24.4–27.1)
P_{30} (95% CI), %§			
CKD-EPI	84.1 (83.0–85.3)	79.9 (78.1–81.7)	88.3 (86.9–89.7)
MDRD Study	80.6 (79.5–82.0)	77.2 (75.5–79.0)	84.7 (83.0–86.3)
Root mean square error (95% CI)			
CKD-EPI	0.250 (0.241–0.259)	0.284 (0.270–0.298)	0.213 (0.203–0.223)
MDRD Study	0.274 (0.265–0.283)	0.294 (0.280–0.308)	0.248 (0.238–0.258)

Papers in Press. Published October 18, 2017 as doi:10.1373/clinchem.2017.276683
The latest version is at http://hwmaint.clinchem.aaccjnls.org/cgi/doi/10.1373/clinchem.2017.276683

Clinical Chemistry 64:3
000–000 (2018)

Reviews

Systematic Review and Metaanalysis Comparing the Bias and Accuracy of the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration Equations in Community-Based Populations

Emily C. McFadden,[1] Jennifer A. Hirst,[1] Jan Y. Verbakel,[1] Julie H. McLellan J,[1] F.D. Richard Hobbs,[1,3] Richard J. Stevens,[1] Chris A. O'Callaghan,[2,3] and Daniel S. Lasserson[2,3,4*]

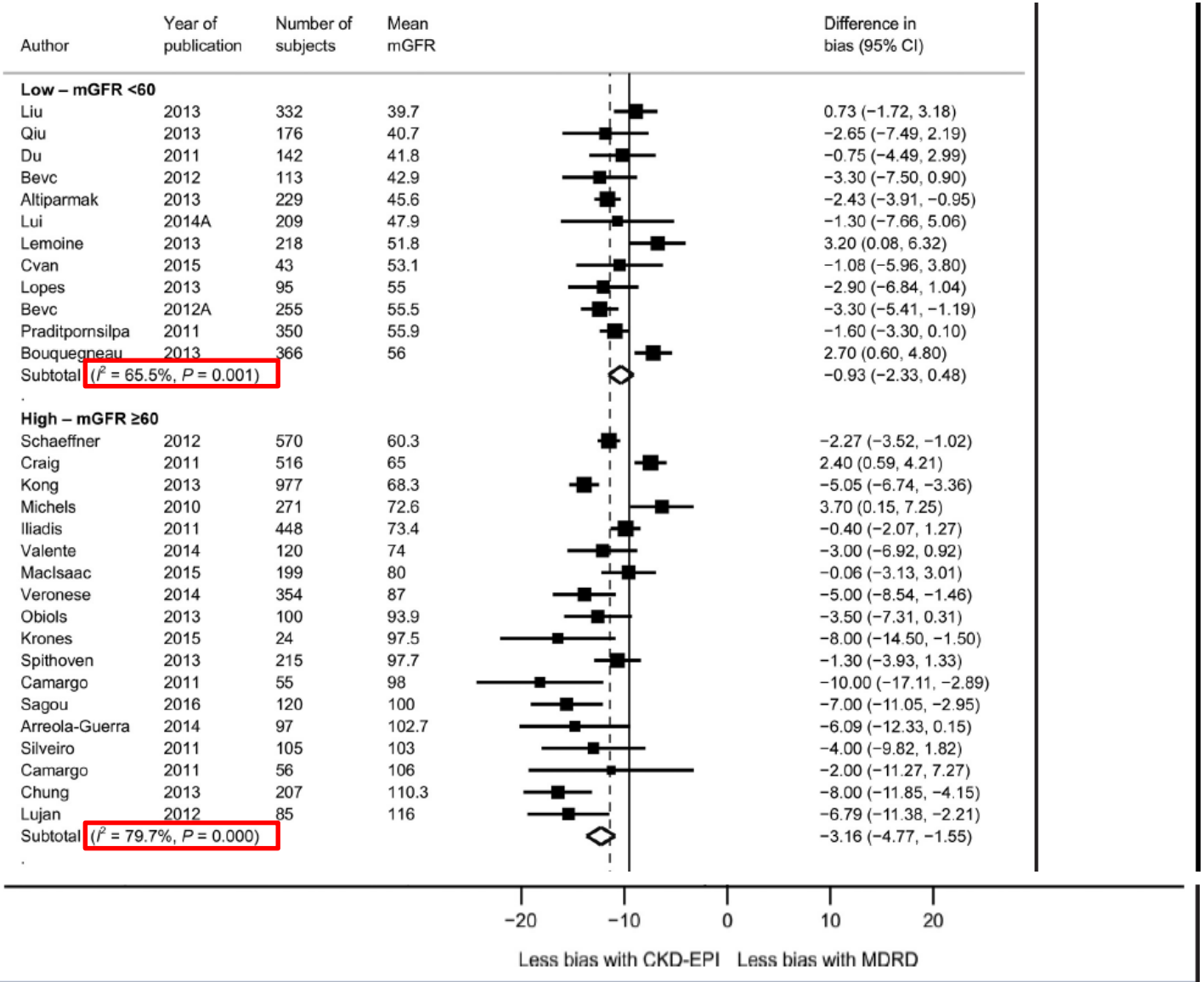


Fig. 2. Difference in mean bias from CKD-EPI and mean bias from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random-effects metaanalysis.

Horizontal bars and diamond width denote 95% CIs, and box sizes indicate relative weight in the analysis.

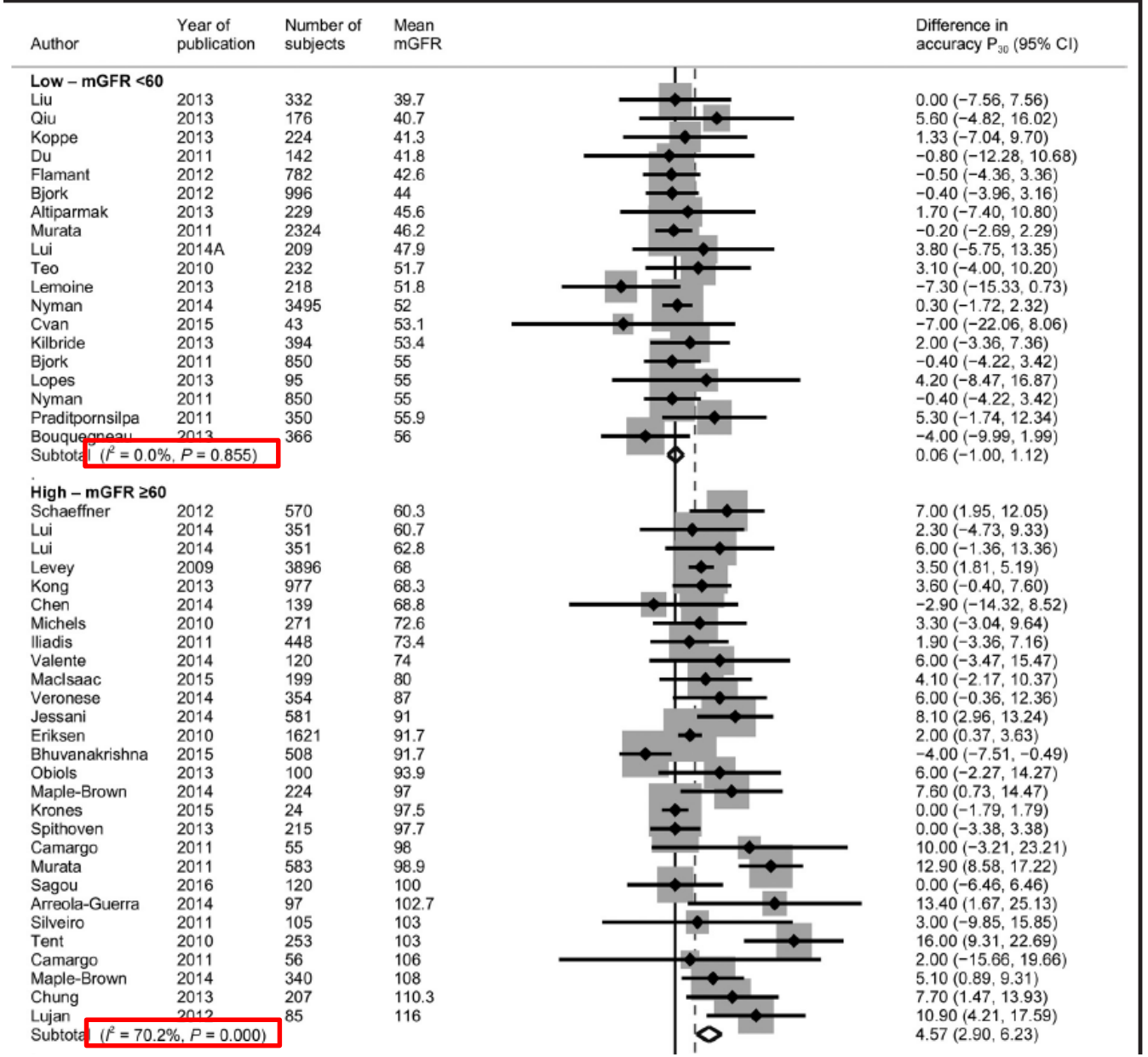


Fig. 4. Difference in mean accuracy from CKD-EPI and mean accuracy from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random-effects metaanalysis. P_{30}, proportion of eGFR results within 30% of mGFR result. Horizontal bars and diamond width denote 95% CIs, and box sizes indicate relative weight in the analysis.

Discussion:
MDRD or CKD-EPI ?

- Lower CKD prevalence in epidemiological studies
- Better prediction of CVD => better at the population level
- Better bias in GFR >60 (90?) ml/min/1.73m² but not better precision => not better at the individual level

- Ethnicity factor: probably not better
- Impact of the analytical error is less in high GFR

Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396

The price to pay…

Relative Performance of the MDRD and CKD-EPI Equations for Estimating Glomerular Filtration Rate among Patients with Varied Clinical Presentations

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Summary

Background The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed using both CKD and non-CKD patients to potentially replace the Modification of Diet in Renal Disease (MDRD) equation that was derived with only CKD patients. The objective of our study was to compare the accuracy of the MDRD and CKD-EPI equations for estimating GFR in a large group of patients having GFR measurements for diverse clinical indications.

Design, setting, participants, and measurements A cross-sectional study was conducted of patients who underwent renal function assessment for clinical purposes by simultaneous measurements of serum creatinine and estimation of GFR using the MDRD and CKD-EPI equations and renal clearance of iothalamate (n = 5238).

Results Bias compared with measured GFR (mGFR) varied for each equation depending on clinical presentation. The CKD-EPI equation demonstrated less bias than the MDRD equation in potential kidney donors (−8% *versus* −18%) and postnephrectomy donors (−7% *versus* −15%). However, the CKD-EPI equation was slightly more biased than the MDRD equation in native CKD patients (6% *versus* 3%), kidney recipients (8% *versus* 1%), and other organ recipients (9% *versus* 3%). Among potential kidney donors, the CKD-EPI equation had higher specificity than the MDRD equation for detecting an mGFR <60 ml/min per 1.73 m^2 (98% *versus* 94%) but lower sensitivity (50% *versus* 70%).

Conclusions Clinical presentation influences the estimation of GFR from serum creatinine, and neither the CKD-EPI nor MDRD equation account for this. Use of the CKD-EPI equation misclassifies fewer low-risk patients as having reduced mGFR, although it is also less sensitive for detecting mGFR below specific threshold values used to define CKD stages.

