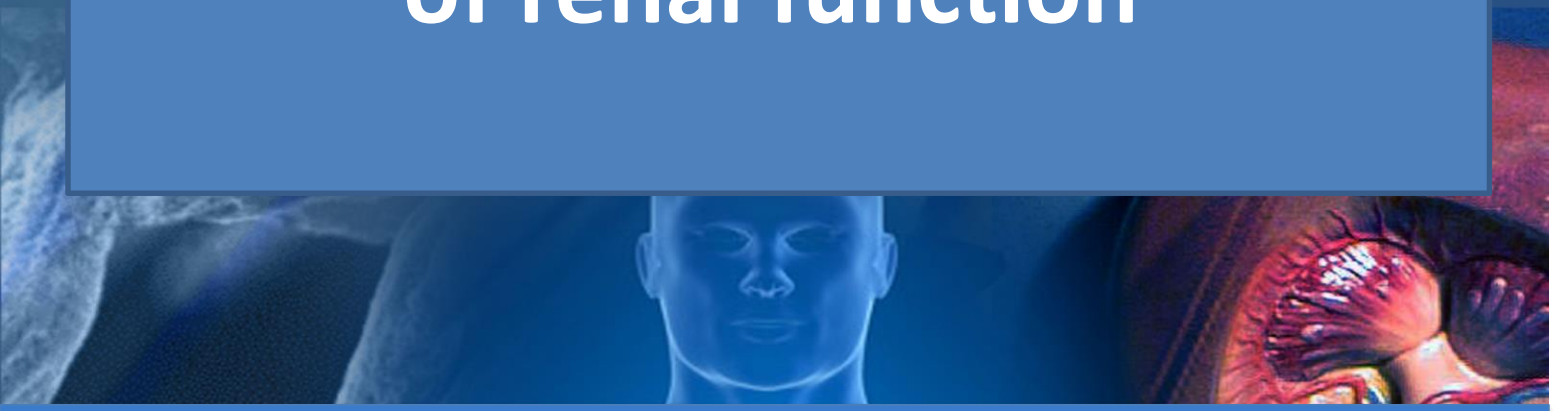
Measurement and Estimation of renal function



Professeur Pierre Delanaye
Université de Liège
CHU Sart Tilman
BELGIQUE

LIÈGE université

ckj OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2018, 1–13

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Original Article

Published: 19 April 2018

ORIGINAL ARTICLE

Citation classics: ranking of the top 100 most cited articles in nephrology

Vincenzo Montinaro[1], Marica Giliberti[1,2], Chiara Villani[1,2] and Adriano Montinaro[1,2]

[1]Division of Nephrology, Azienda Ospedaliero-Universitaria Policlinico, Bari, Italy and [2]Post-graduate specialty program in Nephrology, Department of Emergency and Organ Transplantation, School of Medicine, University 'Aldo Moro', Bari, Italy

Correspondence and offprint requests to: Vincenzo Montinaro; E-mail: vincenzo.montinaro1@gmail.com

Table 2. Subcategories of the top 100 most cited articles

Number	Article group	Description	Abbreviation	Number of articles	Article number	Number of citations (total)	% total
1	Renal function assessment	Studies on modalities of renal function assessment and laboratory methods	RF	16	1, 2, 4, 17, 19, 26, 27, 31–33, 39, 52, 56, 78, 81, 95	67 938	23.8
2	Randomized trials/ pharmacology	Randomized clinical trials and pharmacology of relevant kidney diseases	RT	16	6–8, 14, 35, 36, 44, 46, 51, 57, 60, 72, 73, 87, 98, 100	46 652	16.4
3	Dialysis transplantation	Studies involving uraemic patients treated by dialysis or transplantation	DT	14	24, 28, 34, 41, 45, 53, 58, 59, 62, 70, 82, 83, 88, 90	29 424	10.3

