Renal function in the geriatric patient

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Department of Nephrology, Dialysis and Transplantation
CHU Sart Tilman
University of Liège
BELGIUM

- Normal function

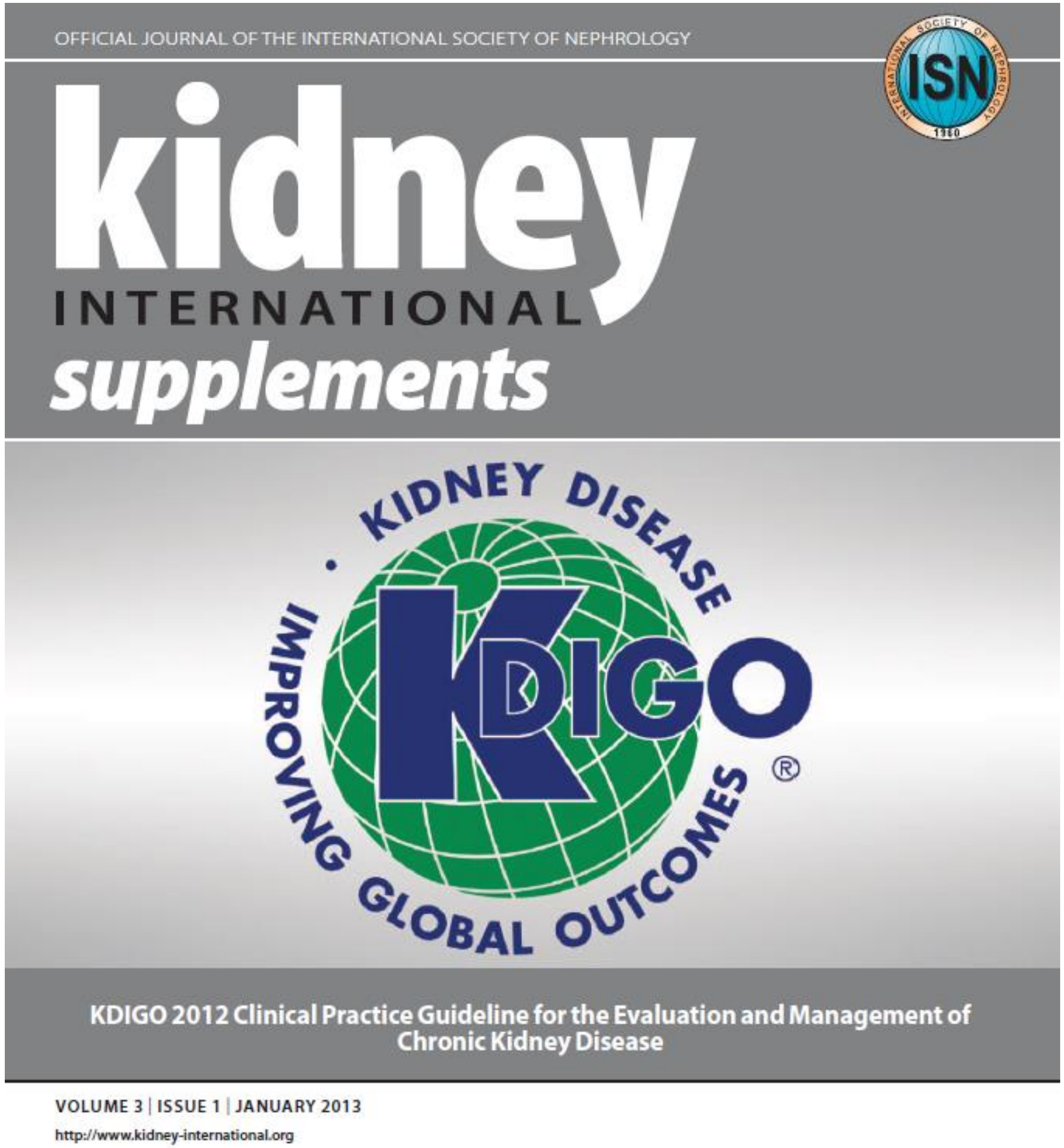
- How to estimate GFR?

- Normal function
- How to estimate GFR?

What is (normal) renal function in geriatrics?