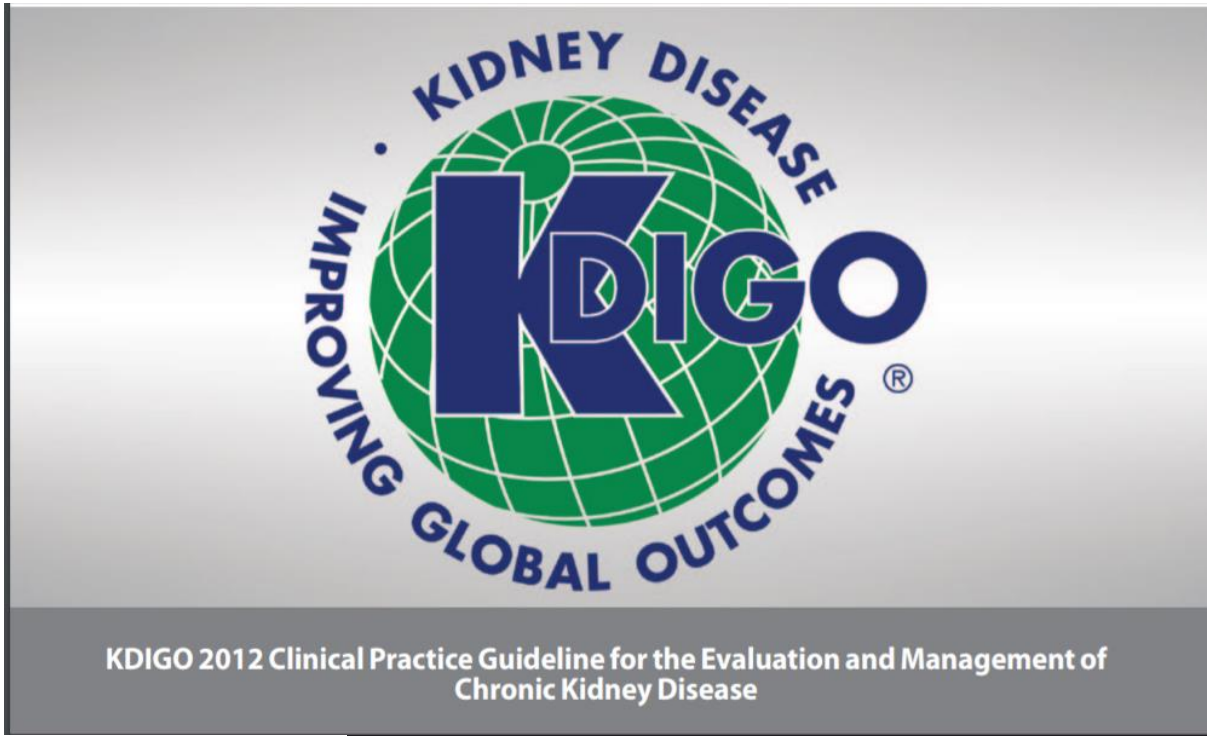
Clin J Am Soc Nephrol 6: 1963–1972, 2011. doi: 10.2215/CJN.02300311

The price to pay…

- What would be your choice?

Better estimate the GFR of a *subject* with measured GFR between 90 and 120 mL/min/1.73 m^2?

Better estimate the GFR of a *patient* with measured GFR between 30 and 60 mL/min/1.73 m^2?



Kidney International Supplements (2013) **3,** 3; doi:10.1038/kisup.2012.75

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- report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.

CKD-EPI: limitations = creatinine clinical limitations

Specific population: CKD-EPI is not magic!!
Keep our clinical feeling!!

Anorexia Nervosa (Delanaye P, Clin Nephrol, 2009, 71, 482)

Cirrhotic (Skluzacek PA, Am J Kidney Dis, 2003, 42, 1169)

Intensive Care (Delanaye P, BMC Nephrology, 2014, 15, 9)

Severely ill (Poggio ED, Am J Kidney Dis, 2005, 46, 242)

Heart transplanted (Delanaye P, Clin Transplant, 2006, 20, 596)

Kidney transplantation (Masson I, Transplantation, 2013, 95, 1211)

Obese (Bouquegneau A, NDT, 2013, 28, iv122)

Elderly (Schaeffner E, Ann Intern Med, 2012, 157, 471)

MDRD – CKD-EPI: nothing else?

- The Bis Equation
- The Lund-Malmö equation
- The FAS equation
- Other biomarkers: cystatin C

Schaeffner, Ann intern Med, 2012, 157, 471
Bjork, Scand J Urol Nephrol, 2012, 46, 212
Pottel H, Nephrol Dial Transplant, 2016
Seronie-Vivien, CCLM, 2008

Ulf Nyman*, Anders Grubb, Anders Larsson, Lars-Olof Hansson, Mats Flodin, Gunnar Nordin, Veronica Lindström and Jonas Björk

The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population

Clin Chem Lab Med 2014, 52(6), 815-824

Revised Lund-Malmö Study equation (LM Revised) [34]

$$e^{X-0.0158\times Age+0.438\times \ln(Age)}$$

Female	pCr<150 µmol/L:	$X=2.50+0.0121\times(150-pCr)$
Female	pCr≥150 µmol/L:	$X=2.50-0.926\times\ln(pCr/150)$
Male	pCr<180 µmol/L:	$X=2.56+0.00968\times(180-pCr)$
Male	pCr≥180 µmol/L:	$X=2.56-0.926\times\ln(pCr/180)$

- Lund-Malmo study
- n=3495 (chez 2847 sujets), iohexol, standardized creatinine
- Mean GFR = 52 mL/min/1,73 m²

Nephrol Dial Transplant (2016) 31: 798–806
doi: 10.1093/ndt/gfv454
Advance Access publication 29 February 2016

An estimated glomerular filtration rate equation for the full age spectrum

Hans Pottel[1], Liesbeth Hoste[1], Laurence Dubourg[2], Natalie Ebert[3], Elke Schaeffner[3], Bjørn Odvar Eriksen[4], Toralf Melsom[4], Edmund J. Lamb[5], Andrew D. Rule[6], Stephen T. Turner[6], Richard J. Glassock[7], Vandréa De Souza[8], Luciano Selistre[9], Christophe Mariat[10], Frank Martens[11] and Pierre Delanaye[12]

Example 1: A healthy 18-year-old male with a body height (L) of 180 cm and SCr of 0.90 mg/dL:

Paediatric equation (Schwartz): $eGFR = 0.413 \times L/SCr = 0.413 \times 180/0.90 = 83$ mL/min/1.73 m^2.

Adult equation (CKD-EPI): $eGFR = 141 \times (0.90/0.90)^{-1.209} 0.993^{18} = 124$ mL/min/1.73 m^2.

+50%

N=6870, 735 children

Table 1. *Q*-values [=median serum creatinine in µmol/L (mg/dL)] for the FAS equation, according to age or height (from refs [4, 5, 10])

Age, years	Height[a], cm	*Q*[b], µmol/L (mg/dL)
Boys and girls		
1	75.0	23 (0.26)
2	87.0	26 (0.29)
3	95.5	27 (0.31)
4	102.5	30 (0.34)
5	110.0	34 (0.38)
6	116.7	36 (0.41)
7	123.5	39 (0.44)
8	129.5	41 (0.46)
9	135.0	43 (0.49)
10	140.0	45 (0.51)
11	146.0	47 (0.53)
12	152.5	50 (0.57)
13	159.0	52 (0.59)
14	165.0	54 (0.61)
Male adolescents		
15	172.0	64 (0.72)
16	176.0	69 (0.78)
17	178.0	72 (0.82)
18	179.0	75 (0.85)
19	180.0	78 (0.88)
Male adults		
≥20	≥181.5	80 (0.90)
Female adolescents		
15	164.5	57 (0.64)
16	166.0	59 (0.67)
17	166.5	61 (0.69)
18	167.0	61 (0.69)
19	167.5	62 (0.70)
Female adults		
≥20	≥168.0	62 (0.70)

[a]Height is the median height of a child or adolescent at the specified age (Belgian growth curves).

Table 3. Prediction performance results of different eGFR equations on the pooled databases according to age group and measured GFR categories (mGFR below or above 60 mL/min/1.73 m^2)

Pooled data	eGFR equivalent	RMSE (95% CI)	Constant bias (95% CI)	Proportional bias (95% CI)	P10, % (95% CI)	P30, % (95% CI)
Children and adolescents <18 years						
All (n = 735)	FAS	20.1 (18.5, 21.6)	−1.7 (−3.1, −0.2)*,†	1.01 (0.99, 1.03)*,†	40.1 (36.6, 43.7)	87.5 (85.1, 89.9)*
mGFR = 94.5	FAS-height	19.8 (18.1, 21.4)	−2.7 (−4.1, −1.3)*,‡	1.00 (0.98, 1.01)*,‡	41.9 (38.3, 45.5)	88.8 (86.6, 91.1)†
	Schwartz	21.7 (19.5, 23.7)	6.0 (4.5, 7.5)†,‡	1.09 (1.07, 1.11)†,‡	40.1 (36.6, 43.7)	83.8 (81.1, 86.5)*,†
mGFR < 60 (n = 99)	FAS	14.6 (8.5, 18.9)	6.2 (3.6, 8.9)*,†	1.15 (1.09, 1.21)*,†	34.3 (24.8, 43.9)	75.8 (67.2, 84.3)
mGFR = 45.1	FAS-height	13.5 (4.2, 18.6)	4.7 (2.2, 7.2)*,‡	1.12 (1.06, 1.17)*,‡	39.4 (25.6, 49.2)	77.8 (69.4, 86.1)*
	Schwartz	16.7 (8.2, 22.1)	9.4 (6.7, 12.2)†,‡	1.22 (1.16, 1.28)†,‡	31.3 (22.0, 40.6)	70.7 (61.6, 79.8)*
mGFR ≥ 60 (n = 636)	FAS	20.8 (19.1, 22.4)	−2.9 (−4.5, −1.3)*,†	0.99 (0.97, 1.00)*,†	41.0 (37.2, 44.9)	89.3 (86.9, 91.7)*
mGFR = 102.2	FAS-height	20.6 (18.9, 22.3)	−3.8 (−5.4, −2.3)*,‡	0.98 (0.96, 0.99)*,‡	42.3 (38.4, 46.1)	90.6 (88.3, 92.8)†
	Schwartz	22.4 (20.0, 24.5)	5.4 (3.7, 7.1)†,‡	1.07 (1.05, 1.09)†,‡	41.5 (37.7, 45.3)	85.8 (83.1, 88.6)*,†
Adults 18–70 years						
All (n = 4371)	FAS	17.2 (16.6, 17.8)	5.0 (4.5, 5.5)*	1.12 (1.11, 1.12)*	40.4 (38.9, 41.9)*	81.6 (80.4, 82.7)
mGFR = 78.6	CKD-EPI	16.4 (15.8, 16.9)	6.3 (5.9, 6.8)*	1.13 (1.12, 1.14)*	42.5 (41.1, 44.0)*	81.9 (80.7, 83.0)
mGFR < 60 (n = 1089)	FAS	19.0 (17.7, 20.2)	13.4 (12.6, 14.2)*	1.35 (1.33, 1.37)*	19.1 (16.8, 21.4)*	52.2 (49.3, 55.2)*
mGFR = 42.3	CKD-EPI	19.2 (18.1, 20.3)	12.7 (11.8, 13.5)*	1.31 (1.29, 1.34)*	21.9 (19.4, 24.3)*	55.2 (52.2, 58.1)*
mGFR ≥ 60 (n = 3282)	FAS	16.6 (15.9, 17.2)*	2.2 (1.6, 2.7)*	1.04 (1.03, 1.04)*	47.5 (45.8, 49.2)*	91.3 (90.3, 92.3)
mGFR = 90.6	CKD-EPI	15.3 (14.7, 15.8)*	4.2 (3.7, 4.7)*	1.07 (1.06, 1.07)*	49.4 (47.7, 51.1)*	90.7 (89.7, 91.7)
Older adults ≥70 years						
All (n = 1764)	FAS	11.2 (10.7, 11.7)*	−1.1 (−1.6, −0.6)*	1.02 (1.01, 1.03)*	39.7 (37.5, 42.0)*	86.1 (84.4, 87.7)*
mGFR = 55.6	CKD-EPI	12.9 (12.4, 13.4)*	5.6 (5.1, 6.2)*	1.13 (1.12, 1.15)*	35.0 (32.8, 37.3)*	77.6 (75.7, 79.6)*
	BIS1[a]	12.0 (11.4, 12.6)	−1.2 (−1.9, −0.6)	1.05 (1.03, 1.07)	34.7 (32.0, 37.4)	81.8 (79.7, 84.0)
mGFR < 60 (n = 986)	FAS	9.5 (8.8, 10.1)*	2.2 (1.6, 2.7)*	1.09 (1.07, 1.11)*	36.6 (33.6, 39.6)*	81.0 (78.6, 83.5)*
mGFR = 40.7	CKD-EPI	13.1 (12.3, 13.8)*	6.9 (6.2, 7.6)*	1.19 (1.17, 1.21)*	29.5 (26.7, 32.4)*	67.7 (64.8, 70.7)*
	BIS1[a]	9.7 (9.0, 10.3)	3.7 (3.0, 4.4)	1.16 (1.13, 1.18)	35.3 (31.8, 38.8)	75.4 (72.2, 78.5)
mGFR ≥ 60 (n = 778)	FAS	13.1 (12.3, 13.8)	−5.2 (−6.1, −4.4)*	0.94 (0.93, 0.95)*	43.7 (40.2, 47.2)	92.4 (90.6, 94.3)
mGFR = 74.4	CKD-EPI	12.7 (12.1, 13.3)	4.1 (3.2, 4.9)*	1.07 (1.06, 1.08)*	42.0 (38.6, 45.5)	90.1 (88.0, 92.2)
	BIS1[a]	14.8 (13.7, 15.7)	−8.6 (−9.7, −7.5)	0.90 (0.88, 0.91)	33.9 (29.6, 38.1)	91.5 (89.0, 94.0)