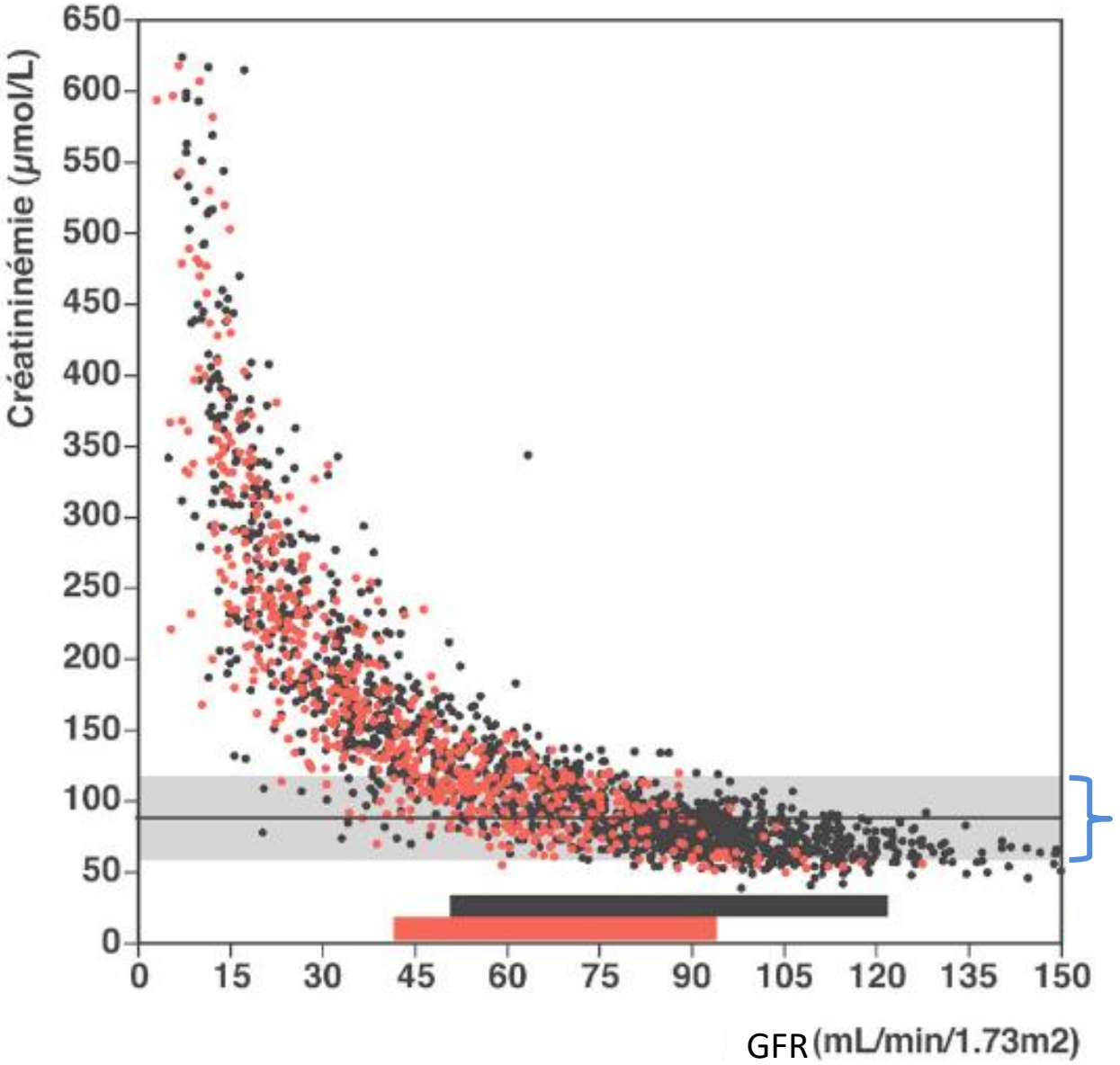
- How to estimate GFR?
- How to measure GFR?

- How to estimate GFR?
- How to measure GFR?

Serum creatinine

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

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



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

Analytical limitations

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

Significant improvement in the standardization (IDMS traceable)

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

Physiological limitations

- Extra-renal production

- 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

Physiological limitations

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

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

Creatinine: to the trash?

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

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

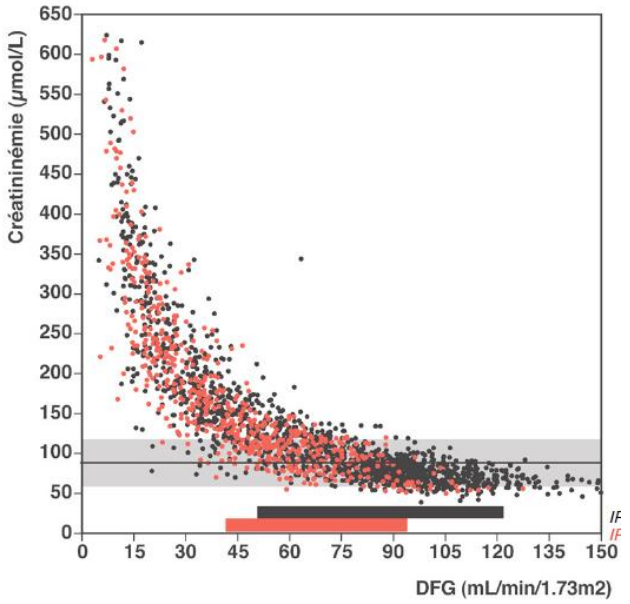
large intra-individual variability for creatinine excretion

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

Creatinine-based equations

Why such equations?

- Conceptualize the hyperbolic assocation between creatinine and GFR?
- Interpreting the result of creatinine by gender, age, ethnicity
- Decrease the IC (?)



Which one?

- Cockcroft
- MDRD
- CKD-EPI
- Others

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

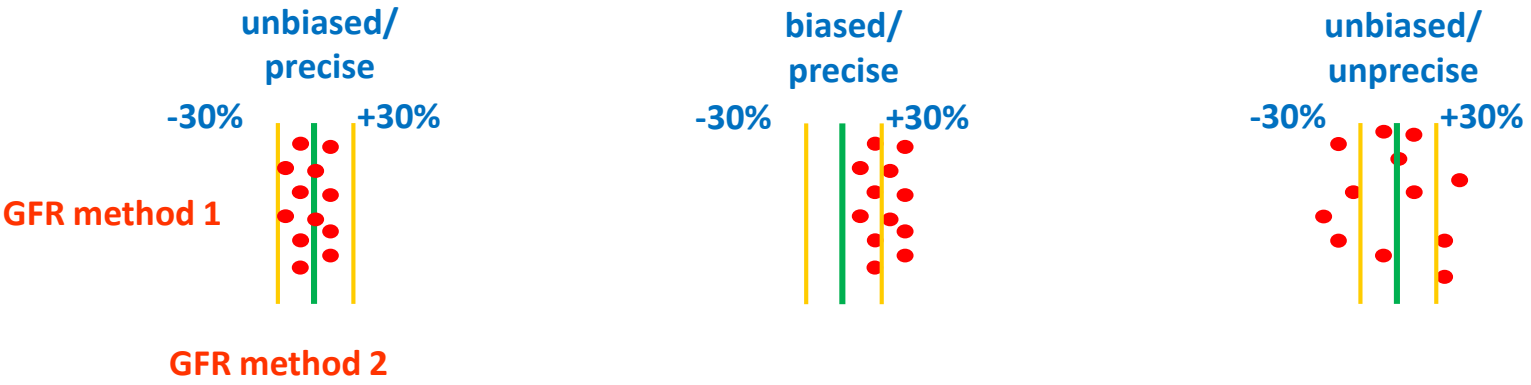


Table 1. MDRD study equations and Cockcroft equation commonly used for GFR estimation

