Glomerular Filtration Rate

Estimations and Measurements

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Summary

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

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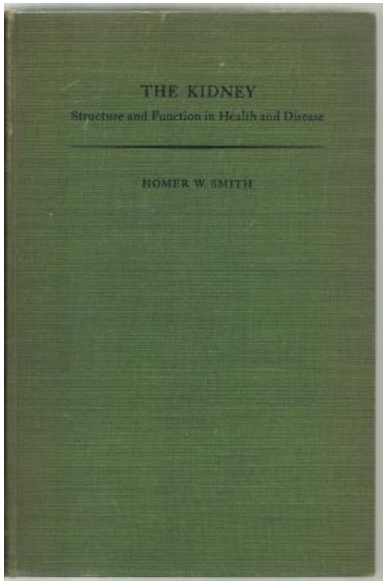
- Measuring GFR

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

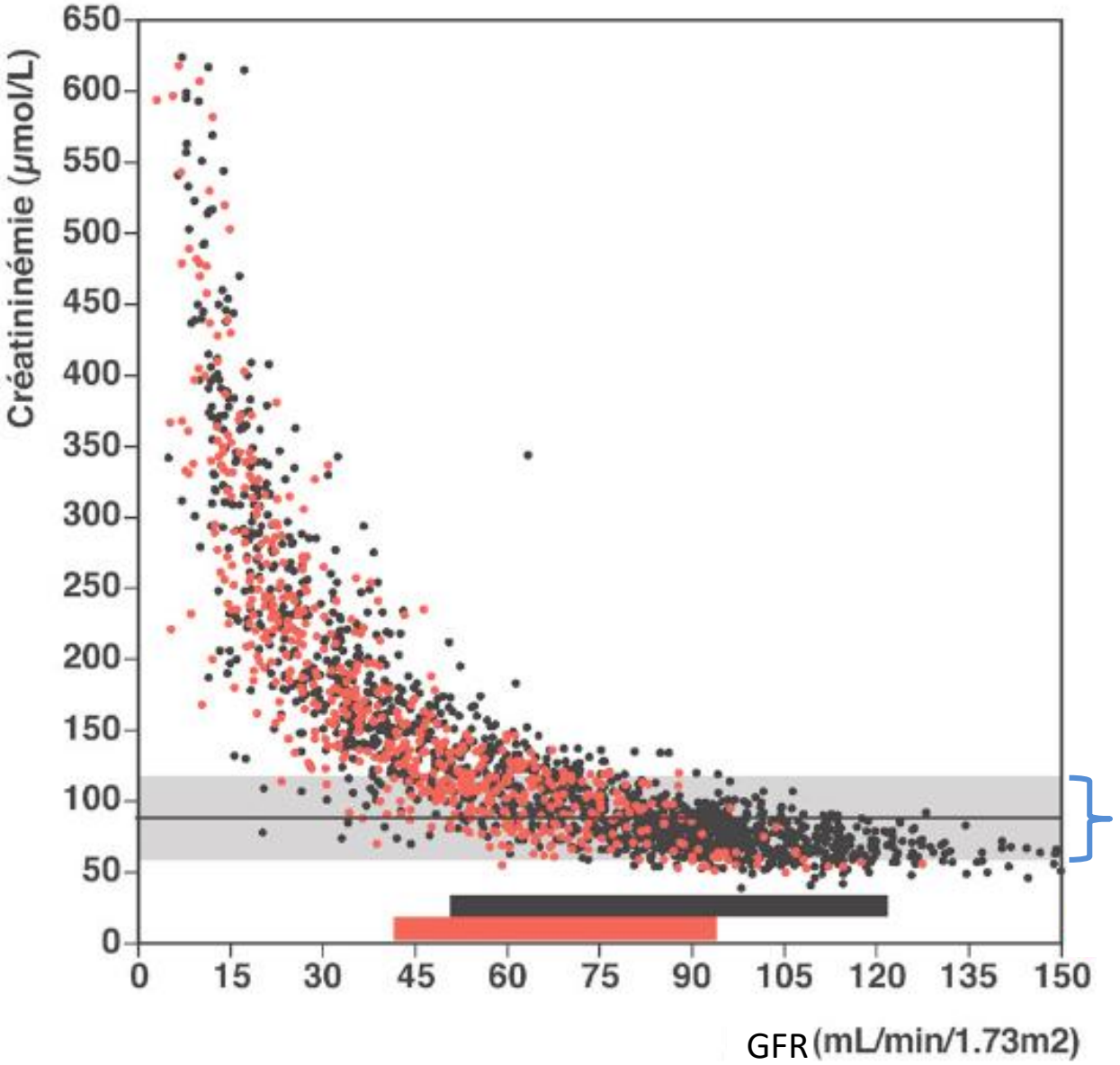
Drugs interaction with creatinine

- 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

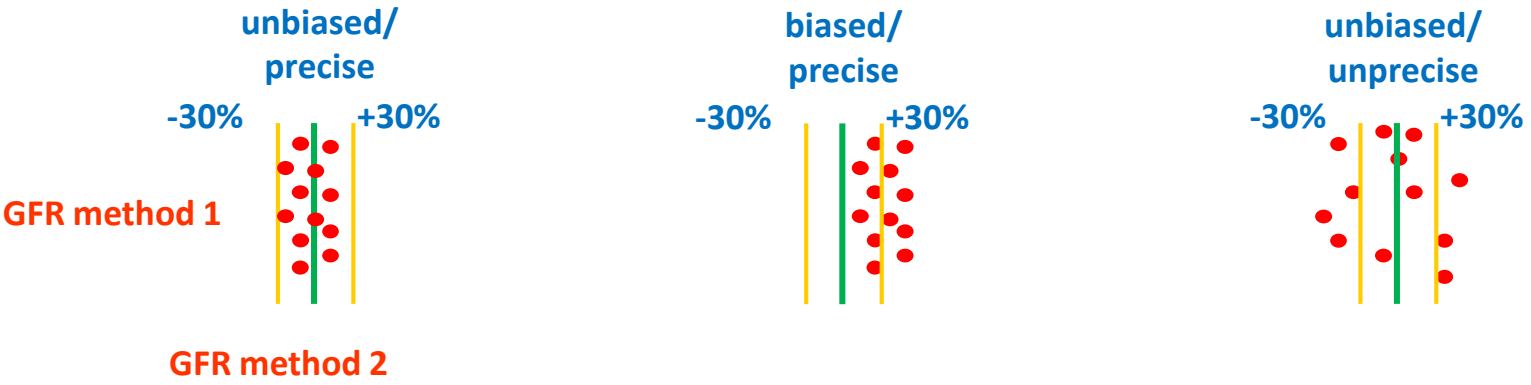
Cockcroft versus MDRD

	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

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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.

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.

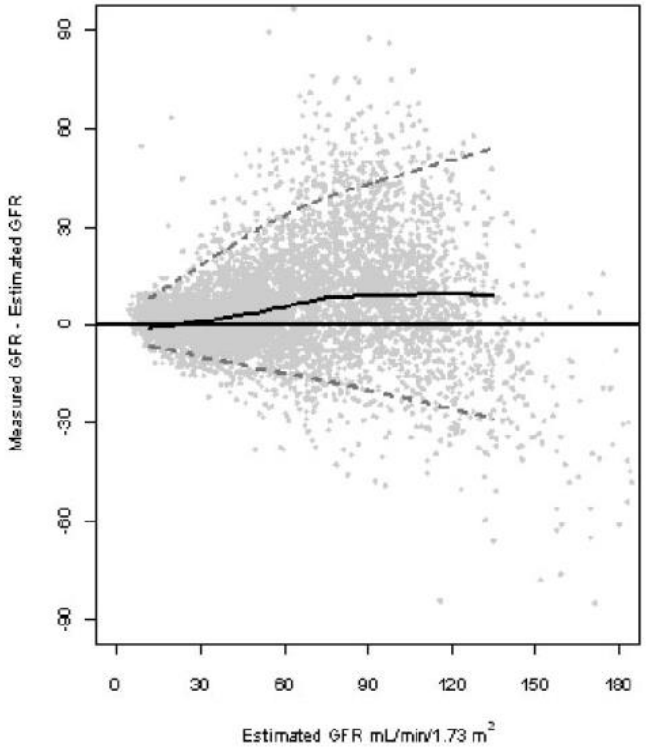


Figure 2. Difference of the MDRD Study equation by level of eGFR. Difference is calculated as (mGFR − eGFR). Solid horizontal

Table 2. Comparison of performance of MDRD Study equation by level of eGFR[a]

eGFR	*N*	Difference		% Difference		P_{30} (CI)
		Median (CI)	IQR	Median (CI)	IQR	
Overall	5504	2.7 (2.4 to 3.1)	16.4	5.8 (5.1 to 6.4)	27.6	83 (83 to 84)
>120	325	−9.0 (−12.3 to −5.9)	31.2	−7.1 (−10.1 to −4.6)	26.6	82 (80 to 84)
90 to 119	941	11.1 (9.7 to 12.6)	25.6	9.9 (8.6 to 11)	20.8	89 (88 to 90)
60 to 89	1364	9.5 (8.3 to 10.7)	25.4	11.7 (10.2 to 12.7)	28.0	82 (81 to 83)
30 to 59	1782	1.7 (1.1 to 2.3)	13.0	3.5 (2.4 to 4.9)	27.4	84 (83 to 85)
16 to 29	793	0.0 (−0.4 to 0.5)	6.7	0.0 (−1.8 to 2.4)	31.4	81 (80 to 82)
<15	299	0.8 (0.3 to 1.4)	5.0	6.3 (2.5 to 11.1)	34.5	72 (69 to 75)

[a]Units of GFR are in ml/min per 1.73 m². Difference is calculated as mGFR − eGFR. Percentage difference is calculated as (mGFR − eGFR)/mGFR. Median values measure bias, and IQR measure precision. mGFR ranges in the rows correspond to GFR cutoffs for CKD stages: Stage 1, GFR >90; stage 2, GFR 60 to 89; stage 3, GFR 30 to 59; stage 4, GFR 15 to 29; stage 5, GFR <15. CI, confidence interval.