The same symbols (*,†,‡) within each subgroup and column indicate significant differences (paired t-test for constant and proportional bias, McNemar's test for P10 and P30 = % of subjects with an eGFR value within 10% and 30% of measured GFR).

[a]For the BIS1 performance results, the data (n= 570) from the BIS1 study were not included (therefore, no comparisons with FAS and CKD-EPI were made).

MDRD – CKD-EPI: nothing else?

- The Bis Equation
- The Lund-Malmö equation
- The FAS equation
- Other biomarkers: cystatin C

Schaeffner, Ann intern Med, 2012, 157, 471
Bjork, Scand J Urol Nephrol, 2012, 46, 212
Pottel H, Nephrol Dial Transplant, 2016
Seronie-Vivien, CCLM, 2008

Cystatin C

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

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N Engl J Med 2012;367:20-9.

Table 1. Characteristics of Study Participants, According to Data Set.*

Characteristic	Development and Internal Validation (N = 5352)	External Validation (N = 1119)	P Value
Age — yr	47±15	50±17	<0.001
Age group — no. (%)			
<40 yr	2008 (38)	357 (32)	<0.001
40–65 yr	2625 (49)	530 (47)	
>65 yr	719 (13)	232 (21)	
Male sex — no. (%)	3107 (58)	663 (59)	0.46
Black race — no. (%)†	2123 (40)	30 (3)	<0.001
Diabetes — no. (%)	1726 (32)	594 (53)	<0.001
Body-mass index‡			
Mean	28±6	25±4	<0.001
<20 — no. (%)	214 (4)	81 (7)	<0.001
20–24 — no. (%)	1585 (30)	503 (45)	
25–30 — no. (%)	1881 (35)	386 (35)	
>30 — no. (%)	1671 (31)	149 (13)	
Mean weight — kg	83±20	74±15	<0.001
Mean height — cm	171±10	170±9	0.017
Mean body-surface area — m^2	1.94±0.24	1.85±0.21	<0.001
Mean serum cystatin C — ml/liter	1.4±0.7	1.5±0.8	0.01
Mean serum creatinine — mg/dl§	1.6±0.9	1.6±1.1	0.15
Mean measured GFR — ml/min/1.73 m^2 of body-surface area	68±39	70±41	0.13
Measured GFR — no. (%)			
<15 ml/min/1.73 m^2	160 (3)	51 (5)	<0.001
15–29 ml/min/1.73 m^2	785 (15)	166 (15)	
30–59 ml/min/1.73 m^2	1765 (33)	316 (28)	
60–89 ml/min/1.73 m^2	1105 (21)	215 (19)	
90–119 ml/min/1.73 m^2	862 (16)	199 (18)	
>120 ml/min/1.73 m^2	675 (13)	172 (15)	

Table 2. Creatinine Equation (CKD-EPI 2009), Cystatin C Equation (CKD-EPI 2012), and Creatinine–Cystatin C Equation (CKD-EPI 2012) for Estimating GFR, Expressed for Specified Sex, Serum Creatinine Level, and Serum Cystatin C Level.*

Basis of Equation and Sex	Serum Creatinine†	Serum Cystatin C	Equation for Estimating GFR
	mg/dl	*mg/liter*	
CKD-EPI creatinine equation‡			
Female	≤0.7		$144 \times (\text{Scr}/0.7)^{-0.329} \times 0.993^{\text{Age}}$ [× 1.159 if black]
Female	>0.7		$144 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{Age}}$ [× 1.159 if black]
Male	≤0.9		$141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{Age}}$ [× 1.159 if black]
Male	>0.9		$141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{Age}}$ [× 1.159 if black]
CKD-EPI cystatin C equation§			
Female or male		≤0.8	$133 \times (\text{Scys}/0.8)^{-0.499} \times 0.996^{\text{Age}}$ [× 0.932 if female]
Female or male		>0.8	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{Age}}$ [× 0.932 if female]
CKD-EPI creatinine–cystatin C equation¶			
Female	≤0.7	≤0.8	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Female	>0.7	≤0.8	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Male	≤0.9	≤0.8	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Male	>0.9	≤0.8	$135 \times (\text{Scr}/0.9)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135 \times (\text{Scr}/0.9)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]

Table 3. Use of the CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012), and CKD-EPI Creatinine–Cystatin C Equations (2012) in the External-Validation Data Set Comprising 1119 Participants.*

Variable	Estimated GFR			
	Overall	<60	60–89	≥90
		ml/min/1.73 m² of body-surface area		
Bias — median difference (95% CI)				
Creatinine equation	3.7 (2.8 to 4.6)	1.8 (1.1 to 2.5)	6.6 (3.5 to 9.2)	11.1 (8.0 to 12.5)
Cystatin C equation	3.4 (2.3 to 4.4)	0.4 (–0.5 to 1.4)	6.0 (4.6 to 8.5)	8.5 (6.5 to 11.2)
Creatinine–cystatin C equation	3.9 (3.2 to 4.5)	1.3 (0.5 to 1.8)	6.9 (5.0 to 8.9)	10.6 (9.5 to 12.7)
Average of creatinine and cystatin C†	3.5 (2.8 to 4.1)	0.4 (–0.3 to 0.8)	6.5 (4.6 to 8.4)	11.9 (9.9 to 13.9)
Precision — IQR of the difference (95% CI)				
Creatinine equation	15.4 (14.3 to 16.5)	10.0 (8.9 to 11.0)	19.6 (17.3 to 23.2)	25.0 (21.6 to 28.1)
Cystatin C equation	16.4 (14.8 to 17.8)	11.0 (10.0 to 12.4)	19.6 (16.1 to 23.1)	22.6 (18.8 to 26.3)
Creatinine–cystatin C equation	13.4 (12.3 to 14.5)	8.1 (7.3 to 9.1)	15.9 (13.9 to 18.1)	18.8 (16.8 to 22.5)
Average of creatinine and cystatin C equations†	13.9 (12.9 to 14.7)	7.9 (7.1 to 9.0)	15.8 (13.9 to 17.7)	18.6 (16.1 to 22.2)
Accuracy — % (95% CI)‡				
$1-P_{30}$				
Creatinine equation	12.8 (10.9 to 14.7)	16.6 (13.6 to 19.7)	10.2 (6.4 to 14.2)	7.8 (5.1 to 11.0)
Cystatin C equation	14.1 (12.2 to 16.2)	21.4 (18.2 to 24.9)	12.7 (8.5 to 17.4)	2.2 (0.6 to 3.9)
Creatinine–cystatin C equation	8.5 (7.0 to 10.2)	13.3 (10.7 to 16.1)	5.3 (2.7 to 8.2)	2.3 (0.9 to 4.2)
Average of creatinine and cystatin C equations†	8.2 (6.7 to 9.9)	12.1 (9.5 to 14.8)	6.4 (3.6 to 9.7)	2.9 (1.3 to 4.9)
$1-P_{20}$				
Creatinine equation	32.9 (30.1 to 35.7)	37.2 (33.1 to 41.2)	31.1 (25.1 to 37.4)	26.5 (21.7 to 31.4)
Cystatin C equation	33.0 (30.3 to 35.7)	42.1 (38.2 to 46.1)	29.3 (23.6 to 35.4)	19.4 (15.4 to 23.7)
Creatinine–cystatin C equation	22.8 (20.4 to 25.2)	28.6 (25.1 to 32.4)	17.8 (13.3 to 22.9)	16.2 (12.4 to 20.5)
Average of creatinine and cystatin C equations†	23.7 (21.3 to 26.1)	29.1 (25.7 to 32.8)	17.6 (13.2 to 22.4)	18.8 (14.6 to 23.2)

Nephrol Dial Transplant (2017) 32: 497–507

ndt
Nephrology Dialysis Transplantation

Original Article

Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C

Hans Pottel[1], Pierre Delanaye[2], Elke Schaeffner[3], Laurence Dubourg[4], Bjørn Odvar Eriksen[5], Toralf Melsom[5], Edmund J. Lamb[6], Andrew D. Rule[7], Stephen T. Turner[7], Richard J. Glassock[8], Vandréa De Souza[9], Luciano Selistre[9,10], Karolien Goffin[11], Steven Pauwels[12,13], Christophe Mariat[14], Martin Flamant[15] and Natalie Ebert[3]

$$FAS_{cysC} = \frac{107.3}{\frac{ScysC}{Q_{cysC}}} \times \left[0.988^{(Age-40)} \text{ when age} > 40 \text{ years}\right].$$

$$FAS_{combi} = \frac{107.3}{\alpha \times \frac{Scr}{Q_{crea}} + (1-\alpha) \times \frac{ScysC}{Q_{cysC}}} \times \left[0.988^{(Age-40)} \text{ when age} > 40 \text{ years}\right].$$

Table 5. Patient characteristics in the different age groups (mean ± SD)

Group	*n*	No. of males	No. of females	mGFR	Scr	ScysC
Children ≤18 years	368	193	175	89.2 ± 30.4	0.65 ± 0.31	1.15 ± 0.42
Adults 18–70 years	4295	2301	1994	80.2 ± 25.6	1.00 ± 0.50	0.99 ± 0.51
Older adults ≥70 years	1469	771	698	58.5 ± 20.0	1.13 ± 0.52	1.24 ± 0.51
Total	6132	3265	2867			

n, number of patients; mGFR, measured glomerular filtration rate (mL/min/1.73 m^2); Scr, serum creatinine (mg/dL); ScysC, serum cystatin C (mg/L).