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 (special)	Jaffe calibré
% 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

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*†§

*Department of Physiology and Biophysics, Georges Pompidou Hospital (AP-HP); †INSERM U652 and IFR 58; ‡Department of Nephrology, Georges Pompidou Hospital (AP-HP); §René Descartes Medical School, Paris V University; and ‖Paris VI University, Paris, France

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.

- 55
- Ca

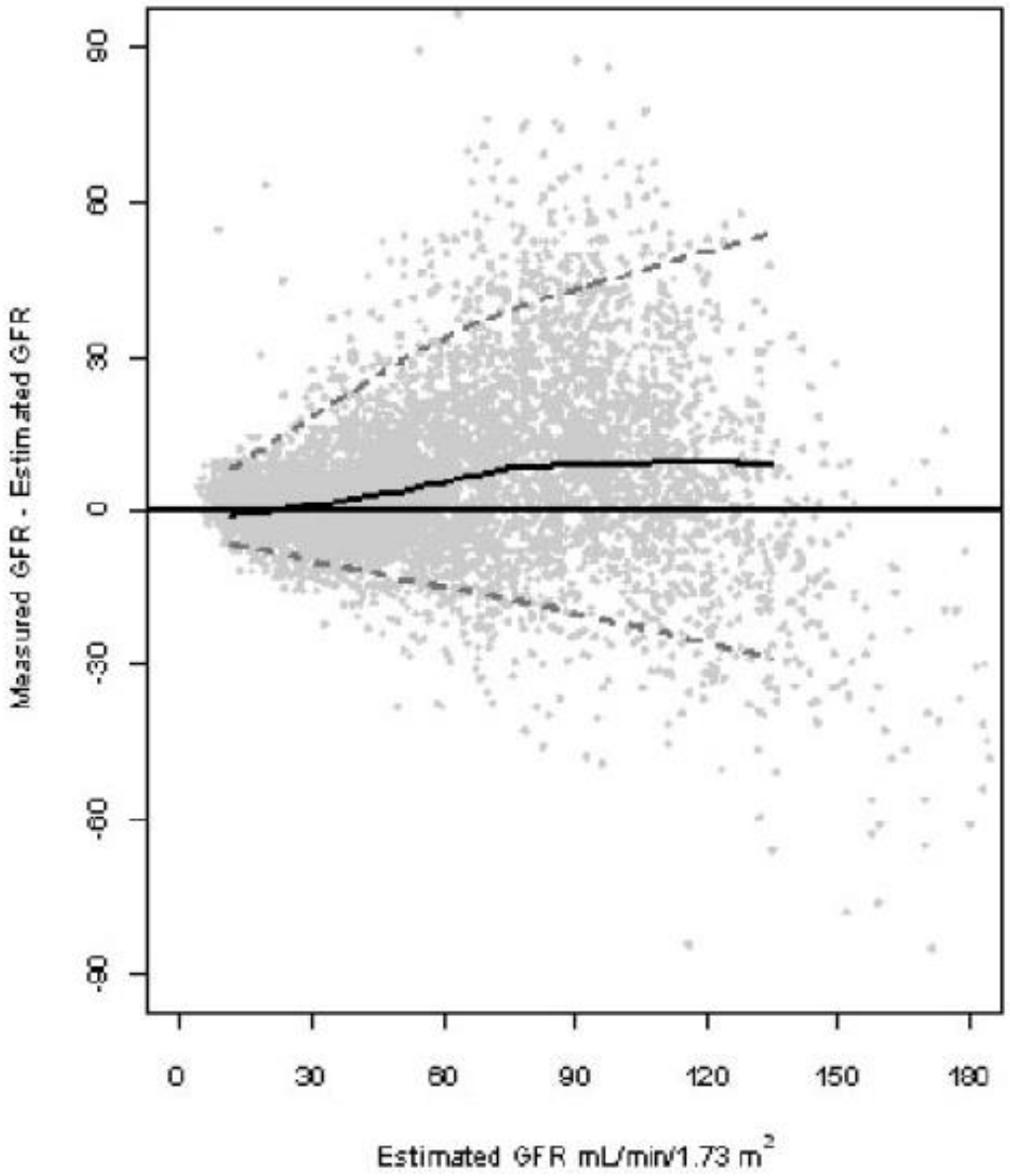


Figure 2. Difference of the MDRD Study equation by level of eGFR. Difference is calculated as (mGFR − eGFR). Solid horizontal

MDRD: the strengths

- Good accuracy in stage 3-4 CKD
- Best accuracy observed: 80-85%
- Better than Cockcroft especially in precision

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

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.