MDRD: the strengths

- 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)

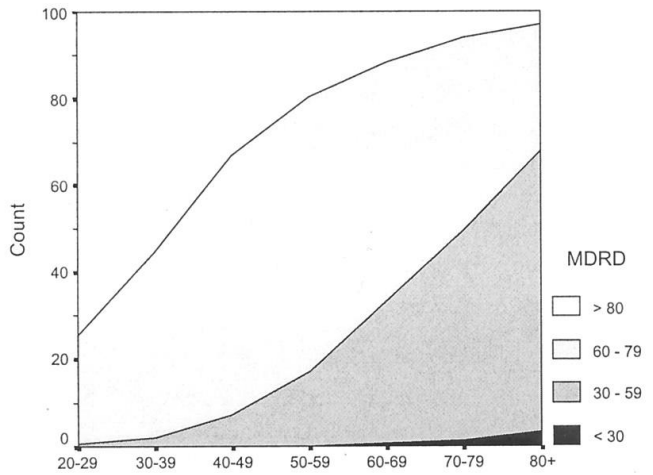
If creatinine is 1 mg/dL: difference in eGFR will be 21 ml/min/1.73m² with MDRD

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

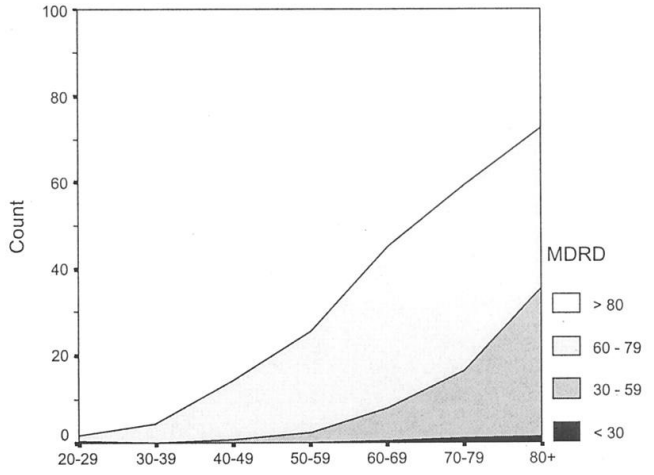
MDRD: limitations = creatinine
1) analytical limitation

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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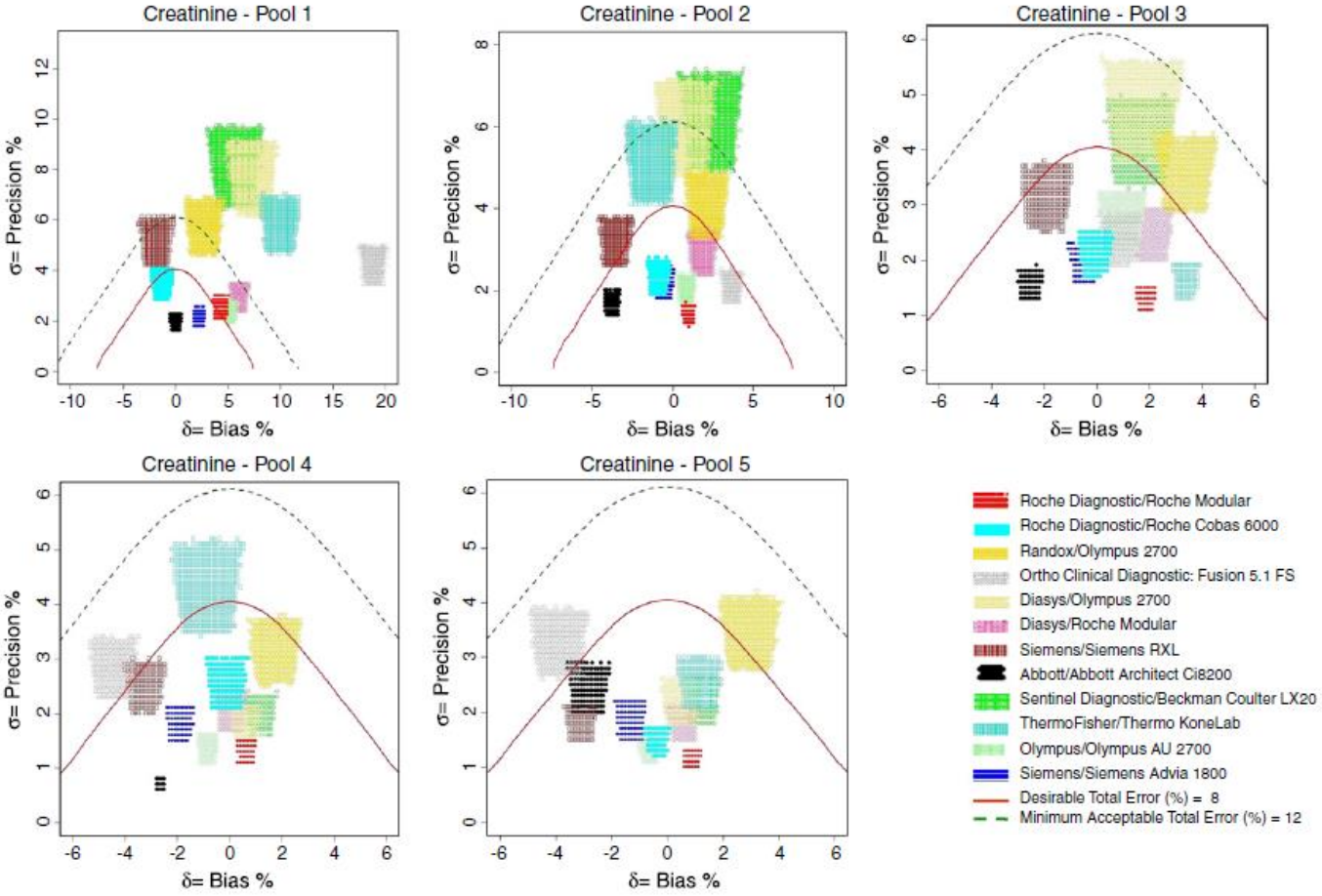
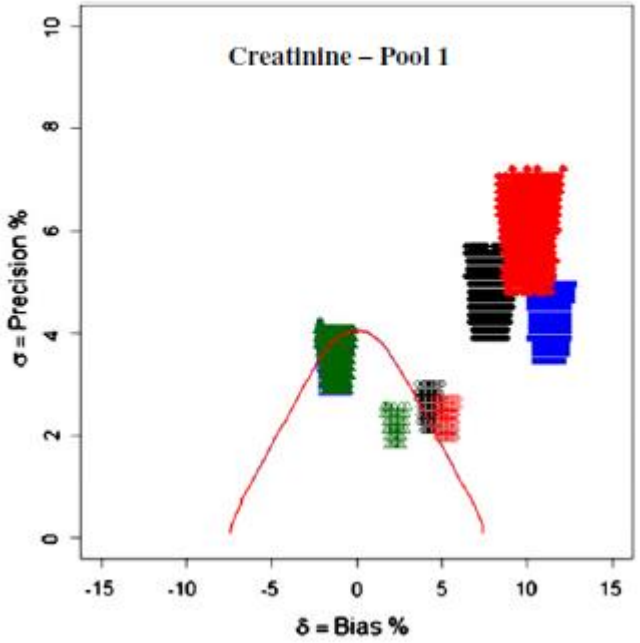
Clinica Chimica Acta 412 (2011) 2070–2075

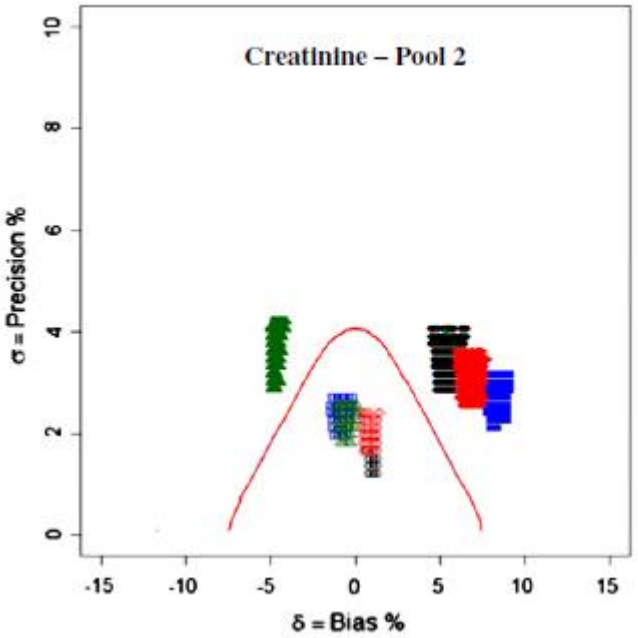
MDRD: 186 => 175

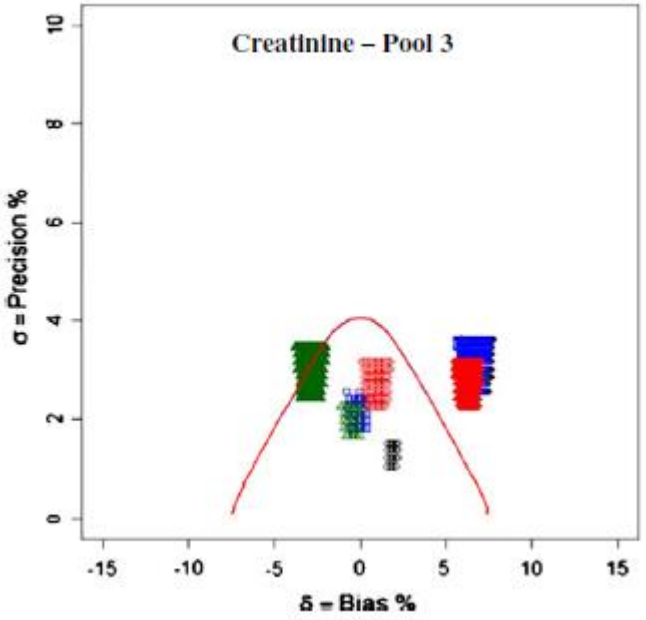
Results of GC-IDMS from LNE

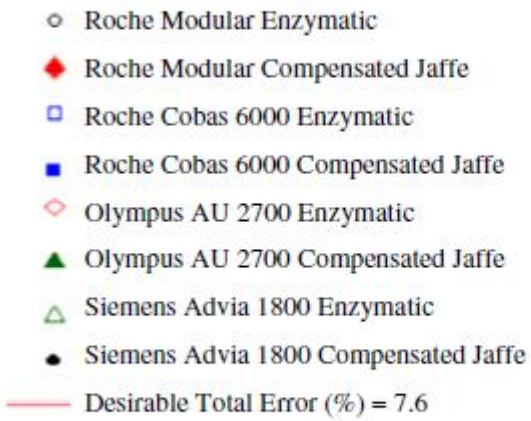
Pool 5: 174.5 +/-3.1 µmol/L
Pool 4: 149.7 +/-2.9 µmol/L
Pool 3: 97.9 +/-1.7 µmol/L
Pool 2: 74.4 +/-1.4 µmol/L
Pool 1 : 35.9 +/-0.9 µmol/L











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

MDRD: limitations = creatinine
1) 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
2) the ethnicity factors

- Asian factor: Chinese: 1.233 Japan: 0.808

  How explain this discrepancy?

Delanaye P, Kidney Int, 2011 80, 439

- African-American factor: 1.21

  Factor too high in AA "healthy" population

Delanaye P, Clin J Am Soc, 2011, 6, 906

Yayo E, Nephrol Dial Transplant, 2017, in press

Epidemiological paradox

Peralta CA, NDT, 2010, 25, 3934

MDRD: limitations = creatinine
3) 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.