- To be old
- This is just to be young for a longer time than others
- That's all

International guidelines in Nephrology



GFR categories in CKD **Chronic Kidney Disease**

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥ 90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

1.4.1: Evaluation of chronicity

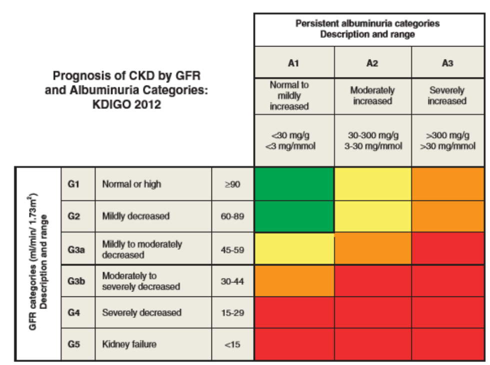
1.4.1.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (*Not Graded*)

- If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.

60 mL/min/1.73 m^2

Justification of this unique cut-off

- Simplicity
- Half of measured GFR in young adults but arbitrary (and maybe not correct)
- Because GFR < 60 mL/min/1.73 m^2 is associated with a higher mortality risk



Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73m^2) Description and range			Persistent albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30-300 mg/g 3-30 mg/mmol	A3 Severely increased >300 mg/g >30 mg/mmol
G1	Normal or high	≥90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29			
G5	Kidney failure	<15			

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How to define a disease?

- as a statistical departure from normality
- as a condition that is associated causally with an increased risk of a disease -defined event or death

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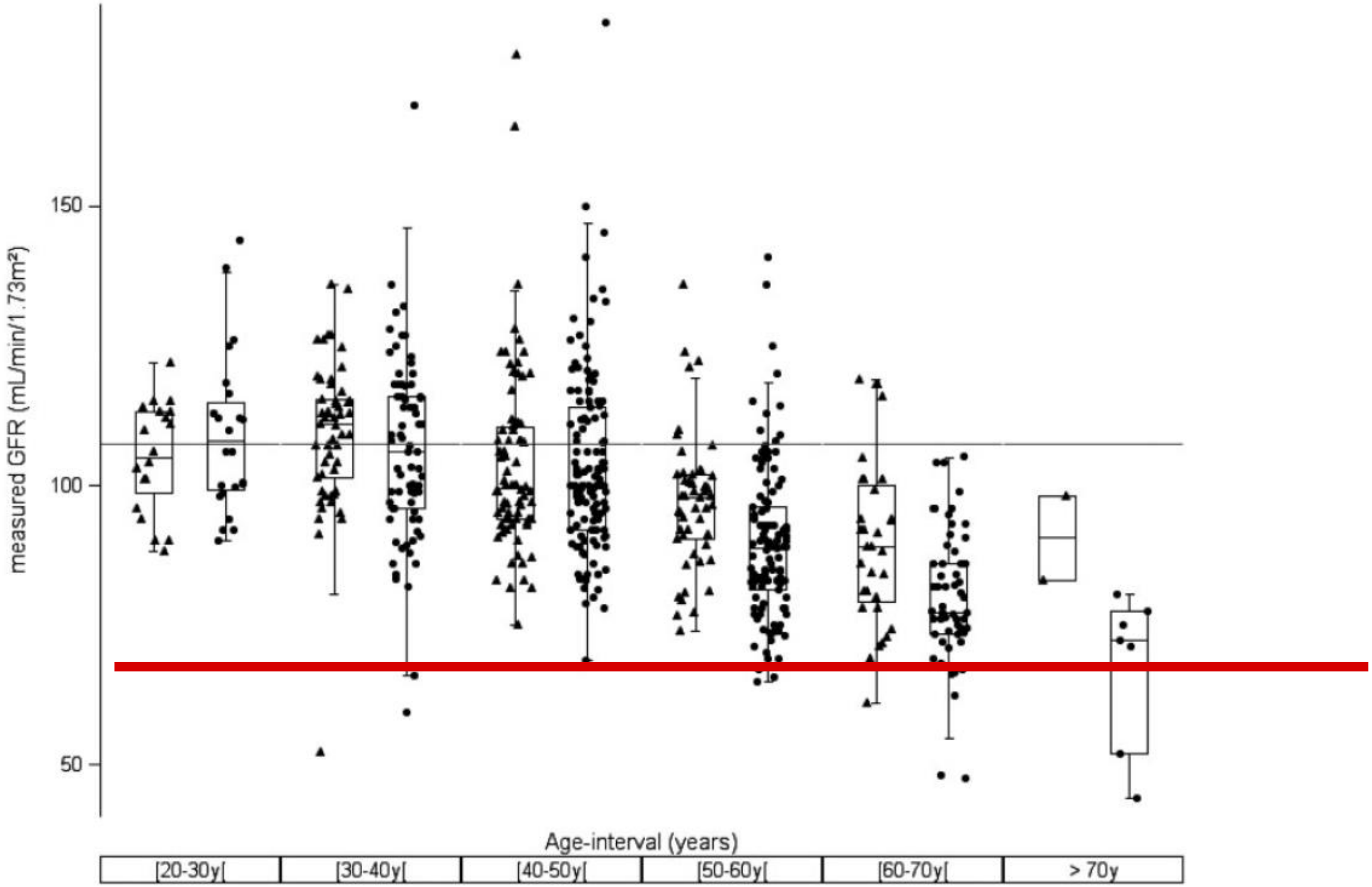