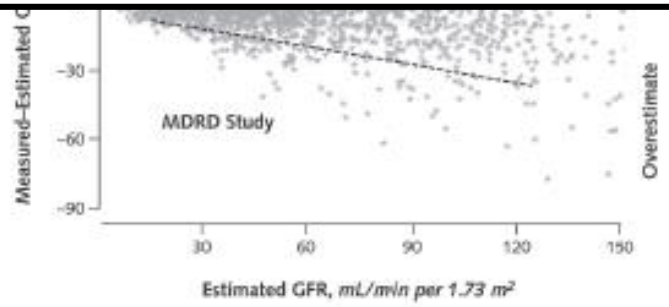


Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

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)

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

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

A 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*†*

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

*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

Correspondence: Dr. John C. Lieske, Mayo Clinic Division of Nephrology and Hypertension, 200 First Street SW, Rochester, MN 55905. Phone: 507-266-7960; Fax: 507-266-7891; E-mail: Lieske.John@mayo.edu

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?

(provocation!)

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

Ethnic factors in Africa

NO

RESEARCH LETTER

Performance of GFR Estimating Equations in African Europeans: Basis for a Lower Race-Ethnicity Factor Than in African Americans

Flamant M et al Am J Kidney Dis, 2013, 62, p179

Néphrologie & Thérapeutique 12 (2016) 454–459

Article original

Inadéquation du facteur ethnique pour l'estimation du débit de filtration glomérulaire en population générale noire-africaine : résultats en Côte d'Ivoire

Inadequacy of the African-American ethnic factor to estimate glomerular filtration rate in an African general population: Results from Côte d'Ivoire

Éric Sagou Yayo [a], Mireille Aye [a], Jean-Louis Konan [a], Arlette Emième [b], Marie-Laure Attoungbre [a], Appolinaire Gnionsahé [c], Étienne Cavalier [d], Dagui Monnet [a], Pierre Delanaye [e,*]

PLOS ONE

RESEARCH ARTICLE

Performance of glomerular filtration rate estimation equations in Congolese healthy adults: The inopportunity of the ethnic correction

Justine B. Bukabau[1]*, Ernest K. Sumaili[1], Etienne Cavalier[2], Hans Pottel[3], Bejos Kifakiou[1], Aliocha Nkodila[1], Jean Robert R. Makulo[1], Vieux M. Mokoli[1], Chantal V. Zinga[1], Augustin L. Longo[1], Yannick M. Engole[1], Yannick M. Nlandu[1], François B. Lepira[1], Nazaire M. Nseka[1], Jean Marie Krzesinski[4], Pierre Delanaye[4]

1 Renal Unit, Department of Internal medicine, Kinshasa University Hospital, University of Kinshasa, Kinshasa, Democratic Republic of the Congo, 2 Division of Clinical Chemistry, CHU Sart Tilman (ULg CHU), University of Liège, Liège, Belgium, 3 Division of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium, 4 Division of Nephrology-Dialysis-Transplantation, CHU Sart Tilman (ULg CHU), University of Liège, Liège, Belgium

* justinebuk@yahoo.fr

Yayo ES, Nephrol Ther, 2016 , 12 , 454
Flamant M, Am J Kdiney Dis, 2013, 62, 179
Bukabau JB, Plos One, 2018, 13, e0193384

MDRD – CKD-EPI: What else?

- Equation Bis
- Equation Lund-Malmö
- Equation FAS
- Another biomarker: 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

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

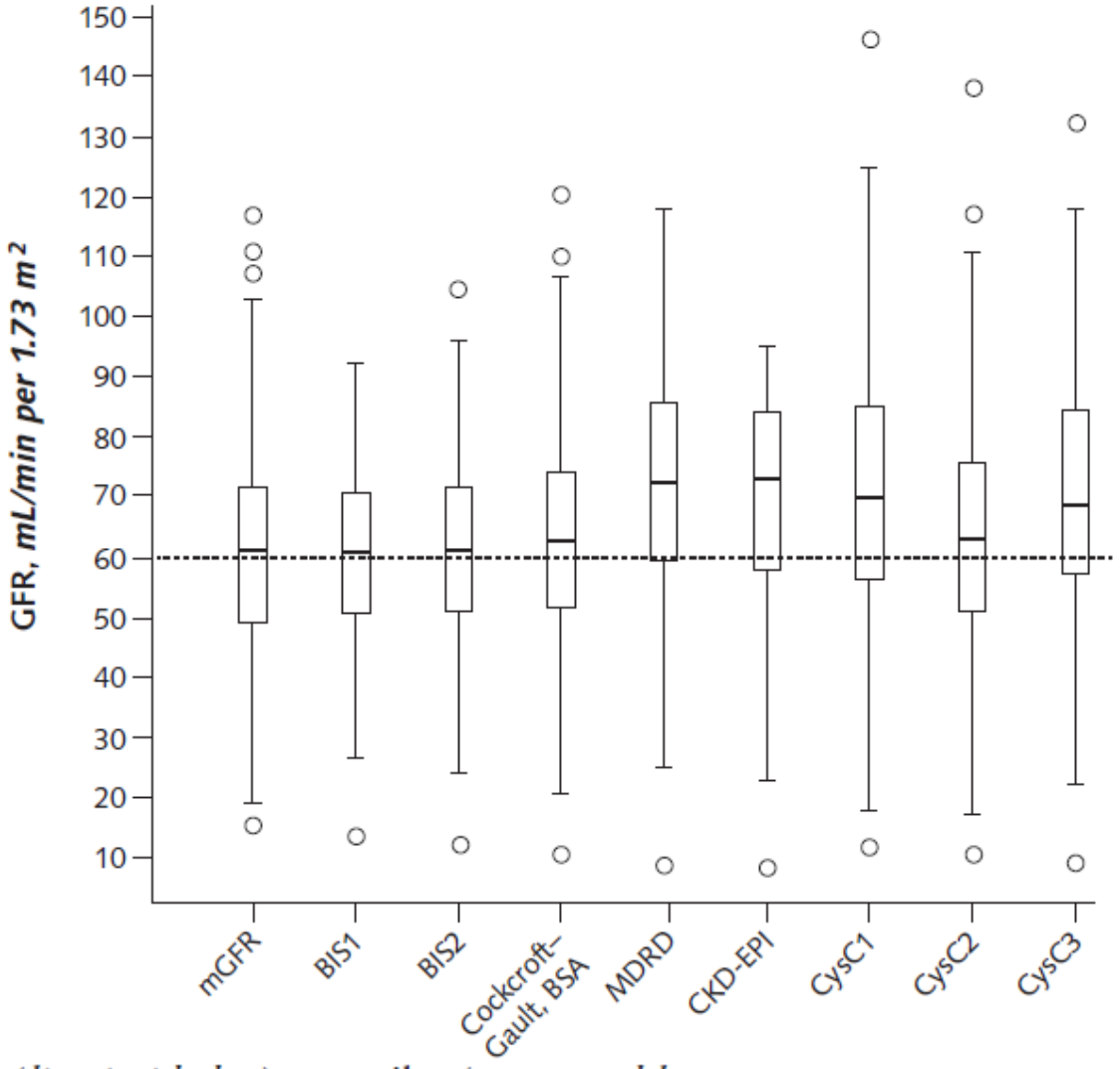
BIS1:

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

- n=610, iohexol, IDMS traceable enzymatic method
- Mean = 52 mL/min/1,73 m²

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.

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
- n=3495 (by 2847 subkects), iohexol, IDMS serum creatinine
- Mean GFR = 60 mL/min/1,73 m^2

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, including 735 children

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).

Cystatin C

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

Lesley A. Inker, M.D., Christopher H. Schmid, Ph.D., Hocine Tighiouart, M.S., John H. Eckfeldt, M.D., Ph.D., Harold I. Feldman, M.D., Tom Greene, Ph.D., John W. Kusek, Ph.D., Jane Manzi, Ph.D., Frederick Van Lente, Ph.D., Yaping Lucy Zhang, M.S., Josef Coresh, M.D., Ph.D., and Andrew S. Levey, M.D., for the CKD-EPI Investigators*

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

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)

BIS2: $767 \times \text{cystatin C}^{-0.61} \times \text{creatinine}^{-0.40} \times \text{age}^{-0.57} \times 0.87$ (if female)

CKD-EPI:

$$\text{eGFR} = 130 \times \text{cystatin C}^{-1.069} \times \text{age}^{-0.117} - 7.$$

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

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

Cystatin C

- + for Combined, children
- “Cost-effectiveness?”
- Some imprecision still persists at the individual level

Aging


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

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.

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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

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.

Jonas Björk, Sten Erik Bäck, Natalie Ebert, Marie Evans, Anders Grubb, Magnus Hansson, Ian Jones, Edmund J. Lamb, Peter Martus, Elke Schaeffner, Per Sjöström and Ulf Nyman*

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).

AJKD

Correspondence

RESEARCH LETTER

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

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

	CKD-EPI Validation (n=3896)	CKD-EPI Development (n=8254)
Age (years)	49.5 ± 14.7	47.0 ± 14.8
<18	0 (0%)	0 (0%)
18-39	1066 (27%)	2921 (35%)
40-65	2262 (58%)	4309 (52%)
>65	568 (15%)	1024 (12%)
Sex		
Male	2129 (55%)	4648 (56%)
Female	1767 (45%)	3606 (44%)
Race		
Non-African American	3512 (90%)	5653 (68%)
African American	384 (10%)	2601 (32%)
Measured GFR (ml/min/1.73m^2)	67.9 ± 35.8	67.6 ± 39.6
Geographic regions	North America Europe	North America Europe
GFR measurement method	Urinary clearance of iothalamate and EDTA, plasma	Urinary clearance of iothalamate

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)**

Limitations of eGFR = creatinine

Specific population: eGFR 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)

Hyperfiltration (Gaspari F, Kidney Int, 2013, 84, 164)

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

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?

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

- How to estimate GFR?
- How to measure GFR?

- How to estimate GFR?
- How to measure GFR?

Measuring GFR: Why? Question of precision!

- The decision to initiate dialysis
- Sarcopenic individuals
- Extreme body size
- Cirrhosis, ICU, Hyperfiltration
- Living kidney donation
- Dosing a potentially nephrotoxic drug (=>2)
- Clinical research, EMA
- No definitive proof…

How to proceed?