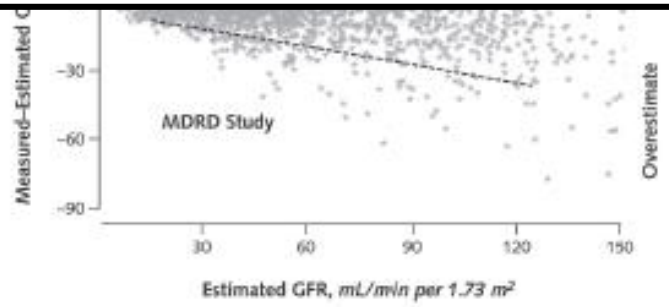


Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

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*]

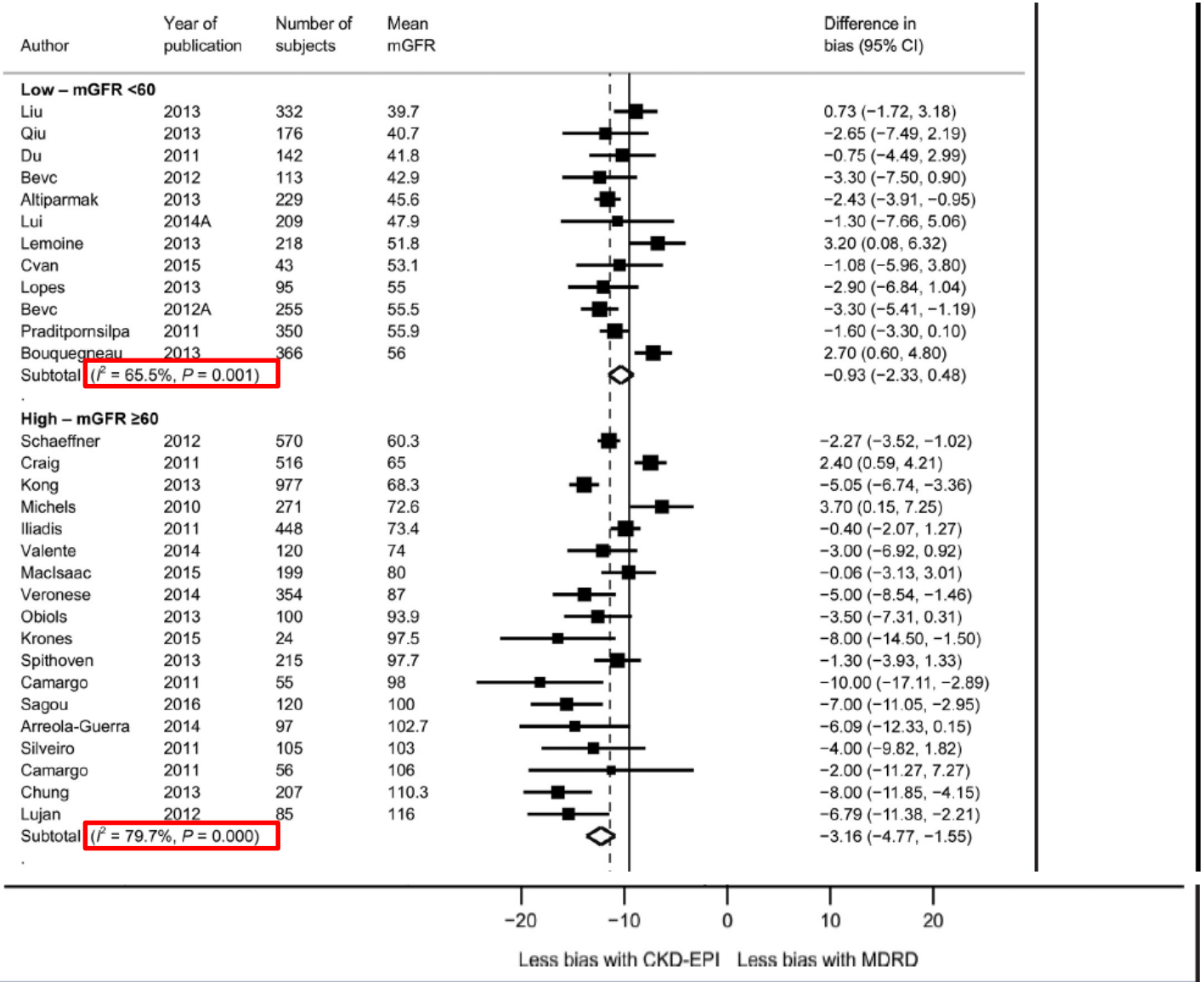


Fig. 2. Difference in mean bias from CKD-EPI and mean bias from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random-effects metaanalysis.

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

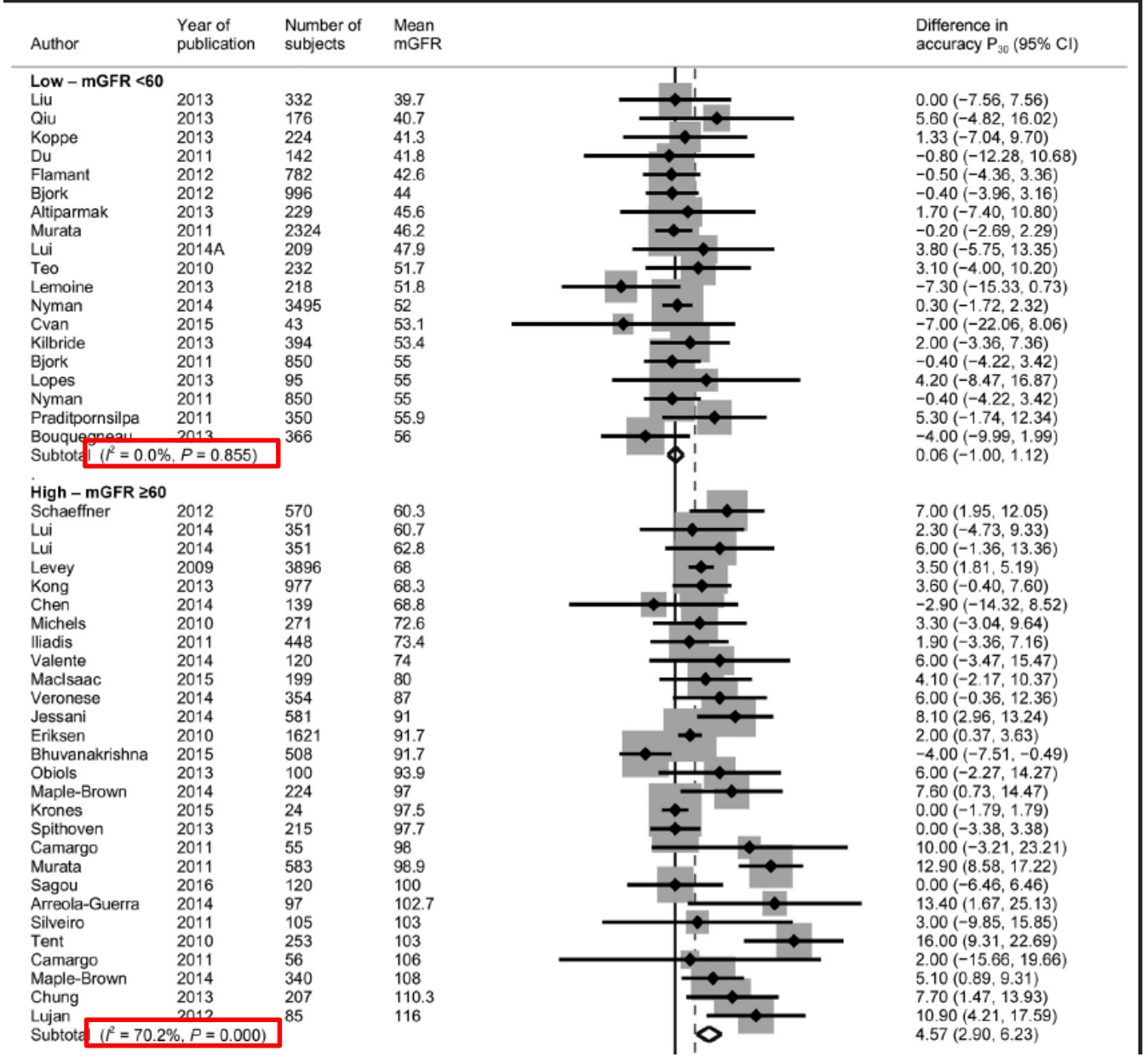


Fig. 4. Difference in mean accuracy from CKD-EPI and mean accuracy from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random-effects metaanalysis. P_{30}, proportion of eGFR results within 30% of mGFR result. Horizontal bars and diamond width denote 95% CIs,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

Kazunori Murata, Nikola A. Baumann,* Amy K. Saenger,* Timothy S. Larson,*† Andrew D. Rule,†‡ and John C. Lieske*†*

*Department of Laboratory Medicine and Pathology, †Department of Internal Medicine, Division of Nephrology and Hypertension, and ‡Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, Minnesota

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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.

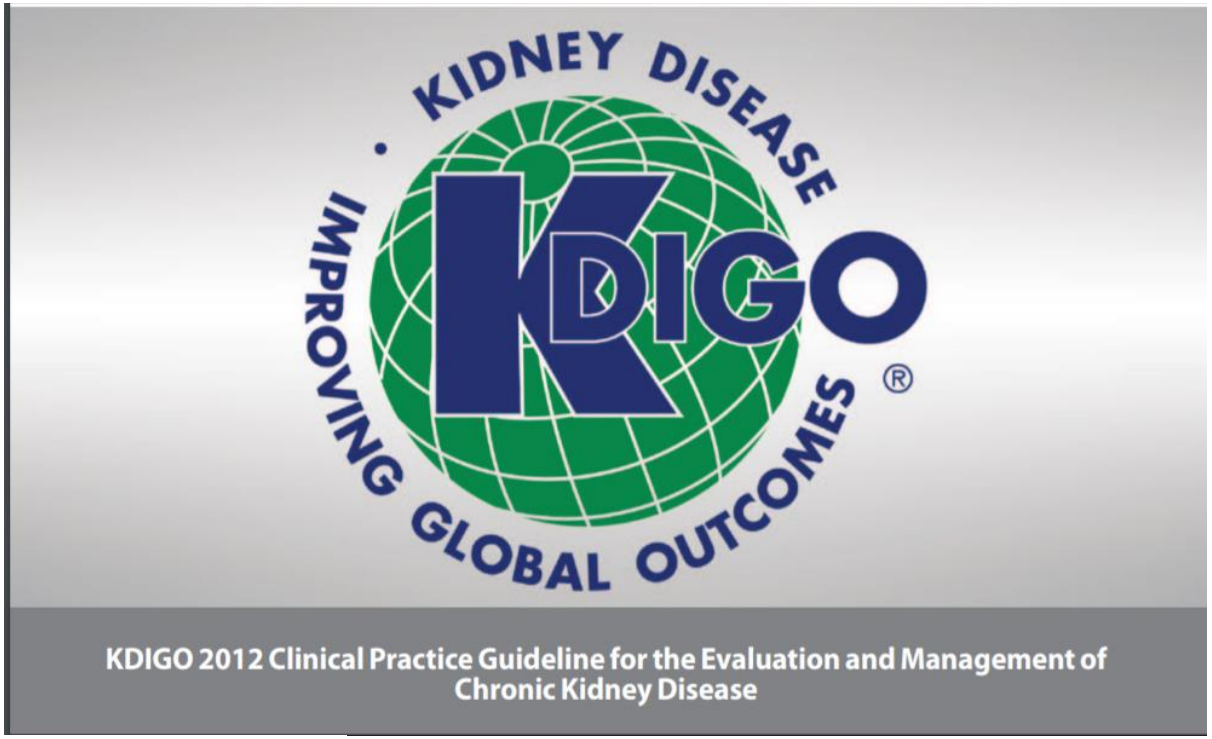
Clin J Am Soc Nephrol 6: 1963–1972, 2011. doi: 10.2215/CJN.02300311