Comparaison créatinine/cystatine C

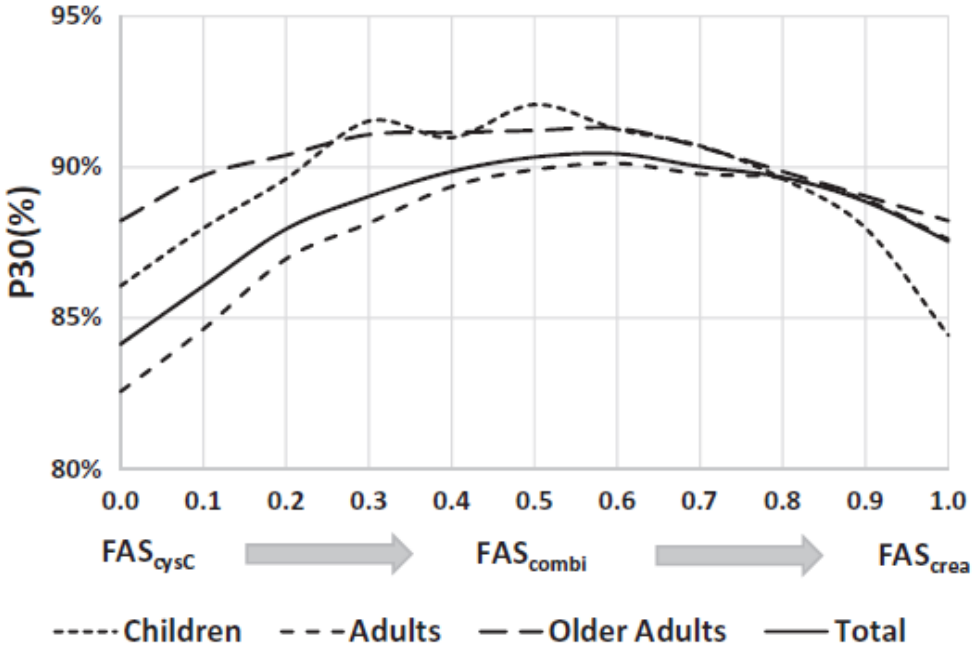


FIGURE 3: P30 as a function of the weighting factor α for the different age groups.

Cystatin C

- Combined
- Better “alone” in pediatrics and very low BMI
- Cost-effectiveness?
- At the individual level, the imprecision remains…

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

Nat. Rev. Nephrol. **9**, 513–522 (2013)

Performance of equations in specific populations

Delanaye *et al. BMC Nephrology* 2014, **15**:9
http://www.biomedcentral.com/1471-2369/15/9

BMC Nephrology

RESEARCH ARTICLE Open Access

Detection of decreased glomerular filtration rate in intensive care units: serum cystatin C *versus* serum creatinine

Pierre Delanaye[1*], Etienne Cavalier[2], Jérôme Morel[3], Manolie Mehdi[4], Nicolas Maillard[4], Guillaume Claisse[4], Bernard Lambermont[5], Bernard E Dubois[1], Pierre Damas[6], Jean-Marie Krzesinski[1], Alexandre Lautrette[7] and Christophe Mariat[4]

47 patients
hemodynamiccaly stable
Avec Scr <1,5 mg/dL
GFR measured by iohexol urinary clearance

SERUM CREATININE
R=0.5

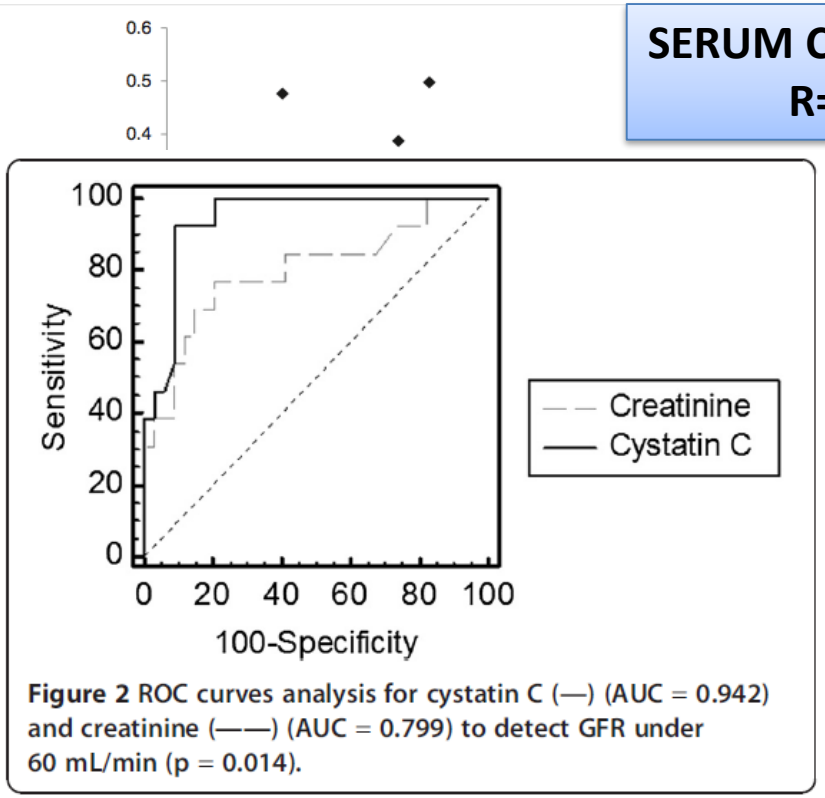


Figure 2 ROC curves analysis for cystatin C (—) (AUC = 0.942) and creatinine (——) (AUC = 0.799) to detect GFR under 60 mL/min (p = 0.014).

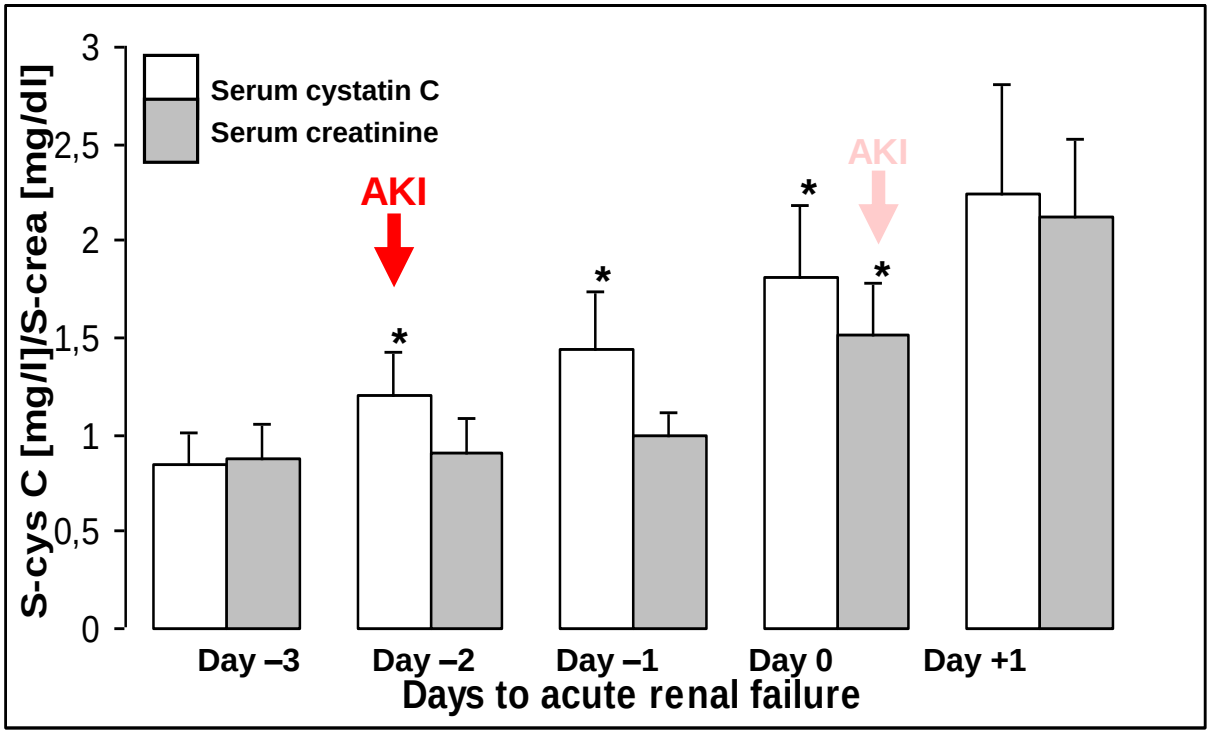
CYSTATINE
=0.7

GFR (iohexol) (mL/min)

Figure 1 Correlations between the inverse of creatinine and GFR (upper) (y = 0,09024 + 0,0009156x) and the inverse of cystatin C and GFR (lower) (y = 0,4939 + 0,004871x).

Delanaye *et al. BMC Nephrology* 2014, **15**:9

DETECTION OF AKI



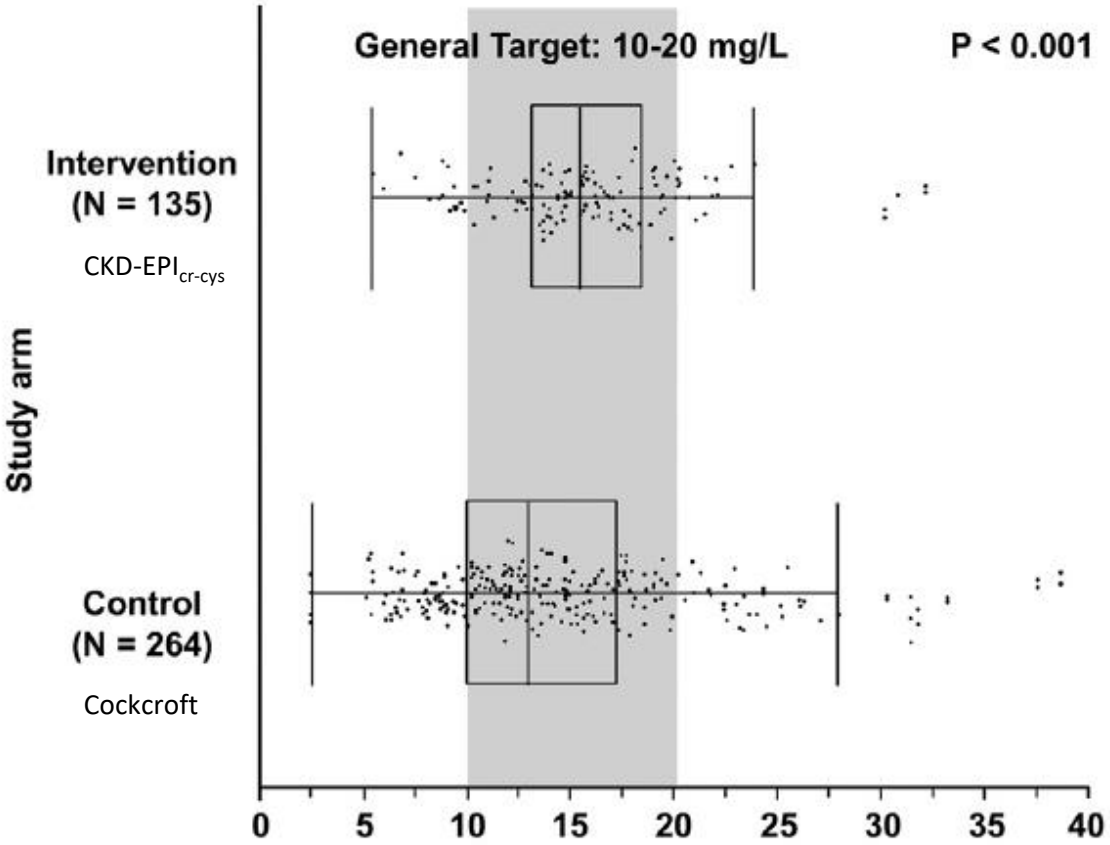
Herget-Rosenthal et al., Kidney Int 2004 85 adultes, general ICU, S-creatinine rise > 50%