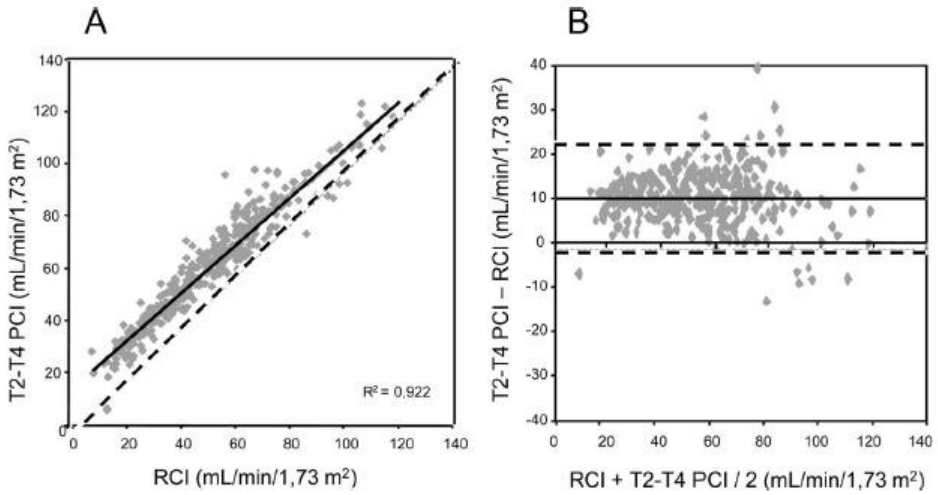
- Urinary clearance

- Plasma clearance

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 systematic

Available on the market…

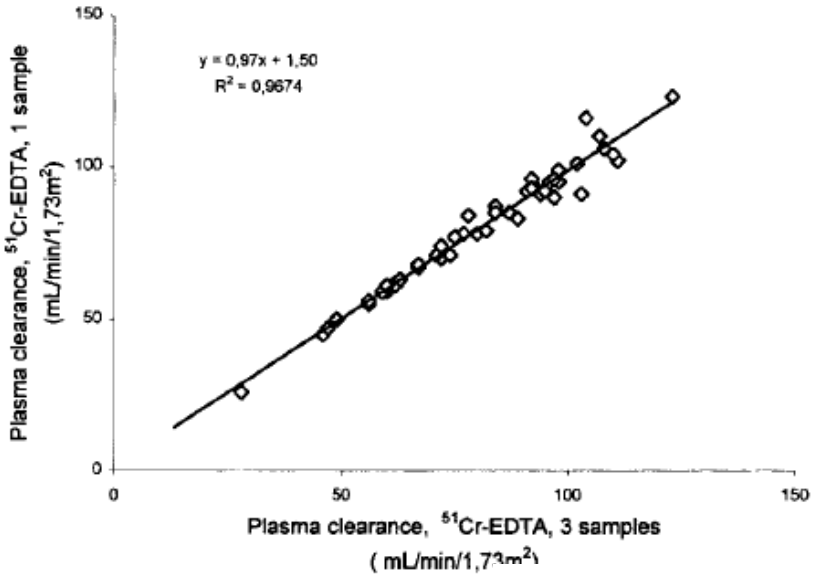
Markers	Strenghts	Limitations
Inulin	Gold standard (or historic) Was Safe…	Costly Dosage neither easy nor standardized Doubt with plasma clearance
Iothalamate	The most popular in USA Isotopic or "cold" method	Tubular secretion Cannot be used if allergy to iodine
Iohexol	The most popular in Europe Cold method	Worldwide available
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



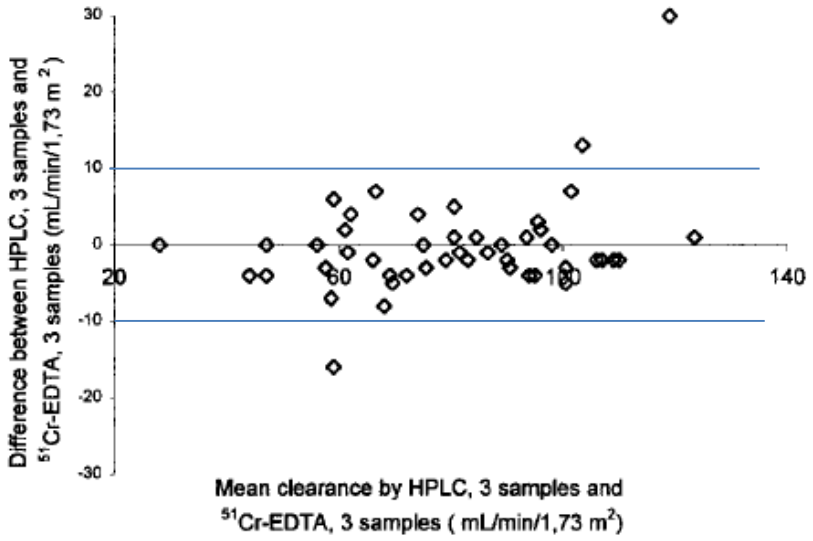


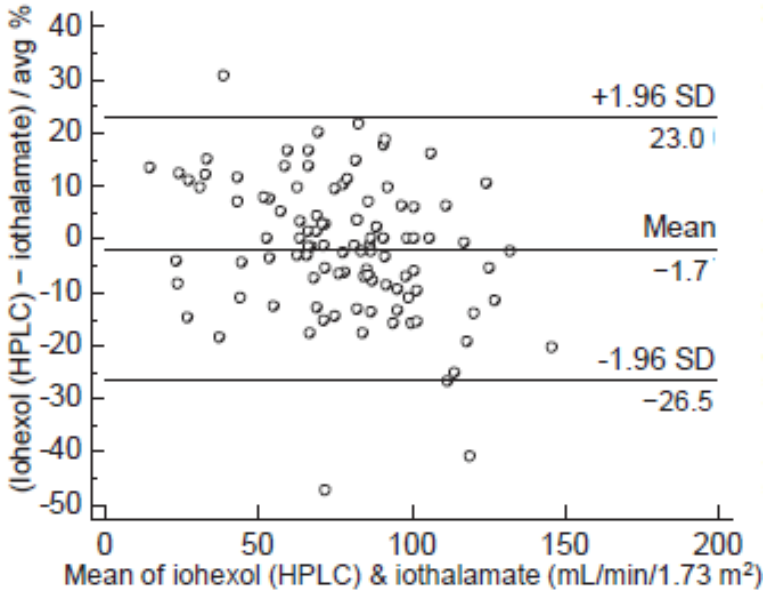
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	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

We need for…
1) 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

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 (withhold in FRANCE!!)
- Iohexol is available worldwide
- Very stable (central and/or “reference” laboratories)
- EQUAS (Equalis, Sweden) is available!