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
3) 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)

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

Performance of Creatinine-Based Estimates of GFR in Kidney Transplant Recipients: A Systematic Review

Christine A. White, MD,[1] David Huang, BSc,[1] Ayub Akbari, MD,[2,3] Jocelyn Garland, MD,[1] and Greg A. Knoll, MD[2,3,4]

Am J Kidney Dis 56:1140-1157.2008

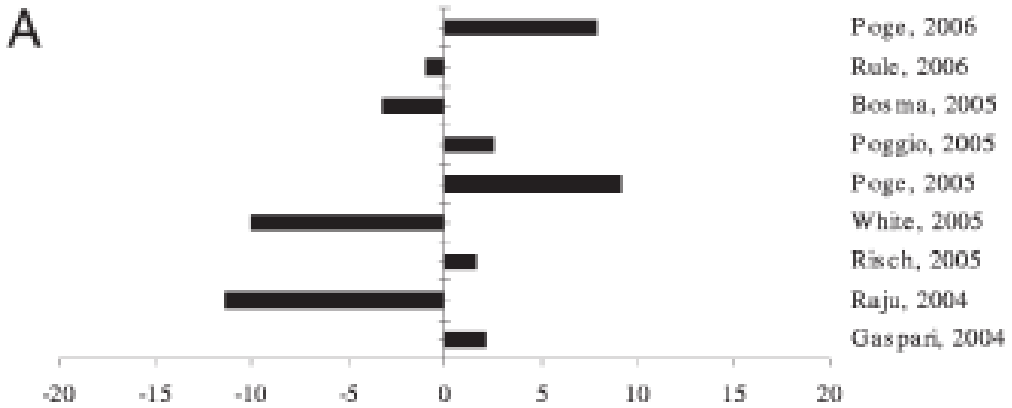


Table 3. Accuracy of Prediction Equations

Equations and Studies	Percent of Estimates Within 10%	20%	30%
4-Variable MDRD Study equation			
Poge et al,[32] 2006	25		67
Gera et al,[16] 2006			69
Bosma et al,[12] 2005	38		88
Poggio et al,[23] 2005		53	
Poge et al,[22] 2005	25		60
White et al,[30] 2005	24		74
Risch & Huber,[26] 2005			66
Raju et al,[25] 2005			66
Gaspari et al,[14] 2004	44	76	
Pooled estimate (95% CI)			
All studies	35 (32-38)	59 (54-65)	76 (74-78)
High quality*	34 (32-37)	53 (46-60)	77 (75-79)

CKD-EPI Equation

Is an Equation that was derived from a population with a mean GFR of 68 ml/min applicable to a transplant population
(with a mean GFR of 50-55 ml/min) ?

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

Kazunori Murata, Nikola A. Baumann,* Amy K. Saenger,* Timothy S. Larson,*† Andrew D. Rule,†‡ and John C. Lieske*†*

(n=1375, urinary clearance iothalamate)

MDRD= 80%

CKD-EPI= 78%

CLINICAL AND TRANSLATIONAL RESEARCH

Estimating Glomerular Filtration Rate in Kidney Transplant Recipients: Performance Over Time of Four Creatinine-Based Formulas

Fanny Buron,[1] Aoumer Hadj-Aissa,[2] Laurence Dubourg,[2] Emmanuel Morelon,[1] Jean-Paul Steghens,[3] Michel Ducher,[4] and Jean-Pierre Fauvel[4,5]

(n=1249, urinary clearance inulin)

MDRD= 85%

CKD-EPI= 81%

CLINICAL AND TRANSLATIONAL RESEARCH

MDRD Versus CKD-EPI Equation to Estimate Glomerular Filtration Rate in Kidney Transplant Recipients

Ingrid Masson,[1] Martin Flamant,[2] Nicolas Maillard,[1] Andrew D. Rule,[3] François Vrtovsnik,[4] Marie-Noëlle Peraldi,[5] Lise Thibaudin,[1] Etienne Cavalier,[6] Emmanuelle Vidal-Petiot,[2] Christine Bonneau,[7] Olivier Moranne,[8] Eric Alamartine,[1] Christophe Mariat,[1] and Pierre Delanaye[9,10]

(n=825, urinary clearance inulin/^{51}Cr-EDTA)

MDRD= 80%

CKD-EPI= 74%

Clinical Nephrology, Vol. 71 – No. 5/2009 (482-491)

Estimation of GFR by different creatinine- and cystatin-C-based equations in anorexia nervosa

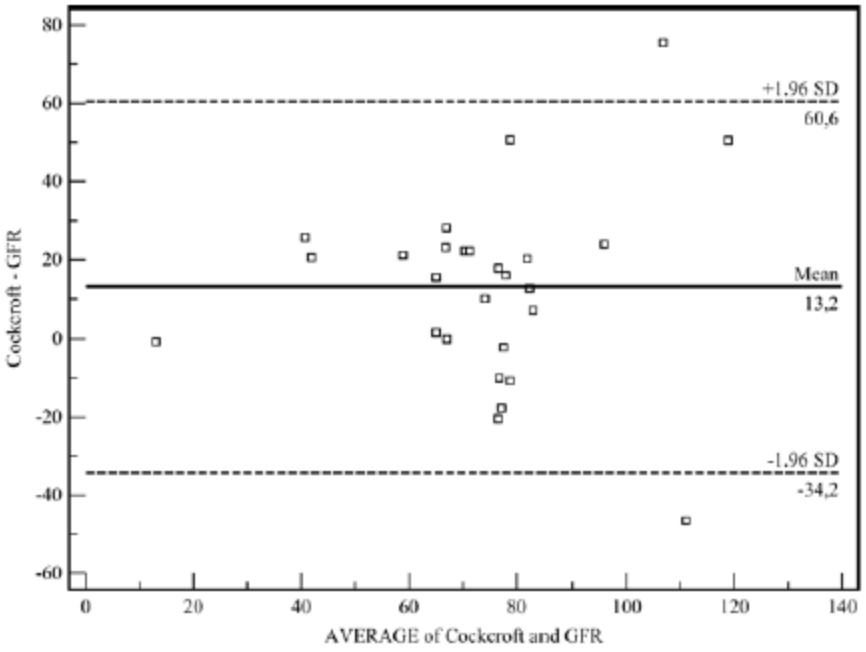
P. Delanaye[1], E. Cavalier[2], R.P. Radermecker[3], N. Paquot[3], G. Depas[4], J.-P. Chapelle[2], A.J. Scheen[3] and J.-M. Krzesinski[1]

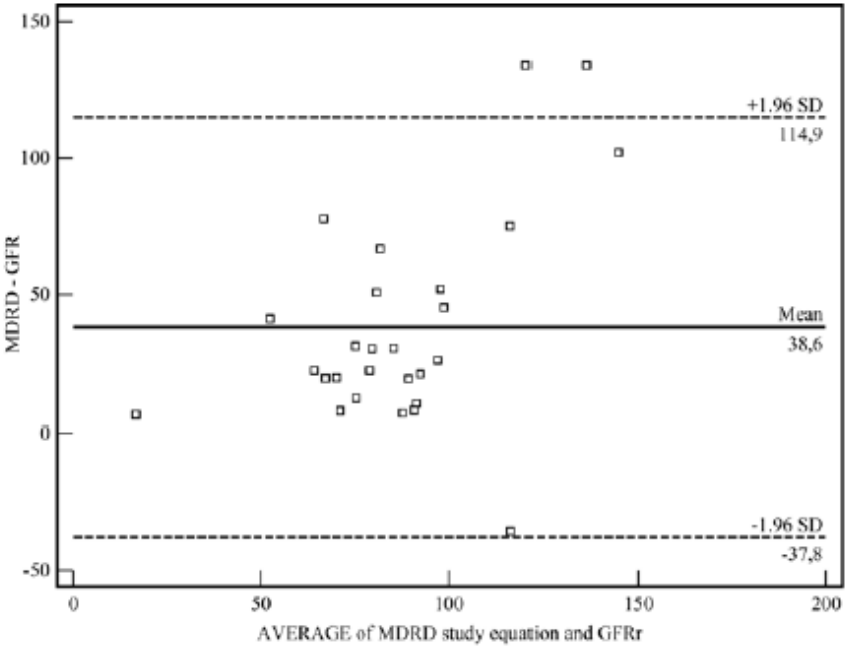
[1]Department of Nephrology-Dialysis, [2]Department of Clinical Chemistry, [3]Department of Diabetes, Nutrition and Metabolic Disorders, and [4]Department of Nuclear Medicine, University of Liège, CHU Sart Tilman, Liège, Belgium

- n=27, ^{51}Cr-EDTA, calibrated creatinine
- Mean GFR = 67 mL/min

	Mean difference with measured GFR (ml/min) for the whole population (n = 27)	SD of difference for the whole population
MDRD study	39	39
Cockcroft and Gault	13	24

If a relative difference was used, the estimated GFR was found within 30% measured GFR in 30% and 63% cases for the MDRD study and the Cockcroft and Gault equations,





What about **obese** subjects

Cockcroft : not good in obese subjects…

- Verhave JC, AJKD 2005
- Cirillo, NDT, 2005
- Rigalleau, Metab Clin Exper, 2005
- Froissart, JASN, 2006
- Cockcroft, Nephron, 1976
- Logical because weight in the equation…

Nephrol Dial Transplant (2013) 28 (Suppl. 4): iv122–iv130
doi: 10.1093/ndt/gft329
Advance Access publication 11 September 2013

ndt
Nephrology Dialysis Transplantation

Original Articles

Modification of Diet in Renal Disease versus Chronic Kidney Disease Epidemiology Collaboration equation to estimate glomerular filtration rate in obese patients

Antoine Bouquegneau[1],
Emmanuelle Vidal-Petiot[2],
François Vrtovsnik[3],
Etienne Cavalier[4],
Marcelle Rorive[5],
Jean-Marie Krzesinski[1],
Pierre Delanaye[1]
and Martin Flamant[2]

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[3]Department of Nephrology, Hôpital Bichat, AP-HP and Denis Diderot University, Paris, France,
[4]Department of Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium and
[5]Department of Diabetology, University of Liège, CHU Sart Tilman, Liège, Belgium

- Paris-Liège
- n=366, ^{51}Cr-EDTA, calibrated creatinine

Main characteristics of the population, $n = 366$	
Age (year)	55 ± 14 [18–86]
Female	185 (51%)
Weight (kg)	100 ± 22 [67–258]
Height (cm)	166 ± 10 [144–193]
African origin	50 (14%)
BMI (kg/m^2)	36 ± 7 [30–77]
30–35 kg/m^2	217 (59%)
35–40 kg/m^2	76 (21%)
>40 kg/m^2	73 (20%)

Table 2. Predictive performances of the MDRD study and CKD-EPI equations in the total obese population and according to different GFR levels

Population	Mean mGFR	Mean mGFR	Mean eGFR	Mean bias	Median bias (IQR)	Relative bias	Accuracy within 30%
	mL/min						%
Total							
MDRD	71 ± 35					± 28.7	80*
CKD-EPI	71 ± 35					± 30.0	76
mGFR < 30 mL/min/1.73 m^2 (n =							
MDRD	26 ± 7					± 44.9	70*
CKD-EPI	26 ± 7					± 45.5	62
30 < mGFR < 59 mL/min/1.73 m^2							
MDRD	55 ± 13					± 22.6	85*
CKD-EPI	55 ± 13					± 25.9	79
mGFR < 60 mL/min/1.73 m^2 (n =							
MDRD	45 ± 18					± 32.0	80*
CKD-EPI	45 ± 18					± 33.9	73
60 < mGFR < 89 mL/min/1.73 m^2							
MDRD	94 ± 17					± 24.1	79
CKD-EPI	94 ± 17					± 23.8	75
mGFR > 90 mL/min/1.73 m^2 (n =							
MDRD	126 ± 15					± 19.0	87
CKD-EPI	126 ± 15					± 16.4	89
mGFR > 60 mL/min/1.73 m^2(n = 139)							
MDRD	103 ± 22	81 ± 15	86 ± 21	4.6 ± 18.4*	2.1 (25.3)*	6.7 ± 23.2	81
CKD-EPI	103 ± 22	81 ± 15	91 ± 20	9.3 ± 17.2	8.5 (23.4)	12.7 ± 22.6	79

*P < 0.05 versus CKD-EPI. **P < 0.05 for SD versus CKD-EPI.