Fig. 1. Box plot for mGFR versus age decades for female (filled circles) and male (filled triangles) potential kidney donors ($n = 633$). A horizontal reference line is drawn at GFR = 107.3 mL/min/1.73 m^2.

Measured GFR in 633 living kidney donors (Belgium, France)

Pottel H, Delanaye P, Clin Kidney J, 2017, p545

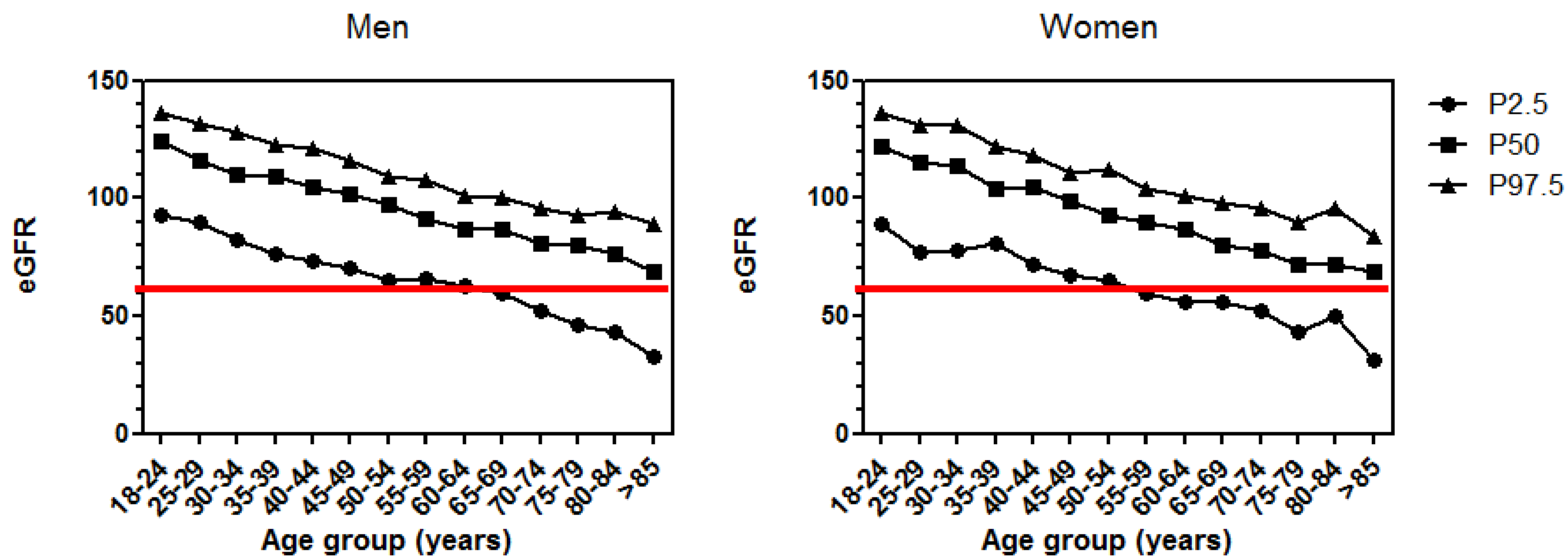
- Healthy population in the Netherlands
- Equation CKD-EPI
- No diabetes, No hypertension, No specific therapy, Normal albuminuria
- 1663 men 2073 women