Iohexol in CHU Liège

- Iohexol (plasma clearance), 5 mL bolus
- 5 hours
- Samples at 2, 3, 4 et 5 hours (longer if very low eGFR)
- Brochner-Mortensen
- 50 to 100 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

Thank you for your attention!

SFNDT 2020 à Liège

SOCIÉTÉ FRANCOPHONE
DE NÉPHROLOGIE
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Nous serons heureux de vous accueillir!!!

pierre_delanaye@yahoo.fr

ACKD

Estimated Glomerular Filtration Rate From a Panel of Filtration Markers—Hope for Increased Accuracy Beyond Measured Glomerular Filtration Rate?

Lesley A. Inker, Andrew S. Levey, and Josef Coresh

The recent Kidney Disease Improving Global Outcomes 2012 CKD guidelines recommend estimating GFR from serum creatinine ($eGFR_{cr}$) as a first-line test to assess kidney function and using cystatin C or measured glomerular filtration rate (GFR) as confirmatory tests. $eGFR_{cr}$ may be inaccurate in people with variation in muscle mass or diet, and $eGFR_{cys}$ is not more accurate than $eGFR_{cr}$. $eGFR_{crcys}$ is more accurate than either, but it is not independent of $eGFR_{cr}$. Measured GFR is not practical and is susceptible to error due to variation in clearance methods and in the behavior of exogenous filtration markers. Over the past few years, we have hypothesized, and begun to test the hypothesis, that a panel of filtration markers (panel eGFR) from a single blood draw would require fewer demographic or clinical variables and could estimate GFR as accurately as measured GFR. In this article, we describe the conceptual background and rationale for this hypothesis and summarize our work thus far including evaluation of novel low-molecular-weight proteins and metabolites and then outline how we envision that such a panel could be used in clinical practice, research, and public health.

Key Words: Glomerular filtration rate, Creatinine, Metabolomics, Cystatin C, Estimated GFR

- B-trace protein
- Metabolomic
- Simple? Cost-effectiveness?

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

Clin Chem. 2018 Mar;64(3):4

Systematic Revie
the Modification
Epidemiology Co

ccuracy of
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McFadden EC[1], Hirst JA[1], Lasserson DS[4,2,5].

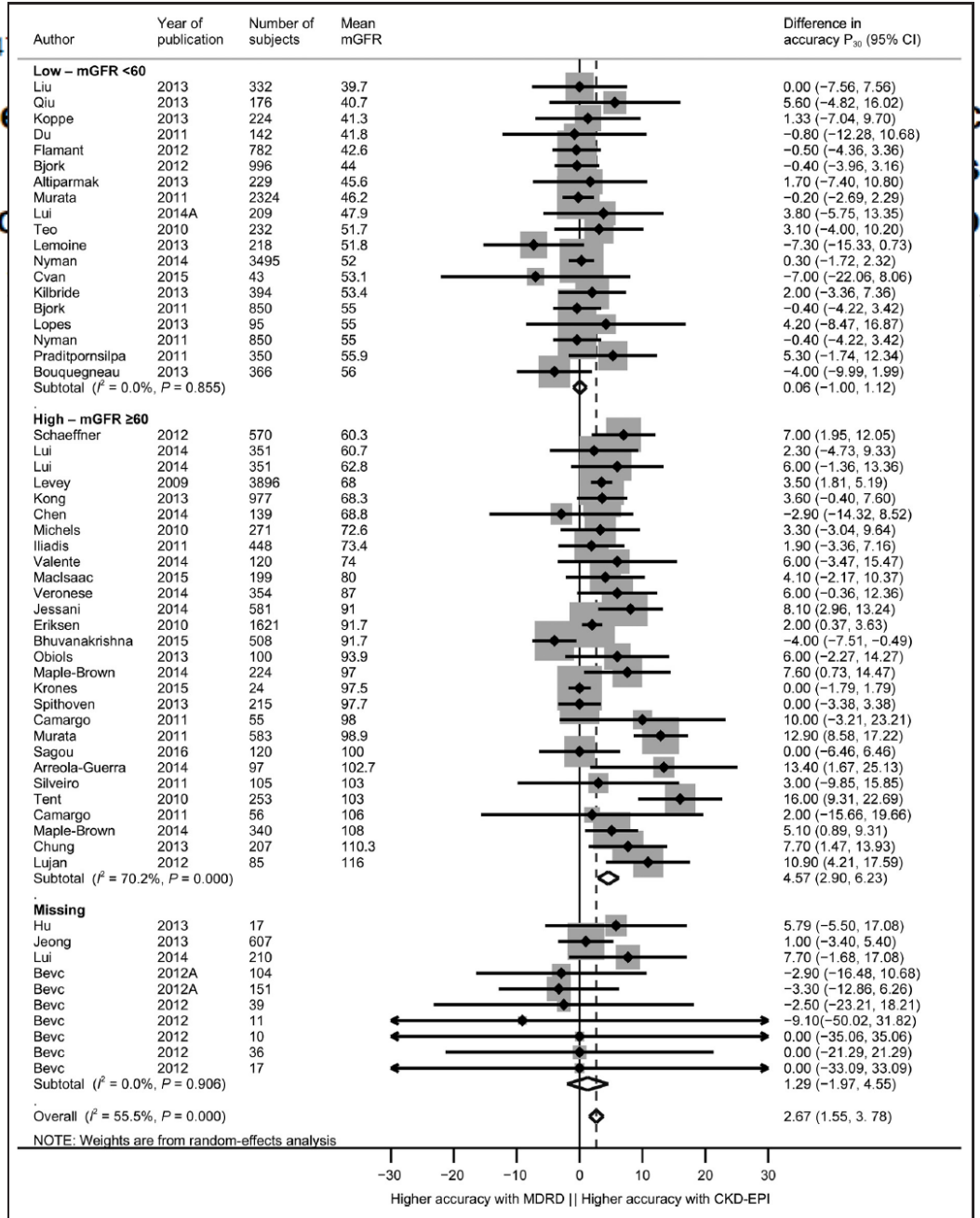
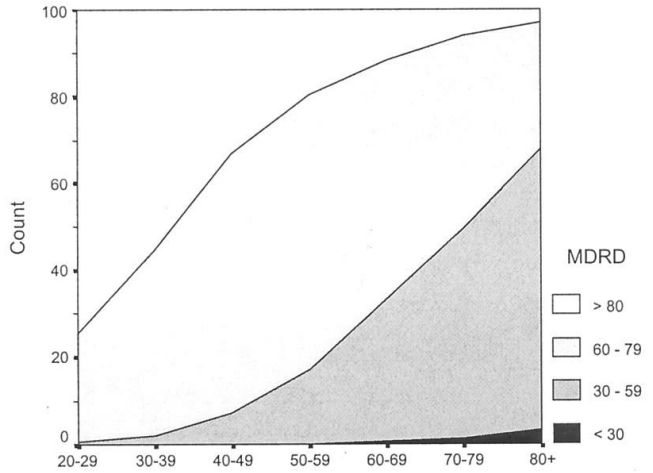