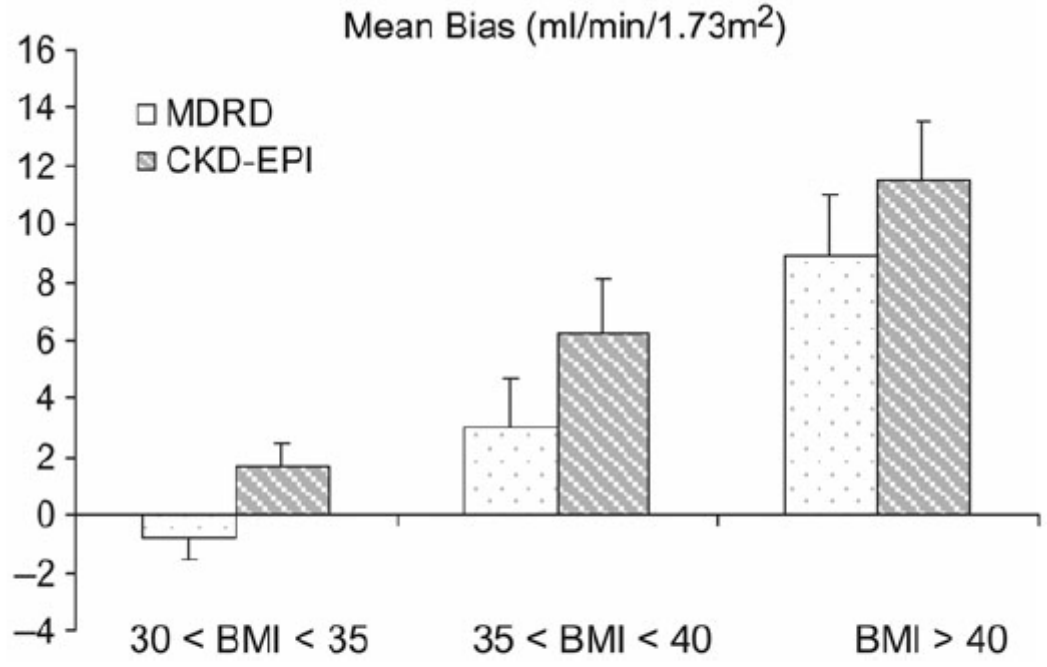


FIGURE 3: Mean bias of the MDRD and CKD-EPI equations in BMI subgroups. Mean bias is significantly lower for the MDRD equation and increases with BMI stage (two-way ANOVA test).

Conclusions from studies

- CKD-EPI = MDRD
- Cockcroft: very bad
- Performance of CKD-EPI (and MDRD) slightly less in obese than in non-obese populations
- Bias increases (or become « positive») with increased BMI and precision decreased
- CKD-EPI (and MDRD) overestimates mGFR (even high)

OK but this is not logical…

Impact of BSA indexation

- Great Impact in obese GFRs
- Over-correction by BSA (GFR too low)

Non-indexed mGFR (mL/min)	71 ± 35 [11–169]
CKD stage	
GFR ≥ 90 mL/min	110 (30%)
GFR 60–89 mL/min	100 (27%)
GFR 30–59 mL/min	107 (29%)
GFR 15–29 mL/min	44 (12%)
Hyperfiltrating status (GFR > 120 mL/min)	37 (10%)
Indexed mGFR (mL/min/1.73 m^2)	56 ± 26 [8–125]
CKD stage	
GFR ≥ 90 mL/min/1.73 m^2	44 (12%)
GFR 60–89 mL/min/1.73 m^2	114 (31%)
GFR 30–59 mL/min/1.73 m^2	137 (37%)
GFR 15–29 mL/min/1.73 m^2	62 (17%)
Hyperfiltrating status (GFR > 120 mL/min/1.73 m^2)	1 (<1%)

Delanaye P, NDT, 2005
Eriksen BO, JASN, 2011

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…

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

The elderly


SI ON AVAIT SON ANNIVERSAIRE DEUX FOIS PAR AN
ON VIVRAIT DEUX FOIS PLUS VIEUX
© casterman - geluck

Annals of Internal Medicine | ORIGINAL RESEARCH

Two Novel Equations to Estimate Kidney Function in Persons Aged 70 Years or Older

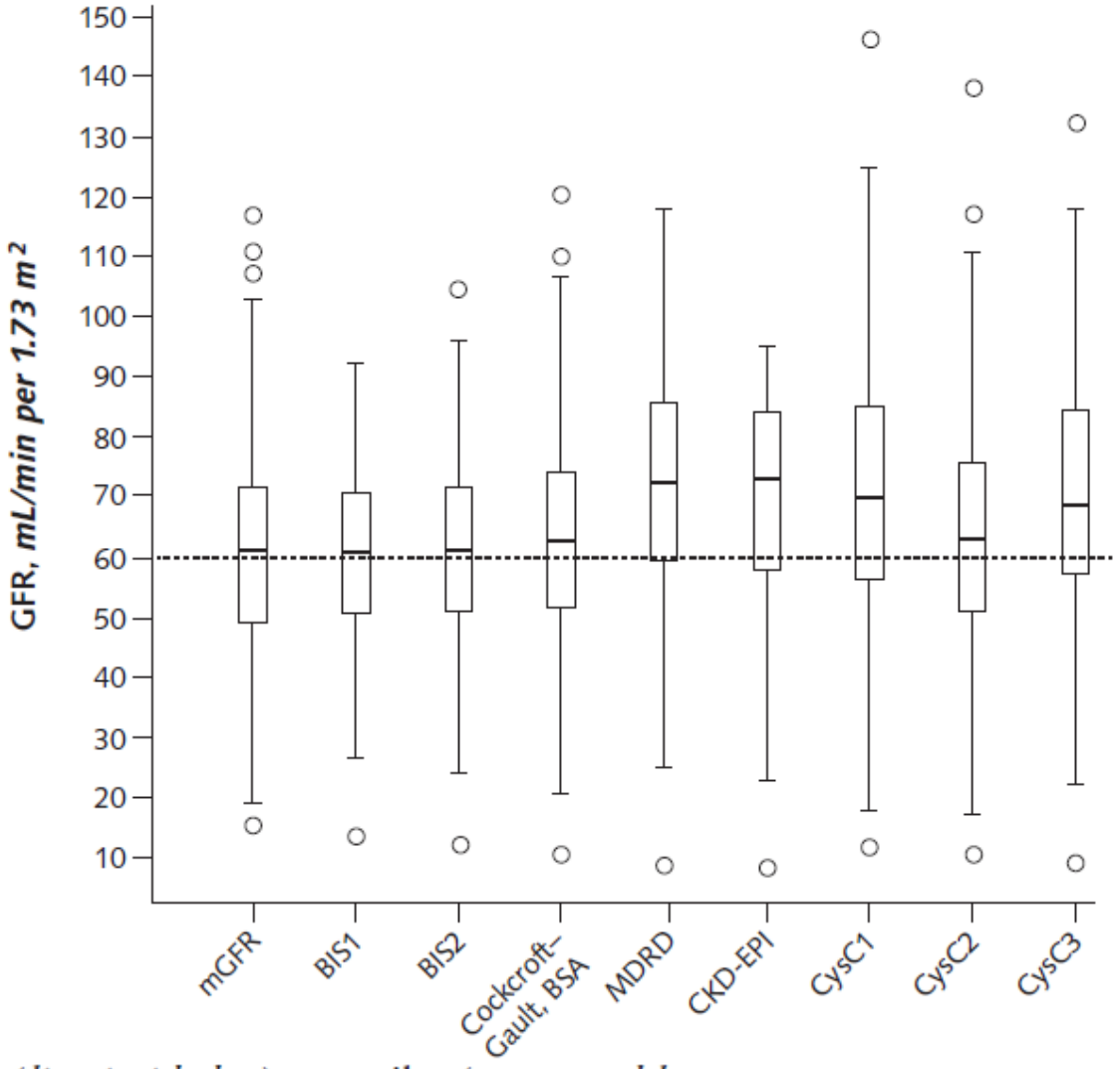
Elke S. Schaeffner, MD, MS*; Natalie Ebert, MD, MPH*; Pierre Delanaye, MD, PhD; Ulrich Frei, MD; Jens Gaedeke, MD; Olga Jakob; Martin K. Kuhlmann, MD; Mirjam Schuchardt, PhD; Markus Tölle, MD; Reinhard Ziebig, PhD; Markus van der Giet, MD; and Peter Martus, PhD

BIS1:

$$3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82 \text{ (if female)}$$

Ann Intern Med. 2012;157:471-481

Figure 1. **Comparison of mGFR with eGFR equations in the validation sample.**



Boxes indicate medians (*line inside box*), quartiles (*upper and lower margins of box*). Antennae are defined by the rule upper–lower box margin ± 1.5 × interquartile range. Circles indicate outliers.

CKD-EPI Equation *vs* BIS Equation

n=5504

- Mean Age: 47
- Mean GFR: 68 ml/min/1.73m^2
- Reference: Iothalamate
- Creatinine Assay: Multiple – recalibration

n=570

- Mean Age: 78.5
- Mean GFR: 60 ml/min/1.73m^2
- Reference: Iohexol
- Creatinine Assay:
- IDMS - Enzymatic

COMPARATIVE ACCURACY-30%
- CKD-EPI vs BIS -

- *Koppe L et al. J Nephrol, 2013*
  - **n=224, Mean Age=75** 72% vs 76%
- *Lopes M et al. BMC Nephrology, 2013*
  - **n=95, Mean Age=85** 75% vs 80%
- *Alshoer I et al. AJKD, 2014*
  - **n=394, Median Age=80** 83% vs 88%
- *Vidal-Petiot E et al. AJKD, 2014*
  - **N=609, Mean Age=76** 82% vs 84%

Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals

Li Fan,*† Andrew S. Levey,* Vilmundur Gudnason,‡§ Gudny Eiriksdottir,‡ Margret B. Andresdottir,‖ Hrefna Gudmundsdottir,§‖ Olafur S. Indridason,‖ Runolfur Palsson,§‖ Gary Mitchell,¶ and Lesley A. Inker*

J Am Soc Nephrol 26: 1982–1989, 2015.