AJKD Am J Kidney Dis. 2017;69(5):658-666

Original Investigation

Cystatin C–Guided Vancomycin Dosing in Critically Ill Patients: A Quality Improvement Project

Erin Frazee, PharmD, MS,[1] Andrew D. Rule, MD,[2,3] John C. Lieske, MD,[2,4] Kianoush B. Kashani, MD,[2,5] Jason N. Barreto, PharmD,[1] Abinash Virk, MD,[6] Philip J. Kuper, PharmD,[1] Ross A. Dierkhising, MS,[7] and Nelson Leung, MD[2]



Cystatin C

- Potentially of interest
- Relatively few studies
- There are also non-GFR determinants of cystatin C
- Drug dosage
- More expensive
- Cost-effectiveness not definitively proven

What about eGFR equations?

- They are valid at the equilibrium

Delanaye *et al. BMC Nephrology* 2014, **15**:9
http://www.biomedcentral.com/1471-2369/15/9

BMC Nephrology

RESEARCH ARTICLE Open Access

Detection of decreased glomerular filtration rate in intensive care units: serum cystatin C *versus* serum creatinine

Pierre Delanaye[1*], Etienne Cavalier[2], Jérôme Morel[3], Manolie Mehdi[4], Nicolas Maillard[4], Guillaume Claisse[4], Bernard Lambermont[5], Bernard E Dubois[1], Pierre Damas[6], Jean-Marie Krzesinski[1], Alexandre Lautrette[7] and Christophe Mariat[4]

Table 3 Predictive performances of the MDRD, CKD-EPI SCr, CKD-EPI SCysC, and combined equations in ICU patients

GFR estimates	Bias (mL/min)	Absolute Precision mL/min	Accuracy 30%
MDRD	+35	70	40
CKD-EPI	+ 1	37	60*
CKD-EPI Scyst	−26	36	53
CKD-EPI combined	−12	35	62

**: $p < 0.05$ versus MDRD study equation.*

SPECIAL ARTICLE www.jasn.org

Retooling the Creatinine Clearance Equation to Estimate Kinetic GFR when the Plasma Creatinine Is Changing Acutely

Sheldon Chen

Division of Nephrology and Hypertension, Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, Illinois

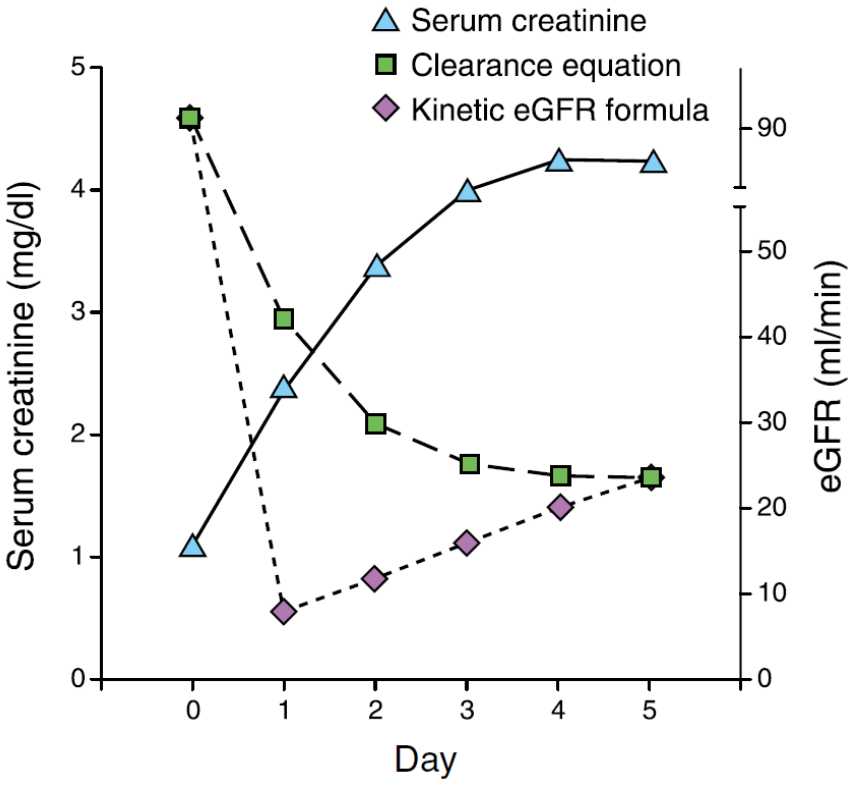
J Am Soc Nephrol 24: 877–888, 2013.

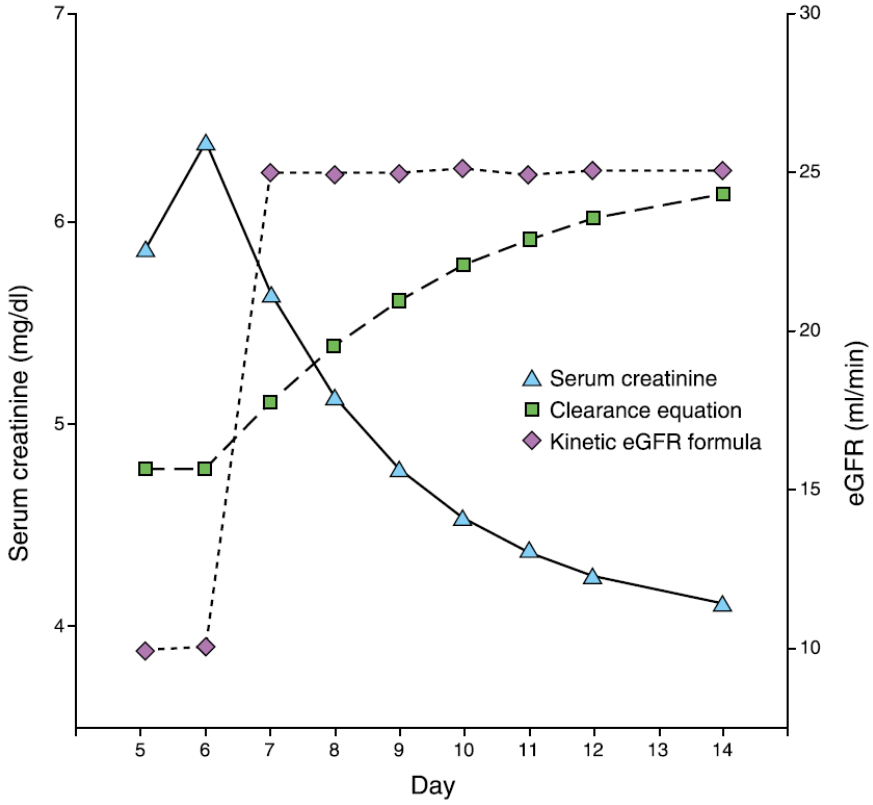
- Kinetic eGFR: to analyze kidney function in the acute setting
- Initial creatinine content, Vd, creatinine production rate and the quantitative difference between consecutive Scr over a short period of time

Kinetic GFR

$$KeGFR = \frac{SSP_{Cr} \times CrCl}{MeanP_{Cr}} \times \left(1 - \frac{24 \times \Delta P_{Cr}}{\Delta Time(h) \times Max\Delta P_{Cr}/Day}\right)$$

SSPCr= baseline creatinine (the lowest known for the patient)
CrCl= MDRD or CKD-EPI
Mean PCr= mean of considered creatinine
ΔPCr= changes in creatinine
Δtime=interval in hours between two creatinine
ΔMaxPcr=the maximal change (increase) in the plasma creatinine that can occur per day if renal function is completely lost ~ 1,7 mg/dL


Serum creatinine
Clearance equation
Kinetic eGFR formula
Serum creatinine (mg/dl)
eGFR (ml/min)
Day
0
1
2
3
4
5
10
20
30
40
50
90


Serum creatinine
Clearance equation
Kinetic eGFR formula
Serum creatinine (mg/dl)
eGFR (ml/min)
Day
4
5
6
7
8
9
10
11
12
13
14
15
20
25
30

PLOS | ONE

RESEARCH ARTICLE

Kinetic Estimation of GFR Improves Prediction of Dialysis and Recovery after Kidney Transplantation

Timothy J. Pianta[1,2]*, Zoltan H. Endre[1,3], John W. Pickering[3], Nicholas A. Buckley[4], Philip W. Peake[1]

1 Prince of Wales Clinical School, University of New South Wales, Sydney, Australia, **2** Melbourne Medical School, University of Melbourne, Melbourne, Australia, **3** Department of Medicine, University of Otago, Christchurch, New Zealand, **4** Clinical Pharmacology, University of Sydney, Sydney, Australia

* timothy.pianta@nh.org.au

PLOS ONE | DOI:10.1371/journal.pone.0125669 May 4, 2015

Kinetic eGFR and Novel AKI Biomarkers to Predict Renal Recovery

Antoine Dewitte,[*†] Olivier Joannès-Boyau,[*] Carole Sidobre,[*] Catherine Fleureau,[*] Marie-Lise Bats,[‡] Philippe Derache,[‡] Sébastien Leuillet,[§] Jean Ripoche,[†] Christian Combe,[†‖] and Alexandre Ouattara*[*¶]*

Clin J Am Soc Nephrol 10: 1900–1910, 2015.