Fig. 4. Difference in mean accuracy from CKD-EPI and mean accuracy from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random-effects metaanalysis. P_{30}, proportion of eGFR results within 30% of mGFR result.
Horizontal bars and diamond width denote 95% CIs,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

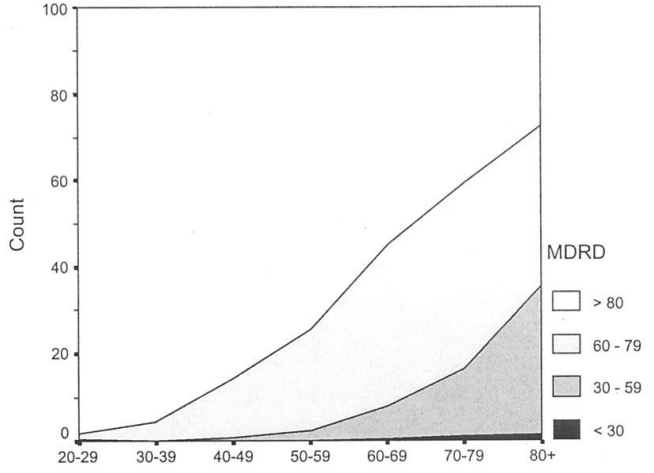
Measurement of serum creatinine: analytical limitations

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

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)

Are they equivalent?

Plasmatic Clearance = Dose / AUC

Theoritically, α and β must be calculated

↓

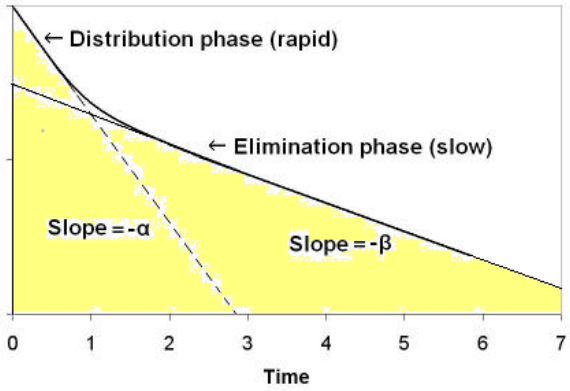
Not easy in practice (many samples)

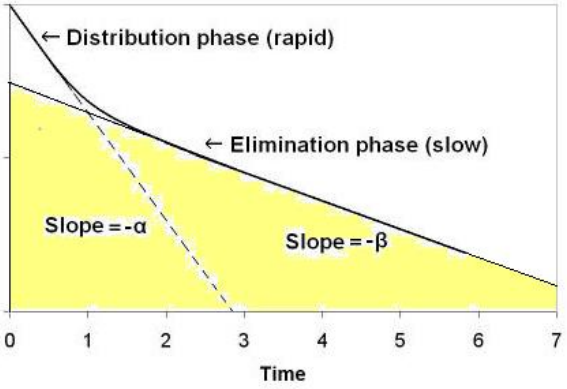
↓

Only slope ß after equilibrium is calculated

↓

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





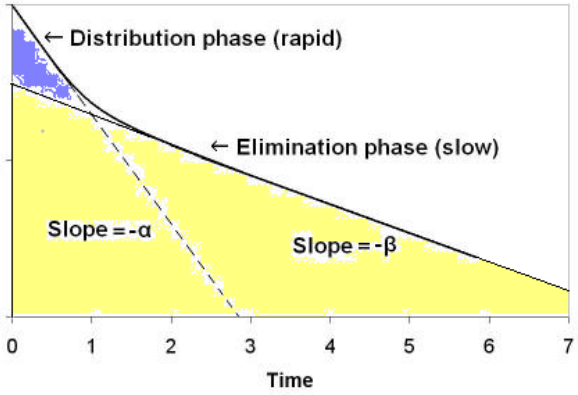


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Table 1. Characteristics of Study Participants, According to Data Set.*

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)	

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