N=805
+74 y

Equation	Bias Median Difference	Precision IQR	Accuracy P_{30}
eGFRcr			
CKD-EPI	−2.7 (−3.3 to −2.1)	12.1 (11.2 to 13.4)	91.7 (89.9 to 93.4)
Japanese	10.5 (9.8 to 11.2)[c]	10.9 (9.7 to 12.1)[a]	86.3 (83.9 to 88.6)[c]
BIS	5.7 (5.1 to 6.4)[c]	11.9 (10.6 to 12.7)[a]	95.8 (94.4 to 97.1)[b]

[a]No different than CKD-EPI.
[b]Better than CKD-EPI.
[c]Worse than CKD-EPI.

Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals

Li Fan,*† Andrew S. Levey,* Vilmundur Gudnason,‡§ Gudny Eiriksdottir,‡ Margret B. Andresdottir,‖ Hrefna Gudmundsdottir,§‖ Olafur S. Indridason,‖ Runolfur Palsson,§‖ Gary Mitchell,¶ and Lesley A. Inker*

J Am Soc Nephrol 26: 1982–1989, 2015.

Words bias or unbiase cited 31 times
Precision or imprecision 9 times

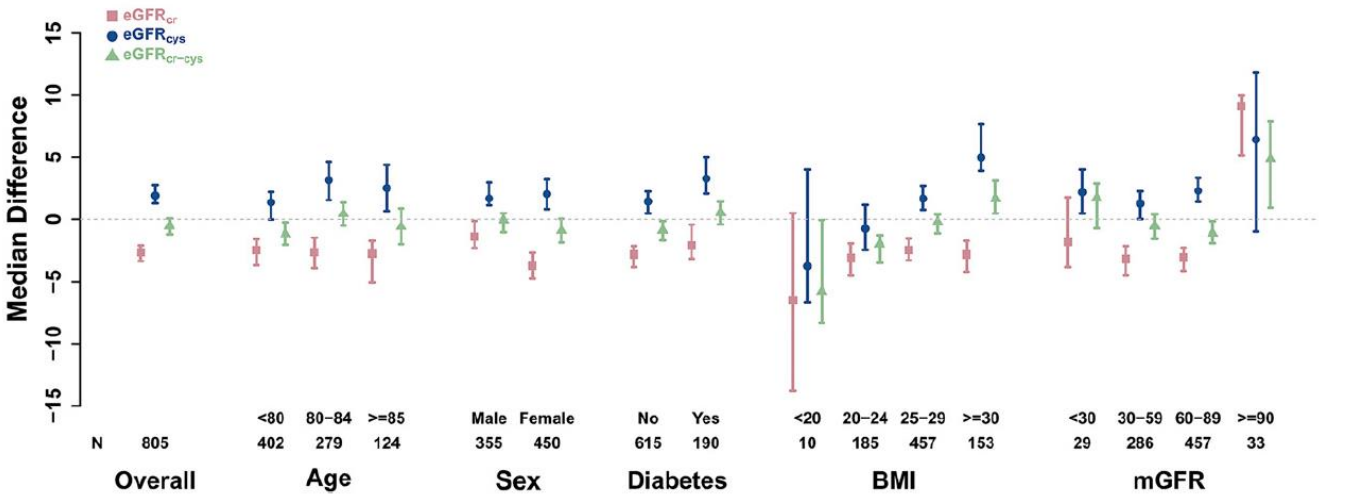


Figure 3. Comparison of bias of the CKD-EPI equations. Bias is calculated as the median difference between mGFR and eGFR. Bars indicate the 95% CIs. N indicates sample size.

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

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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

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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

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

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

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

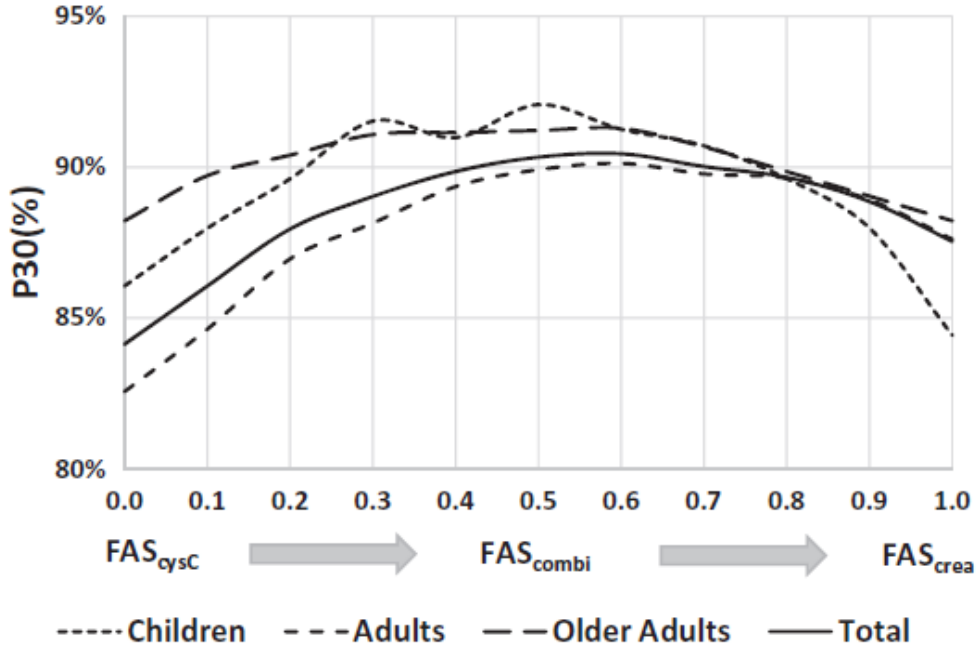

FIGURE 3: P30 as a function of the weighting factor α for the different age groups.

AJKD

Am J Kidney Dis. 2017 Oct;70(4):587-589

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RESEARCH LETTER

Comparing Newer GFR Estimating Equations Using Creatinine and Cystatin C to the CKD-EPI Equations in Adults

Equation	Bias Median Difference (mL/min/1.73 m^2)	Precision IQR of Differences (mL/min/1.73 m^2)	Accuracy 1 – P_{30} (%)	Accuracy RMSE
Performance of Creatinine Equations in Creatinine Validation Database (n=3,896)				
CKD-EPI	2.2 (1.8, 2.6)	16.6 (15.8, 17.2)	15.8 (14.7, 17.0)	0.249 (0.240, 0.259)
LMR	**7.4 (6.8, 7.8)**	**18.2 (17.6, 19.1)**	**20.3 (19.0, 21.6)**	**0.280 (0.272, 0.288)**
FAS	1.4 (1.0, 1.8)	**18.0 (17.3, 18.7)**	**18.3 (17.1, 19.5)**	0.261 (0.252, 0.271)
Performance of Cystatin C Equations in Cystatin C Validation Database (n=1,119)				
CKD-EPI	3.4 (2.3, 4.4)	16.4 (14.8, 17.7)	14.1 (12.1, 16.2)	0.234 (0.220, 0.250)
CAPA	3.8 (2.7, 4.9)	18.2 (16.6, 19.6)	16.3 (14.1, 18.4)	0.247 (0.233, 0.264)
FAS	**0.2 (–0.8, 1.4)**	**20.5 (18.6, 21.6)**	**23.9 (21.4, 26.5)**	**0.288 (0.270, 0.310)**

N=3896 (créatinine) et 1119 (cystatine C)
Validation database, 10% AA

Differences in precision among GFR estimating equations are more important than small differences in bias. Precision reflects how well coefficients for the endogenous filtration marker (creatinine or cystatin C) and the surrogates for their non-GFR determinants (age, sex, and race) model their true relationships to mGFR.

Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals

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J Am Soc Nephrol 26: 1982–1989, 2015.

N=805
+74 y

Equation	Bias Median Difference	Precision IQR	Accuracy P_{30}
eGFRcr			
CKD-EPI	−2.7 (−3.3 to −2.1)	12.1 (11.2 to 13.4)	91.7 (89.9 to 93.4)
Japanese	10.5 (9.8 to 11.2)[c]	10.9 (9.7 to 12.1)[a]	86.3 (83.9 to 88.6)[c]
BIS	5.7 (5.1 to 6.4)[c]	11.9 (10.6 to 12.7)[a]	95.8 (94.4 to 97.1)[b]

[a]No different than CKD-EPI.
[b]Better than CKD-EPI.
[c]Worse than CKD-EPI.

Nephrol Dial Transplant (2017) 1–9
doi: 10.1093/ndt/gfx272

ndt
Nephrology Dialysis Transplantation

Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort

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Table 2. Bias (median eGFR−mGFR, mL/min/1.73 m^2), precision (IQR, mL/min/1.73 m^2), absolute accuracy (median, percent) and P_{30} accuracy (percentage of GFR estimated within 30% of mGFR) of GFR estimating equations based on creatinine and the combination of creatinine and cystatin C in the AGES-Kidney cohort ($n = 805$)

Variables	LMR_{Cr}	FAS_{Cr}	$CKD\text{-}EPI_{Cr}$	$MEAN_{LMR+CAPA}$	FAS_{Cr+Cys}	$CKD\text{-}EPI_{Cr+Cys}$
Bias	−4.8 (−5.4 to − 4.2)[a]	−5.7 (−6.3 to − 5.1)[a]	2.7 (2.1 to 3.3)	−2.7 (−3.2 to − 2.1)[a]	−5.9 (−6.5 to − 5.4)[a]	0.6 (−0.1 to 1.2)
Precision	10.8 (10.1 to 11.5)[b]	10.7 (9.9 to 11.9)[b]	12.1 (11.2 to 13.4)	9.3 (8.5 to 10.1)[c]	10.0 (9.1 to 10.9)[c]	10.2 (9.0 to 11.1)
Absolute accuracy	11.4 (10.3 to 12.3)[c]	12.1 (11.1 to 13.2)[a]	10.2 (9.3 to 11.0)	8.5 (8.0 to 9.2)[c]	11.3 (10.5 to 12.3)[a]	8.1 (7.5 to 8.9)
P_{30} accuracy	95.0 (93.5 to 96.5)[b]	95.8 (94.4 to 97.2)[b]	91.7 (89.9 to 93.4)	97.3 (96.2 to 98.4)[b]	97.8 (96.7 to 98.8)[b]	96.1 (94.8 to 97.4)

Data are presented with 95% CIs.
[a]Significantly worse ($P < 0.05$) than corresponding CKD-EPI equation.
[b]Significantly better ($P < 0.05$) than corresponding CKD-EPI equation.
[c]No statistical difference ($P \geq 0.05$) compared with corresponding CKD-EPI equation.

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GFR estimation based on standardized creatinine and cystatin C: a European multicenter analysis in older adults

5 cohortes > 70 y

Creatinine

Bias: worse for CKD-EPI

Precision: best for LM and FAS

Accuracy: LM>FAS>CKD-EPI

Cystatin C

No difference between

No difference with creat

Combined

+5 to 10% compared to creatinine

LM+CAPA slightly better

Table 2: Bias, precision and accuracy (95% confidence intervals) of creatinine, cystatin C and combined-marker equations in adults ≥70 years.