USI

- Monitoring diuresis and serum creatinine
- Cystatin C: maybe of interest
- eGFR equations lack of precision
- Kinetic eGFR: simple, based on creatinine, but need to be validated in future studies
- Creatinine: maybe the exception (to be repeated)

The GFR and GFR decline cannot be accurately estimated in type 2 diabetics

Flavio Gaspari[1,7], Piero Ruggenenti[1,2,7], Esteban Porrini[1,3,7], Nicola Motterlini[1], Antonio Cannata[1], Fabiola Carrara[1], Alejandro Jiménez Sosa[3], Claudia Cella[1], Silvia Ferrari[1], Nadia Stucchi[1], Aneliya Parvanova[1], Ilian Iliev[1], Roberto Trevisan[4], Antonio Bossi[5], Jelka Zaletel[6] and Giuseppe Remuzzi[1,2]; for the GFR Study Investigators

[1]Clinical Research Center for Rare Diseases 'Aldo & Cele Daccò', Mario Negri Institute for Pharmacological Research, Bergamo, Italy; [2]Unit of Nephrology, Azienda Ospedaliera 'Ospedali Riuniti di Bergamo', Bergamo, Italy; [3]Research Unit, Hospital Universitario de Canarias, Tenerife, Spain; [4]Unit of Diabetology, Azienda Ospedaliera 'Ospedali Riuniti di Bergamo', Bergamo, Italy; [5]Unit of Diabetology, Treviglio Hospital, Treviglio, Italy and [6]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center, Ljubljana, Slovenia

- **Diabetic**
- **GFR measured by iohexol**
- **n=600**
- **Hyperfiltrating (GFR>120 mL/min/1.73 m²) n=90**
- **CKD (<80 mL/min/1.73 m²) n=76**

	Accuracy		Bias		Precision	
	30%		Mean		SD	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
All	85	91	-16	-13	17	16
Normofiltrating (80-120 mL/min/1.73 m²)	88	96	-15	-11	14	12
Hypofiltrating (lower than 80 mL/min/1.73 m²)	88	82	+0.6	+4	16	16
Hyperfiltrating (over 120 mL/min/1.73 m²)	68	77	-33	-33	18	13

All hyperfiltrating status are missed…

Conclusions: eGFR a double message ?

- For General Physicians:

  MDRD (or CKD-EPI or FAS) is probably the best and simplest way to estimate GFR

- For Nephrologists:

  MDRD (or CKD-EPI) is not “magic”, keep our critical feeling, there are several limitations we have to know

→ **Go back to measured GFR if necessary**

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

Today the true question is maybe not about which equation is the best

- When is it necessary to measure GFR?
- « Measuring GFR is costly and cumbersome »

Delanaye P, Nature Rev Nephrol, 2013, 9, 513

Summary

- Estimating GFR (creatinine, eGFR, cystatin C)
- Measuring GFR

Measuring GFR

- WHY?

- How?

Indication = the patient

- Serum creatinine is potentially incorrect
- High Precision required (drug toxicity, kidney donation)

Clin Pharmacokinet (2017) 56:193–205
DOI 10.1007/s40262-016-0434-z

ORIGINAL RESEARCH ARTICLE

Discrepancies between the Cockcroft–Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) Equations: Implications for Refining Drug Dosage Adjustment Strategies

Pierre Delanaye[1] · Fabrice Guerber[2] · André Scheen[3] · Timothy Ellam[4] · Antoine Bouquegneau[1] · Dorra Guergour[5] · Christophe Mariat[6] · Hans Pottel[7]

Males

Age 50		Length 177																									
BSA	W/Scr	0,5	0,6	0,7	0,8	0,9	1	1,1	1,2	1,3	1,4	1,5	1,6	1,7	1,8	1,9	2	2,1	2,2	2,3	2,4	2,5	2,6	2,7	2,8	2,9	3
1,20	25	-25,4	-29,4	-31,9	-33,4	-34,3	-29,5	-25,7	-22,7	-20,2	-18,1	-16,4	-14,9	-13,6	-12,5	-11,5	-10,7	-9,9	-9,2	-8,6	-8,1	-7,6	-7,1	-6,7	-6,3	-6,0	-5,7
1,30	30	-19,9	-25,6	-29,1	-31,4	-32,9	-28,2	-24,4	-21,4	-19,0	-16,9	-15,2	-13,8	-12,5	-11,4	-10,5	-9,6	-8,9	-8,3	-7,7	-7,2	-6,7	-6,3	-5,9	-5,5	-5,2	-4,9
1,39	35	-13,9	-21,1	-25,8	-28,9	-31,0	-26,3	-22,7	-19,8	-17,4	-15,4	-13,8	-12,4	-11,2	-10,1	-9,2	-8,4	-7,8	-7,1	-6,6	-6,1	-5,7	-5,3	-4,9	-4,6	-4,3	-4,0
1,47	40	-7,3	-16,2	-22,0	-25,9	-28,7	-24,2	-20,7	-17,8	-15,6	-13,7	-12,1	-10,8	-9,6	-8,7	-7,8	-7,1	-6,4	-5,9	-5,4	-4,9	-4,5	-4,1	-3,8	-3,5	-3,2	-3,0
1,54	45	-0,3	-10,9	-17,9	-22,7	-26,1	-21,7	-18,4	-15,7	-13,5	-11,8	-10,3	-9,0	-8,0	-7,1	-6,3	-5,6	-5,0	-4,5	-4,0	-3,6	-3,3	-2,9	-2,6	-2,4	-2,1	-1,9
1,62	50	7,0	-5,3	-13,4	-19,1	-23,2	-19,1	-15,9	-13,3	-11,3	-9,7	-8,3	-7,1	-6,2	-5,4	-4,6	-4,0	-3,5	-3,0	-2,6	-2,3	-1,9	-1,7	-1,4	-1,2	-1,0	-0,8
1,68	55	14,7	0,6	-8,8	-15,3	-20,1	-16,2	-13,2	-10,8	-9,0	-7,4	-6,2	-5,2	-4,3	-3,5	-2,9	-2,4	-1,9	-1,5	-1,1	-0,8	-0,6	-0,3	-0,1	0,1	0,3	0,4
1,75	60	22,5	6,7	-3,9	-11,3	-16,8	-13,1	-10,4	-8,2	-6,5	-5,1	-4,0	-3,1	-2,3	-1,6	-1,1	-0,6	-0,2	0,1	0,4	0,7	0,9	1,1	1,3	1,4	1,5	1,6
1,81	65	30,6	13,1	1,2	-7,2	-13,3	-9,9	-7,4	-5,4	-3,9	-2,7	-1,7	-0,9	-0,2	0,3	0,8	1,2	1,5	1,8	2,0	2,2	2,4	2,5	2,6	2,8	2,8	2,9
1,86	70	38,9	19,6	6,5	-2,8	-9,7	-6,6	-4,3	-2,6	-1,2	-0,2	0,7	1,4	1,9	2,4	2,7	3,0	3,3	3,5	3,7	3,8	3,9	4,0	4,1	4,1	4,2	4,2
1,92	75	47,3	26,2	11,9	1,7	-5,9	-3,2	-1,1	0,4	1,5	2,4	3,1	3,7	4,1	4,5	4,7	5,0	5,1	5,3	5,4	5,4	5,5	5,5	5,6	5,6	5,6	5,6
1,97	80	56,0	33,0	17,4	6,3	-2,0	0,4	2,1	3,4	4,4	5,1	5,7	6,1	6,4	6,6	6,8	6,9	7,0	7,1	7,1	7,1	7,1	7,1	7,1	7,0	7,0	6,9
2,02	85	64,7	39,9	23,1	11,0	2,0	4,0	5,5	6,6	7,3	7,8	8,2	8,5	8,7	8,8	8,9	8,9	8,9	8,9	8,9	8,8	8,7	8,7	8,6	8,5	8,4	8,3
2,07	90	73,6	47,0	28,8	15,8	6,1	7,8	9,0	9,7	10,3	10,6	10,9	11,0	11,0	11,0	11,0	11,0	10,9	10,8	10,7	10,5	10,4	10,3	10,2	10,0	9,9	9,8
2,12	95	82,5	54,1	34,7	20,7	10,2	11,6	12,5	13,0	13,3	13,5	13,5	13,5	13,4	13,3	13,2	13,0	12,9	12,7	12,5	12,3	12,1	11,9	11,7	11,6	11,4	11,2
2,17	100	91,6	61,4	40,6	25,7	14,5	15,5	16,0	16,3	16,4	16,4	16,3	16,1	15,9	15,6	15,4	15,1	14,9	14,6	14,3	14,1	13,8	13,6	13,3	13,1	12,9	12,7
2,21	105	100,8	68,7	46,7	30,8	18,8	19,4	19,7	19,7	19,5	19,3	19,0	18,7	18,3	18,0	17,6	17,3	16,9	16,6	16,2	15,9	15,6	15,3	15,0	14,7	14,4	14,1
2,26	110	110,1	76,1	52,8	35,9	23,2	23,5	23,4	23,1	22,7	22,3	21,8	21,3	20,8	20,4	19,9	19,4	19,0	18,5	18,1	17,7	17,3	17,0	16,6	16,3	15,9	15,6
2,30	115	119,4	83,6	59,0	41,1	27,7	27,5	27,1	26,6	26,0	25,3	24,7	24,0	23,4	22,8	22,2	21,6	21,1	20,5	20,0	19,6	19,1	18,7	18,3	17,9	17,5	17,1
2,34	120	128,9	91,2	65,2	46,4	32,3	31,7	30,9	30,1	29,2	28,4	27,5	26,7	25,9	25,2	24,5	23,8	23,2	22,6	22,0	21,4	20,9	20,4	19,9	19,5	19,1	18,6
2,38	125	138,4	98,9	71,6	51,8	36,8	35,8	34,7	33,6	32,5	31,4	30,4	29,4	28,5	27,6	26,8	26,0	25,3	24,6	23,9	23,3	22,7	22,2	21,6	21,1	20,6	20,2

Males

Age 60		Length 177																									
BSA	W/Scr	0,5	0,6	0,7	0,8	0,9	1	1,1	1,2	1,3	1,4	1,5	1,6	1,7	1,8	1,9	2	2,1	2,2	2,3	2,4	2,5	2,6	2,7	2,8	2,9	3
1,20	25	-26,4	-29,7	-31,6	-32,8	-33,5	-28,9	-25,2	-22,3	-19,9	-17,9	-16,2	-14,7	-13,5	-12,4	-11,4	-10,6	-9,9	-9,2	-8,6	-8,1	-7,6	-7,2	-6,8	-6,4	-6,1	-5,7
1,30	30	-21,8	-26,6	-29,5	-31,3	-32,5	-27,9	-24,2	-21,3	-18,9	-16,9	-15,3	-13,8	-12,6	-11,5	-10,6	-9,8	-9,1	-8,4	-7,9	-7,3	-6,9	-6,5	-6,1	-5,7	-5,4	-5,1
1,39	35	-16,7	-22,9	-26,7	-29,3	-31,0	-26,5	-22,9	-20,0	-17,7	-15,7	-14,1	-12,7	-11,5	-10,5	-9,6	-8,8	-8,1	-7,5	-7,0	-6,5	-6,0	-5,6	-5,3	-4,9	-4,6	-4,3
1,47	40	-11,1	-18,7	-23,6	-26,9	-29,2	-24,7	-21,2	-18,4	-16,2	-14,3	-12,7	-11,4	-10,3	-9,3	-8,4	-7,7	-7,0	-6,5	-5,9	-5,5	-5,1	-4,7	-4,4	-4,0	-3,8	-3,5
1,54	45	-5,1	-14,2	-20,1	-24,2	-27,0	-22,7	-19,3	-16,7	-14,5	-12,7	-11,2	-9,9	-8,9	-7,9	-7,1	-6,5	-5,8	-5,3	-4,8	-4,4	-4,0	-3,7	-3,4	-3,1	-2,8	-2,6
1,62	50	1,1	-9,4	-16,4	-21,2	-24,6	-20,5	-17,3	-14,7	-12,6	-10,9	-9,5	-8,4	-7,4	-6,5	-5,8	-5,1	-4,6	-4,1	-3,6	-3,2	-2,9	-2,6	-2,3	-2,1	-1,8	-1,6
1,68	55	7,7	-4,4	-12,4	-18,0	-22,0	-18,1	-15,0	-12,6	-10,6	-9,1	-7,8	-6,7	-5,7	-5,0	-4,3	-3,7	-3,2	-2,7	-2,4	-2,0	-1,7	-1,4	-1,2	-1,0	-0,8	-0,6
1,75	60	14,5	0,9	-8,2	-14,6	-19,2	-15,5	-12,6	-10,4	-8,5	-7,1	-5,9	-4,9	-4,0	-3,3	-2,7	-2,2	-1,8	-1,4	-1,0	-0,7	-0,5	-0,2	0,0	0,1	0,3	0,5
1,81	65	21,5	6,3	-3,9	-11,1	-16,3	-12,8	-10,1	-8,0	-6,3	-5,0	-3,9	-3,0	-2,3	-1,6	-1,1	-0,7	-0,3	0,1	0,3	0,6	0,8	1,0	1,2	1,3	1,4	1,6
1,86	70	28,7	11,9	0,6	-7,4	-13,2	-9,9	-7,5	-5,6	-4,1	-2,8	-1,9	-1,1	-0,4	0,1	0,6	0,9	1,3	1,5	1,8	2,0	2,1	2,3	2,4	2,5	2,6	2,7
1,92	75	36,0	17,7	5,3	-3,5	-10,0	-7,0	-4,7	-3,0	-1,7	-0,6	0,2	0,9	1,5	1,9	2,3	2,6	2,8	3,1	3,2	3,4	3,5	3,6	3,7	3,7	3,8	3,8
1,97	80	43,5	23,6	10,0	0,4	-6,7	-4,0	-1,9	-0,4	0,8	1,7	2,4	3,0	3,4	3,8	4,1	4,3	4,5	4,6	4,7	4,8	4,9	4,9	5,0	5,0	5,0	5,0
2,02	85	51,1	29,6	14,9	4,5	-3,3	-0,8	1,0	2,3	3,3	4,0	4,6	5,1	5,4	5,7	5,9	6,0	6,1	6,2	6,3	6,3	6,3	6,3	6,3	6,3	6,3	6,2
2,07	90	58,8	35,7	19,9	8,6	0,2	2,4	3,9	5,0	5,8	6,4	6,9	7,2	7,4	7,6	7,7	7,8	7,8	7,8	7,8	7,8	7,8	7,7	7,7	7,6	7,5	7,5
2,12	95	66,7	41,9	25,0	12,9	3,8	5,7	6,9	7,8	8,5	8,9	9,2	9,4	9,5	9,6	9,6	9,6	9,5	9,5	9,4	9,3	9,2	9,1	9,0	8,9	8,8	8,7
2,17	100	74,6	48,2	30,2	17,2	7,5	9,0	10,0	10,7	11,1	11,4	11,5	11,6	11,6	11,6	11,5	11,4	11,3	11,2	11,0	10,9	10,7	10,6	10,4	10,3	10,1	10,0
2,21	105	82,6	54,6	35,4	21,6	11,2	12,4	13,2	13,6	13,9	13,9	13,9	13,9	13,8	13,6	13,4	13,3	13,1	12,9	12,7	12,4	12,2	12,0	11,8	11,7	11,5	11,3
2,26	110	90,7	61,1	40,7	26,0	15,1	15,9	16,4	16,6	16,6	16,5	16,4	16,2	15,9	15,7	15,4	15,1	14,9	14,6	14,3	14,0	13,8	13,5	13,3	13,0	12,8	12,6
2,30	115	98,9	67,6	46,1	30,6	18,9	19,4	19,6	19,6	19,4	19,1	18,8	18,5	18,1	17,8	17,4	17,0	16,7	16,3	16,0	15,7	15,3	15,0	14,7	14,4	14,2	13,9
2,34	120	107,1	74,2	51,5	35,2	22,9	23,0	22,9	22,6	22,2	21,8	21,3	20,8	20,4	19,9	19,4	19,0	18,5	18,1	17,7	17,3	16,9	16,5	16,2	15,9	15,5	15,2
2,38	125	115,5	80,9	57,1	39,8	26,8	26,7	26,2	25,7	25,1	24,5	23,8	23,2	22,6	22,0	21,4	20,9	20,4	19,9	19,4	18,9	18,5	18,1	17,7	17,3	16,9	16,6

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/83874/2014
Committee for Medicinal Products for Human use (CHMP)

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

5.2. Measures of renal function

In order to have a reference measure of renal function that is independent of clinical practice at the time of conduct of the pharmacokinetic study, it is recommended that a method accurately measuring GFR using an exogenous marker is used to determine renal function in the subjects in the pharmacokinetic study, if possible.

Measuring GFR

- Why?
- HOW ?

Available on the market…

Markers	Strenghts	Limitations
Inulin		
Iothalamate		
Iohexol		
EDTA		
DTPA		

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

We have biomarkers
Now, how to proceed?

- Urinary clearance

- Plasma clearance

Urinary clearance

- Constant infusion, marker at equilibrium
- Plasma measurement of the marker
- Collect Urine (every half or every hour) and measurement of urine flow, urine measurement of the marker
- Repeated 3 or 4-fold
- Cl = [U] x [V]/ [P] (mean of three collections)

Plasmatic Clearance = Dose / AUC

Theoritically, α and β must be calculated

↓

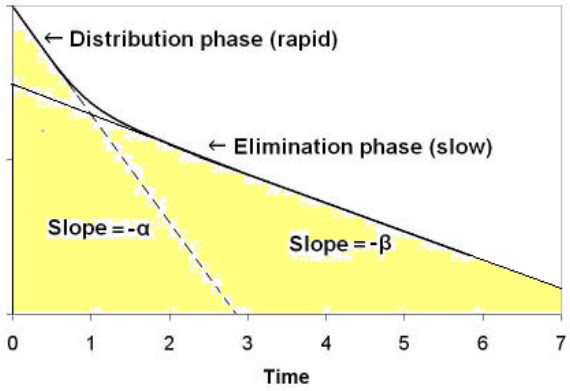
Not easy in practice (many samples)

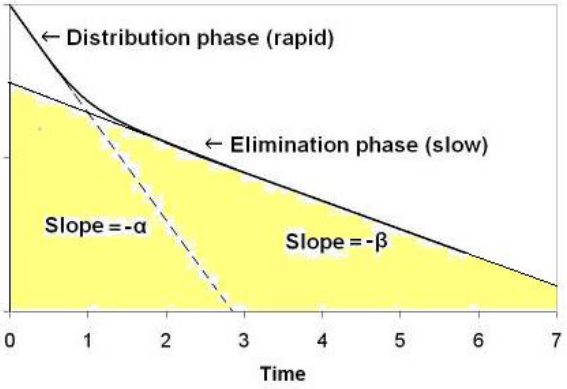
↓

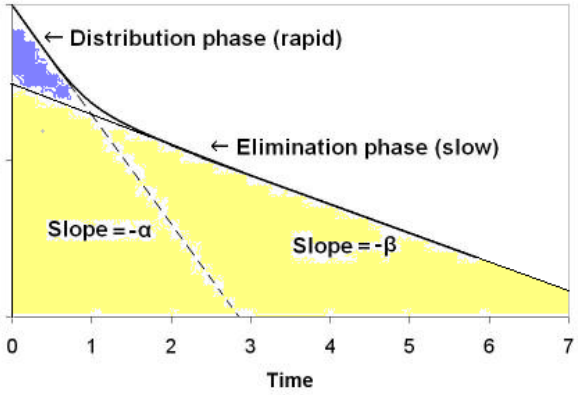
Only slope ß after equilibrium is calculated

↓

Brochner-Mortensen mathematical correction for estimation of distribution phase
= 0,990778 x C2 – 0,001218 $C2^2$







M

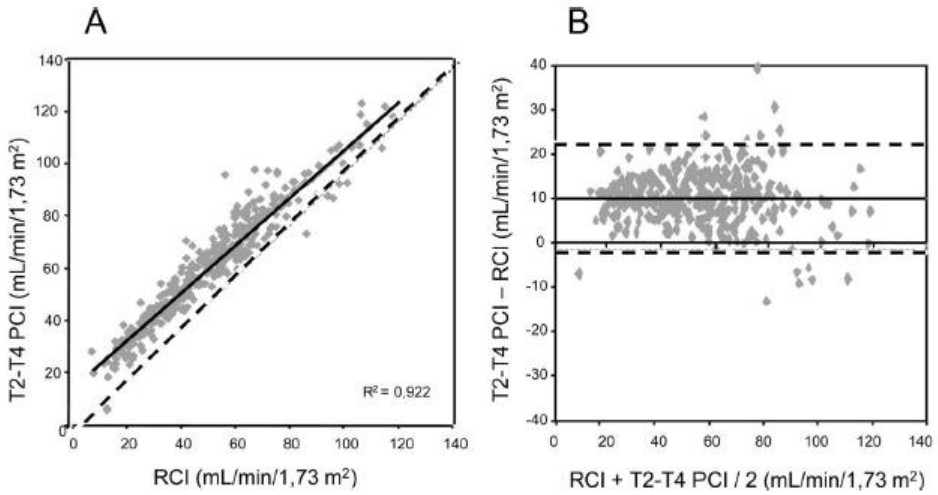
Plasma v urinary:
Are they equivalent?

- A lot of studies showing a good correlation…
- Few studies with Bland and Altman analysis

Plasma versus Urinary clearances

Evaluation of Sample Bias for Measuring Plasma Iohexol Clearance in Kidney Transplantation

Arnaud Stolz,[1] Guillaume Hoizey,[2] Olivier Toupance,[1] Sylvie Lavaud,[1] Fabien Vitry,[3] Jacques Chanard,[1] and Philippe Rieu[1,4,5]



	n	Bias ml/min/1.73m² (%)	Precision (SD) (ml/min/1.73m²)
T2-T4	342	+10 (+27%)	±6
T2-T6	342	+8 (+21%)	±6
T2-T24	215	+3 (+8.8%)	±5

Stolz A, Transplantation, 2010, 89, 440

Urinary and plasma methods: pro-con

- More physiological
- More costly
- More cumbersome
- Less precision, less repeatability (urine recolt!)
- Differences are sytematic

Several plasma clearance procedures are available on the market…

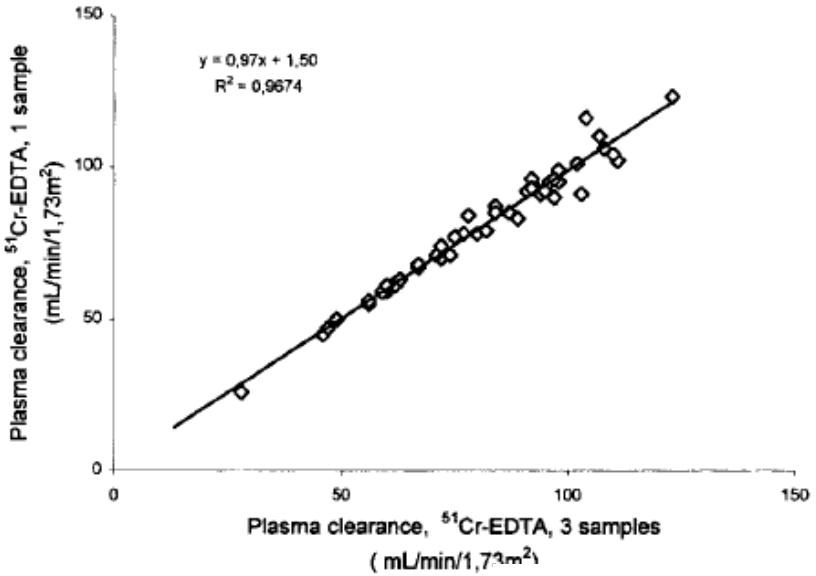
Available on the market…

Markers	Strenghts	Limitations
Inulin	Gold standard (or historic) Safe	Costly Dosage neither easy nor standardized Doubt with plasma clearance
Iothalamate	The most popular in USA Isotopic or "cold" method	Tubular secretion Cannot be used if allergy to iodine
Iohexol		
EDTA	Easy to measure	Only isotopic Not available in USA
DTPA	Easy to measure	Only isotopic Binding to proteins Short half-time