Equations	Bias	Precision	Absolute accuracy	P_{15} accuracy	P_{30} accuracy
Creatinine (n = 3226)					
BIS1	1.7 (1.2 to 2.0)	11.6 (11.1–12.1)	14.8 (14.1–15.5)	50.7 (48.9–52.4)	77.5 (76.1–78.9)
BIS1 (no Berlin data, n = 2569)	2.0 (1.6 to 2.4)	11.6 (11.1–12.1)	16.3 (15.5–17.1)	46.6 (44.7–51.1)	73.8 (72.1–75.5)
CKD-EPI	3.6 (3.2 to 4.0)	12.3 (11.9–13.0)	16.3 (15.6–17.0)	46.3 (44.6–48.0)	76.4 (74.9–77.9)
FAS	0.6 (0.3 to 0.9)	11.1 (10.6–11.5)	14.0 (13.4–14.5)	53.3 (51.5–55.0)	80.9 (79.5–82.3)
LMR	−0.7 (−1.0 to −0.4)	10.5 (10.1–11.0)	13.8 (13.3–14.3)	54.2 (52.4–55.9)	83.5 (82.2–84.8)
LMR (no Lund data, n = 2309)	−1.0 (−1.5 to −0.6)	11.0 (10.5–11.6)	13.9 (13.3–14.4)	53.9 (51.8–55.9)	83.7 (82.2–85.2)
Cystatin C (n = 2638)					
CAPA	−1.4 (−1.8 to −1.0)	11.9 (11.3–12.6)	15.7 (14.9–16.5)	48.2 (46.3–50.1)	80.3 (78.8–81.8)
CAPA (no Lund data, n = 1721)	1.0 (0.5 to 1.6)	13.1 (12.3–13.8)	14.1 (13.3–15.0)	52.3 (49.9–54.7)	82.5 (80.7–84.3)
CKD-EPI	−2.7 (−3.1 to −2.3)	11.8 (11.3–12.5)	16.4 (15.7–17.1)	46.1 (44.2–48.0)	78.8 (77.3–80.4)
FAS	−1.1 (−1.6 to −0.8)	12.2 (11.7–12.8)	15.1 (14.3–16.0)	49.8 (47.9–51.8)	80.9 (79.4–82.4)
Creatinine + cystatin C (n = 2638)					
BIS2	−1.2 (−1.5 to −0.8)	10.5 (10.0–11.0)	12.1 (11.6–12.8)	58.4 (56.5–60.3)	85.7 (84.4–87.0)
BIS2 (no Berlin data, n = 1981)	−1.9 (−2.3 to −1.4)	10.9 (10.4–11.4)	14.0 (13.2–14.7)	52.7 (50.5–54.9)	82.6 (80.9–84.3)
CKD-EPI	−0.1 (−0.4 to 0.2)	10.2 (9.6–10.8)	12.8 (12.3–13.3)	56.8 (54.9–58.7)	86.8 (85.5–88.1)
FAS	−0.8 (−1.1 to −0.5)	10.1 (9.7–10.7)	12.2 (11.5–12.7)	58.7 (56.8–60.6)	85.7 (84.4–87.1)
$MEAN_{LMR+CAPA}$	−1.0 (−1.3 to −0.6)	9.2 (8.8–9.6)	11.9 (11.3–12.4)	61.4 (59.6–63.3)	88.7 (87.5–89.9)
$MEAN_{LMR+CAPA}$ (no Lund data, n = 1721)	0.1 (−0.3 to 0.6)	9.7 (9.1–10.3)	11.1 (10.6–11.8)	63.6 (61.4–65.9)	89.0 (87.5–90.5)

Median bias (eGFR–mGFR) and precision (interquartile range) expressed in mL/min/1.73 m^2, and median absolute accuracy ([eGFR–mGFR]/mGFR) expressed in percent, and P_{15} and P_{30} accuracy (percentage of GFR estimates within 15% and 30% of measured GFR).

Cystatin C

- Combined
- Cost-effectiveness?
- At the individual level, the imprecision remains…

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)

But also in clinical research…

Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial

Anna Caroli, Norberto Perico*, Annalisa Perna*, Luca Antiga, Paolo Brambilla, Antonio Pisani, Bianca Visciano, Massimo Imbriaco, Piergiorgio Messa, Roberta Cerutti, Mauro Dugo, Luca Cancian, Erasmo Buongiorno, Antonio De Pascalis, Flavio Gaspari, Fabiola Carrara, Nadia Rubis, Silvia Prandini, Andrea Remuzzi, Giuseppe Remuzzi*, Piero Ruggenenti*, for the ALADIN study group†*

Lancet 2013; 382: 1485–95

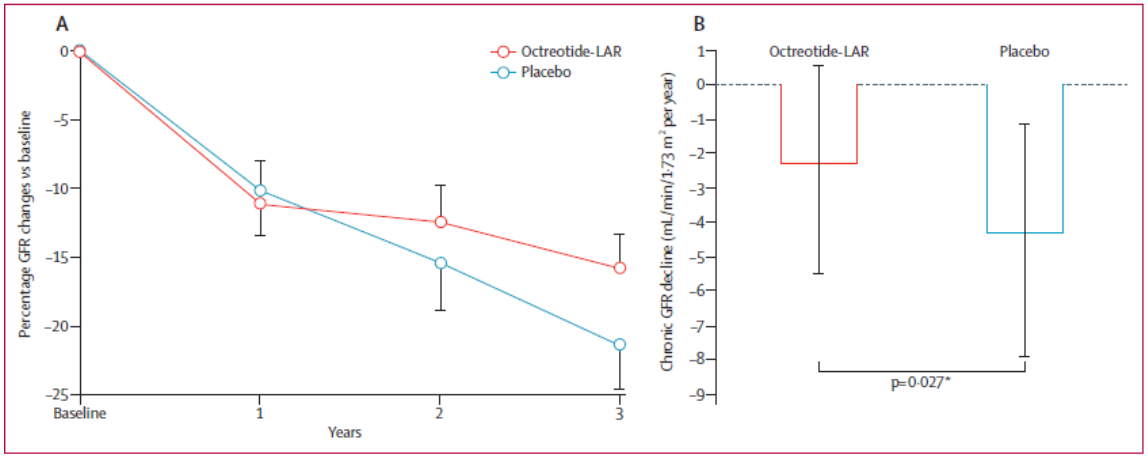


Figure 5: **Effect of placebo or Octreotide-LAR treatment on kidney function**
Percentage change in GFR, measured by iohexol plasma clearance, compared with baseline in placebo and Octreotide-LAR groups during the 3 year treatment (A). Chronic GFR decline from year 1 to year 3 after randomisation in the two treatment groups (B). Values are mean (SEM) and median (IQR). p values calculated after log-tranformation of GFR values. p values from Wilcoxon rank-sum test. GFR=glomerular filtration rate.

	Octreotide-LAR (n=40)	Placebo (n=39)
Age (years)	36 (8)	38 (8)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D., Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D., for the TEMPO 3:4 Trial Investigators*

ABSTRACT

N Engl J Med 2012;367:2407-18.
DOI: 10.1056/NEJMoa1205511

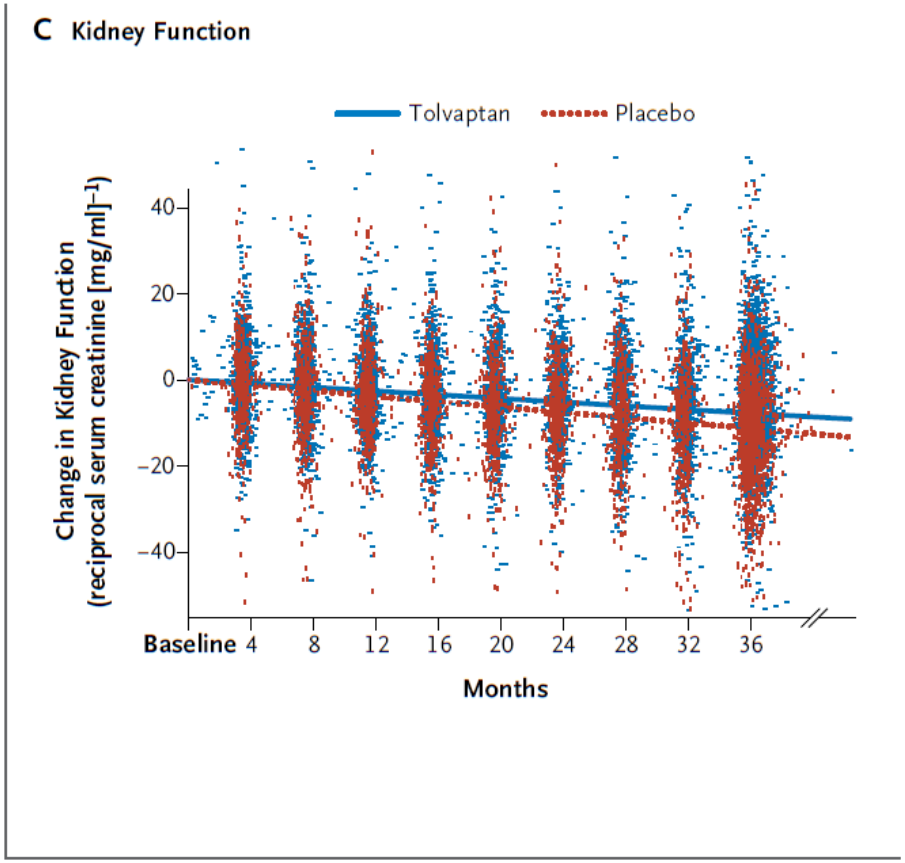


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

N Engl J Med 2016;374:333-43.
DOI: 10.1056/NEJMoa1506027

Belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), selectively inhibits T-cell activation through costimulation blockade.[13-15]

CONCLUSIONS

Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept (both the more-intensive regimen and the less-intensive regimen) than with cyclosporine. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00256750.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Costimulation Blockade with Belatacept in Renal Transplantation

Flavio Vincenti, M.D., Christian Larsen, M.D., Ph.D., Antoine Durrbach, M.D., Ph.D., Thomas Wekerle, M.D., Björn Nashan, M.D., Ph.D., Gilles Blancho, M.D., Ph.D., Philippe Lang, M.D., Josep Grinyo, M.D., Philip F. Halloran, M.D., Ph.D., Kim Solez, M.D., David Hagerty, M.D., Elliott Levy, M.D., Wenjiong Zhou, Ph.D., Kannan Natarajan, Ph.D., and Bernard Charpentier, M.D., for the Belatacept Study Group*

N Engl J Med 2005;353:770-81.

6 months

Table 3. Renal Function and Histologic Findings.*

End Point	Intensive Belatacept	Less-Intensive Belatacept	Cyclosporine
Measured GFR			
No. of patients	32	37	27
Mean GFR — ml/min/1.73 m²†	66.3±20.7	62.1±15.9	53.5±16.4
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	12.8 (2.9 to 22.7)	8.6 (0.4 to 16.8)	—
Calculated GFR			
No. of patients	60	59	50
Mean GFR — ml/min/1.73 m²	72.4±22.5	73.2±22.5	68.0±28.1
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	4.4 (−5.2 to 14.0)	5.2 (−4.4 to 14.8)	—

† $P<0.05$ for the comparison of both belatacept regimens with cyclosporine.