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

EDTA versus iohexol

N=49



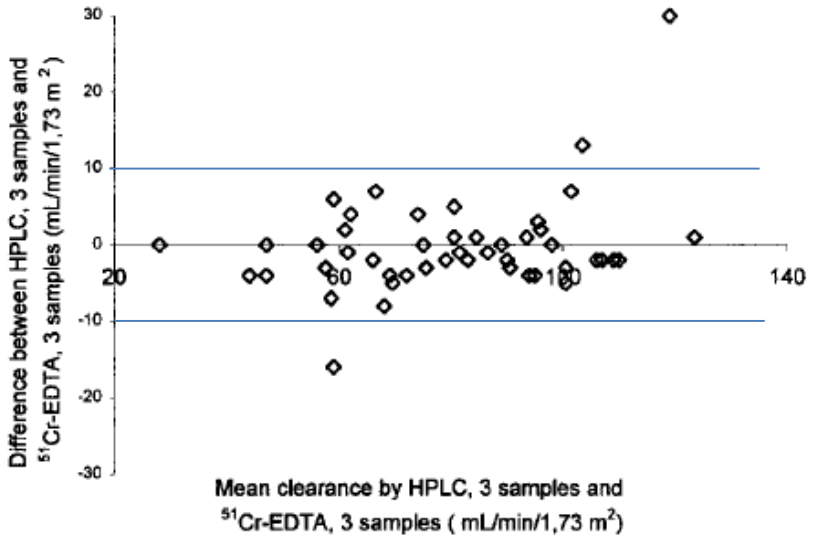


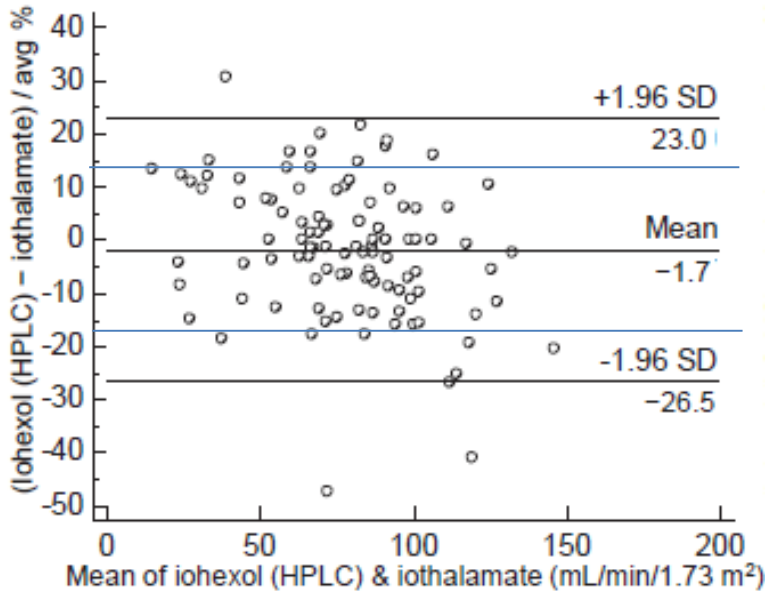
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	Clearance range (ml/min)	Difference (ml/min)	
		Mean	SD
Multiple-point clearance: 3 samples ^{51}Cr-EDTA *vs* 3 samples iohexol			
^{51}Cr-EDTA *vs* HPLC	28–134	−0.16	6.17
^{51}Cr-EDTA *vs* X-ray fluorescence	29–134	0.58	4.95
Single-point clearance: 3 samples ^{51}Cr-EDTA *vs* 1 sample			
^{51}Cr-EDTA *vs* ^{51}Cr-EDTA	26–123	−0.7	3.59
^{51}Cr-EDTA *vs* HPLC	27–125	−1.7	5.94
^{51}Cr-EDTA *vs* X-ray fluorescence	32–116	−1.32	5.78

Brandstrom E, NDT, 1998, 13, 1176

Iothalamate versus iohexol

N=102



Accuracy (concordance):
Within 30%: 98%
Within 15%: 80%

Delanaye, AJKD, 2016, 68, 329

AJKD
Original Investigation

Measuring GFR: A Systematic Review

*Inga Soveri, MD, PhD,[1] Ulla B. Berg, MD, PhD,[2] Jonas Björk, PhD,[3] Carl-Gustaf Elinder, MD, PhD,[4] Anders Grubb, MD, PhD,[5] Ingegerd Mejare, PhD,[6] Gunnar Sterner, MD, PhD,[7] and Sten-Erik Bäck, MSc, PhD,[5] on behalf of the SBU GFR Review Group**

Table 1. Bias and Accuracy of Index Methods Compared to Reference Method When Measuring Glomerular Filtration Rate

	No. of Pts/ Studies	Median Bias[a] (95% CI)	Mean Bias (95 % CI)	P_{30} (95% CI)	P_{10} (95% CI)	Sufficient Accuracy	Scientific Evidence	Comments[b]
Criteria for sufficient precision		≤±5%	≤±10%	≥80%	≥50%			
Index method								
DTPA								
Renal clearance	126/5	−2 (−4 to 2)	−1 (−6 to 5)	87 (81 to 93)	53 (45 to 62)	Yes	⊕⊕◯◯	Inconsistency, −1; imprecision, −1
Plasma clearance	89/2	20 (18 to 35)	13 (5 to 22)	56 (47 to 68)	19 (13 to 29)	No	⊕⊕◯◯	Study limitations −1; imprecision −1
^{51}Cr-EDTA								
Renal clearance	198/9	−5 (−7 to −3)	−2 (−8 to 4)	95 (92 to 98)	56 (50 to 64)	Yes	⊕⊕⊕◯	Imprecision, −1
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Iohexol								
Renal clearance	47/2	−7 (−10 to 0)	−7 (−16 to 2)	100[c]	53 (41 to 70)	Yes	⊕⊕◯◯	Imprecision, −2
Plasma clearance	172/5	3 (0 to 6)	2 (−4 to 9)	86 (81 to 91)	50 (43 to 58)	Yes	⊕⊕⊕◯	Imprecision, −1
Iothalamate								
Renal clearance	548/13	−1 (−2 to 0)	6 (1 to 11)	97 (95 to 98)	66 (62 to 70)	Yes	⊕⊕⊕⊕	
Plasma clearance	61/1	9 (0 to 15)	11 (−6 to 29)	82 (73 to 92)	33 (23 to 47)	—	⊕◯◯◯	Study limitations, −1; imprecision, −2
Inulin								
Plasma clearance	39/2	2 (−3 to 6)	1 (−9 to 11)	100[c]	72 (59 to 87)	Yes	⊕⊕◯◯	Imprecision, −1; indirectness, −1

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage. Renal inulin clearance served as reference method. Mean bias, P_{10}, and P_{30} were estimated using generalized linear mixed models based on normal distribution (mean bias) or Poisson distribution (P_{10}, P_{30}; log-transformed outcome and robust variance estimation), with a random intercept for each study and a fixed effect for each index method ("unadjusted model results"; see Statistical Methods section). All analyses were weighed with respect to number of participants in each study. Estimates were obtained as marginal means.

Abbreviations and definitions: ⊕⊕⊕⊕, strong evidence; ⊕⊕⊕◯, moderately strong evidence; ⊕⊕◯◯, limited evidence; ⊕◯◯◯, insufficient evidence; ^{51}Cr-EDTA, chromium 51–labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; CI, confidence interval; Imprecision, N < 100 in meta-analysis (−1), P_{30} lower 95% CI ≤ 80%, P_{10} lower 95% CI ≤ 50%, or median bias 95% CI ≥ ±5% (−1); Inconsistency, inconsistency in study outcomes that cannot be explained by differences in study design (−1); Indirectness, limited generalizability (−1); P_{10}, percentage of measurements by index method that differed no more than 10% from reference method; P_{30}, percentage of measurements by index method that differed no more than 30% from reference method; pts, patients; Study limitations, risk of bias due to shortcomings in individual studies (−1).

[a]Median bias was calculated directly (using the weights) for each index method together with nonparametric CIs.

[b]Strength of scientific evidence.

[c]The generalized linear mixed model does not yield valid estimates of confidence limits when estimated proportion (eg, P_{30}) is 100%.

Soveri I, Am J Kidney Dis, 2014, 64, 411

Measured GFR:
Need for Standardization

Standardization for the marker

- Only cold methods can easily be implemented worldwide
- Iothalamate is difficult to obtain in Europe
- Inulin is expensive and only available as urinary clearance
- Iohexol is available worldwide
- Very stable (central and/or “reference” laboratories)

Standardization for procedure

- Urinary versus plasma
- Number of samples and timing of samples
- Whatever the marker…

Table 4. Available procedures to perform iohexol clearance

Methodology	Indication in clinical practice	Indication in clinical research	Bibliographic examples where the procedure is described into details
Urinary clearance	Increased extracellular volume (oedema, ascites, intensive care units, etc.)	Basic (physiologic) studies Specific populations (cirrhotic, intensive care, nephrotic syndrome, oedema, etc.)	[36, 77, 125, 170]
Plasma clearance			
Multiple samples (first or fast, second or slow exponential curves and calculation of area under the curve)	High GFR values ('hyperfiltrating') subjects	Development of equations to estimate GFR Studies in hyperfiltrating patients	[52, 93, 171]
Multiple samples only for second and slow component (2 h after injection, 4 samples over 5 or 6 h, 1 sample/h) + BM correction	High precision determination (see text)	Development of equations to estimate GFR Clinical research with GFR as main endpoint	[126, 172]
Idem + late sample (8 h or 24 h)	Pre-dialysis subjects	Research in pre-dialysis subjects	[52, 77]
Simplified two or three sample method (2 samples: first at 2 or 3 h and second at 4 or 5 h) + BM correction	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint	[69, 116]
Simplified single-sample method + Jacobsson correction [110]	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint Epidemiological research	[14, 173]

Suggestions (expert opinion-based) according to the clinical or experimental context.
GFR, glomerular filtration rate; CKD, chronic kidney disease; BM, Brochner-Mortensen correction [116].

Delanaye P, Clin Kidney J, 2016, 9, 700

Iohexol in CHU Liège

- Iohexol (plasma clearance)
- 5 hours
- Samples at 2, 3, 4 et 5 hours
- 150 euros

Nephrol Dial Transplant (2017) 1–7
doi: 10.1093/ndt/gfx323

ndt
Nephrology Dialysis Transplantation

Iohexol plasma clearance simplified by dried blood spot testing

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Conclusions

- Measuring GFR is not so cumbersome
- Standardization (marker, procedure and measurement) might still be improved
- Iohexol is the best balance between physiology and feasibility
- Iohexol is safe
- Iohexol is the only chance for a worldwide standardized mGFR

I thank you for your attention!

Jupiler

Questions?