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

↓

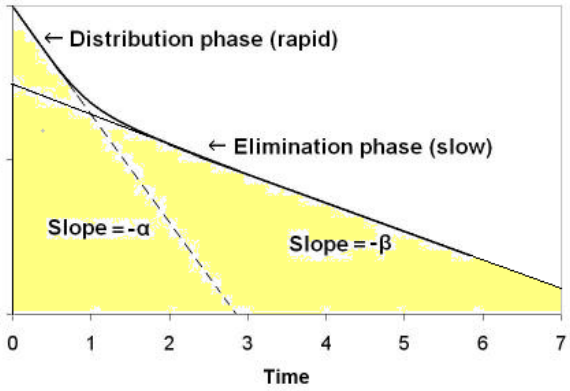
Not easy in practice (many samples)

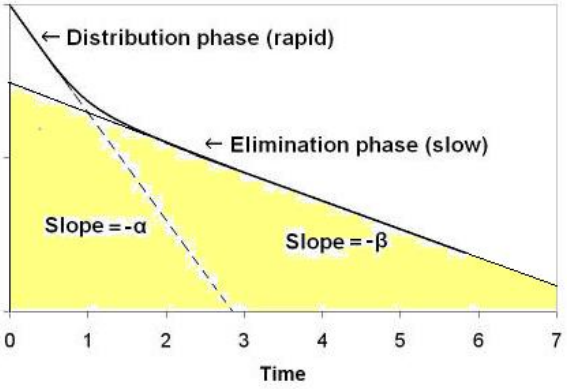
↓

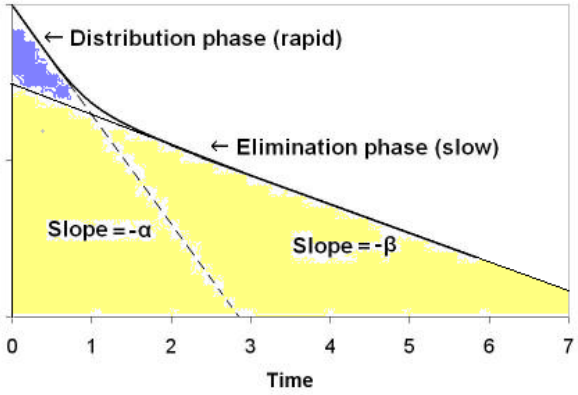
Only slope ß after equilibrium is calculated

↓

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







M

Are they equivalent?

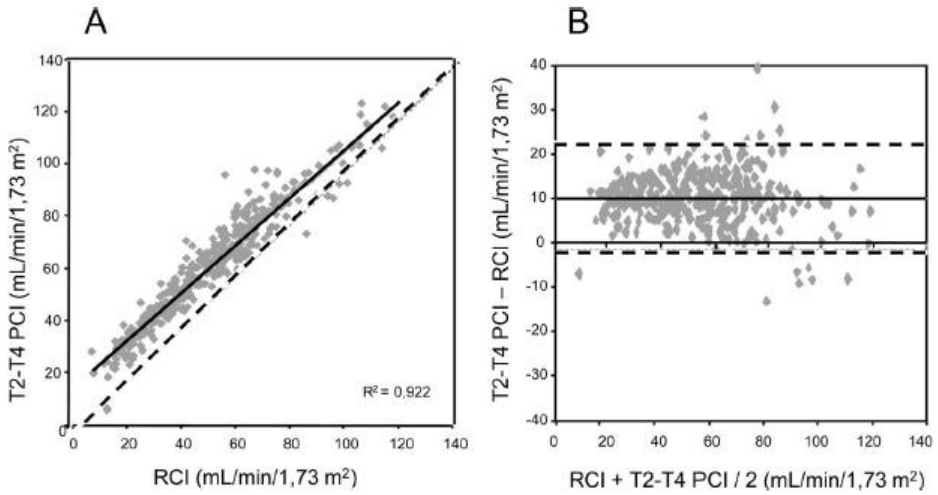
Plasma v urinary:
Are they equivalent?

- 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…

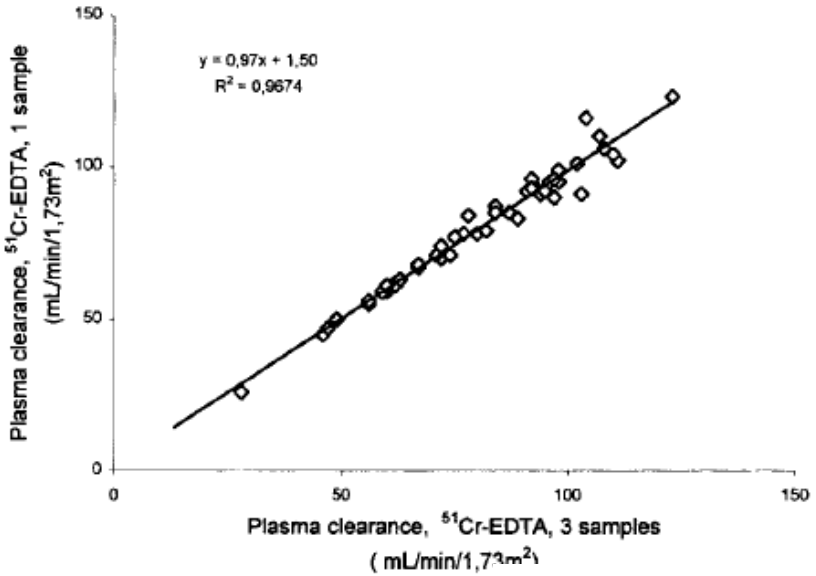
Markers	Strenghts	Limitations
Inulin	Gold standard (or historic) Safe	Costly Dosage neither easy nor standardized Doubt with plasma clearance
Iothalamate	The most popular in USA Isotopic or "cold" method	Tubular secretion Cannot be used if allergy to iodine
Iohexol		
EDTA	Easy to measure	Only isotopic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

Are they equivalent?

EDTA versus iohexol

N=49



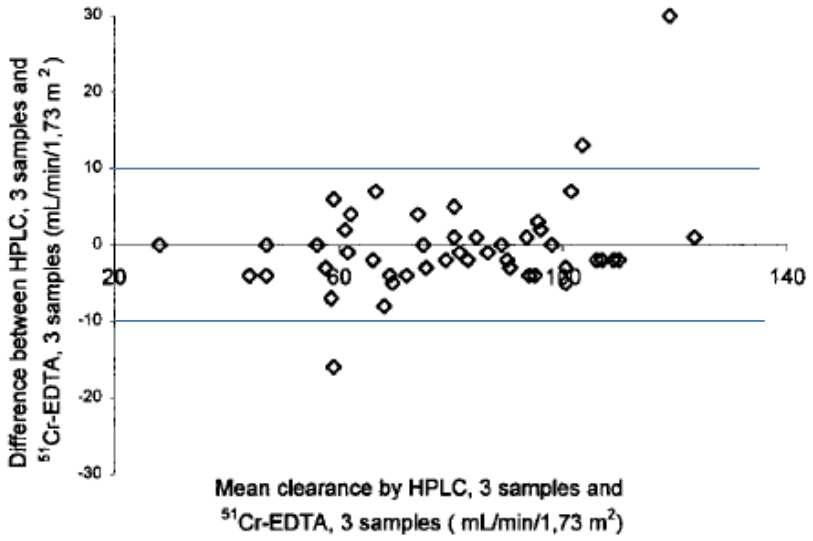


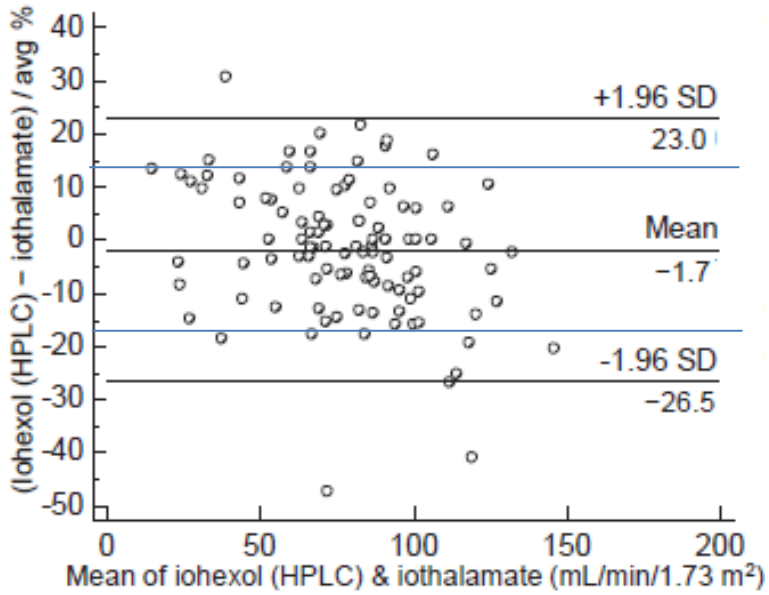
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	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

What about Isotopic nephrogram (Gates method)

OPEN ACCESS Freely available online

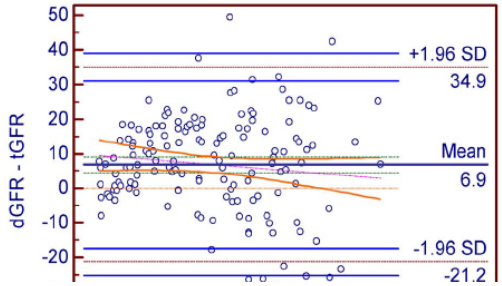
PLOS ONE

^{99m}Tc-DTPA Renal Dynamic Imaging Method May Be Unsuitable To Be Used as the Reference Method in Investigating the Validity of CDK-EPI Equation for Determining Glomerular Filtration Rate

Peng Xie[1]*, Jian-Min Huang[1], Xiao-Mei Liu[1], Wei-Jie Wu[1], Li-Ping Pan[1], Hai-Ying Lin[2]

1 Department of Nuclear Medicine, The Third Hospital, Hebei Medical University, Shijiazhuang, P.R. China, 2 Department of Nephrology, The Third Hospital, Hebei Medical University, Shijiazhuang, P.R. China

May 2013 | Volume 8 | Issue 5 | e62328



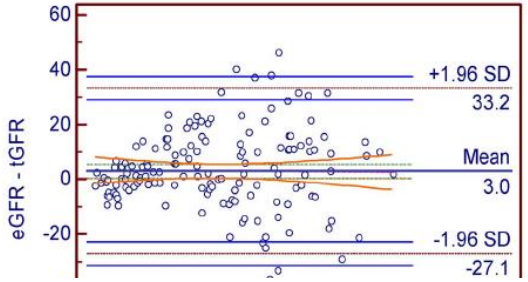


Table 1. The comparison of the dynamic renal imaging method and the CDK-EPI equation on the performance in estimating GFR.

Method	Bias (Mean)	Precision (SD)	Accuracy with 50%, %	Accuracy with 30%, %	Accuracy wwith 15%, %
Whole cohort (n = 149)					
dGFR	6.85	14.34	83.22	66.44	41.61
eGFR	3.01**	15.39*	91.28**	71.14*	48.99*

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

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?