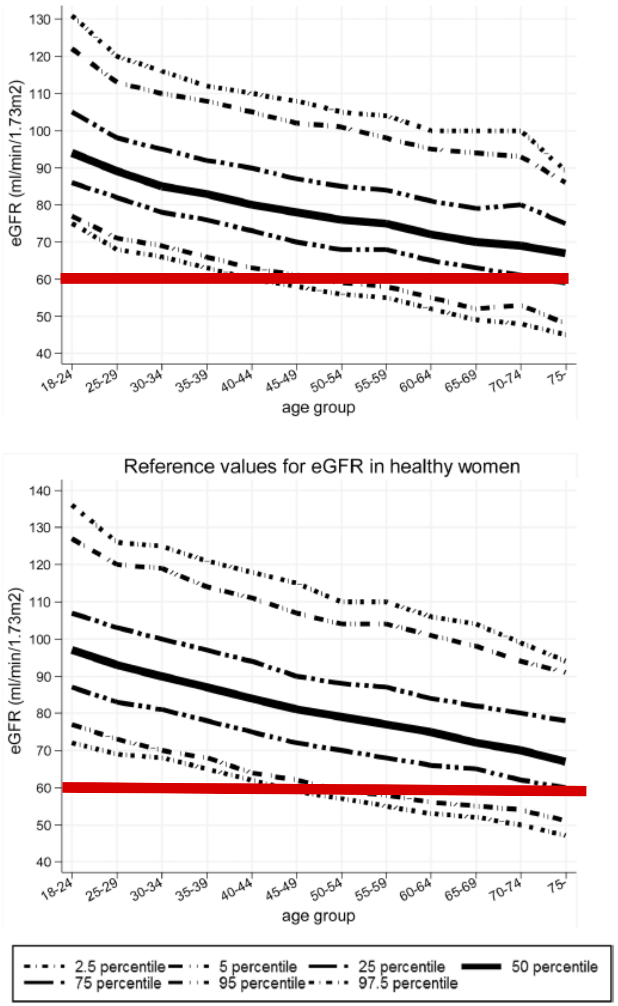
Nephrol Dial Transplant (2011) 26: 3176–3181
doi: 10.1093/ndt/gfr003
Advance Access publication 16 February 2011

Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population

Jan A.J.G. van den Brand[1], Gerben A.J. van Boekel[1], Hans L. Willems[2], Lambertus A.L.M. Kiemeney[3], Martin den Heijer[3,4] and Jack F.M. Wetzels[1]

[1]Department of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [2]Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands, [3]Department of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Medical Centre, Nijmegen, The Netherlands and [4]Department of Endocrinology, Radboud University Medical Centre, Nijmegen, The Netherlands


Men
Women
eGFR
150
100
50
0
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
>85
Age group (years)
P2.5
P50
P97.5



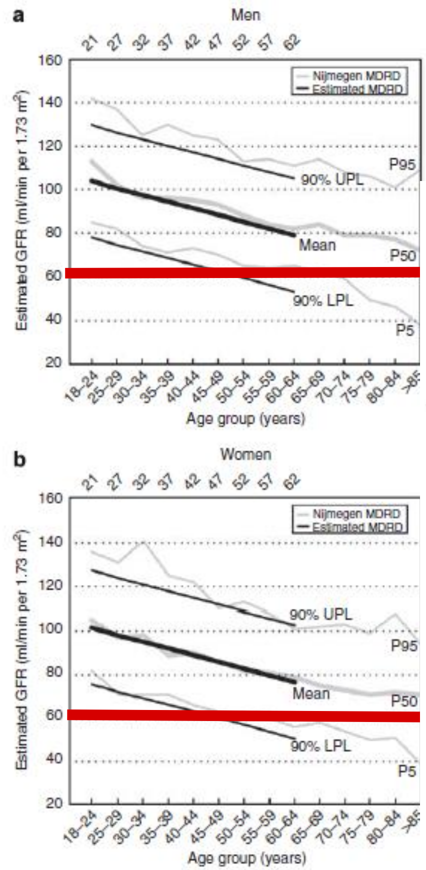
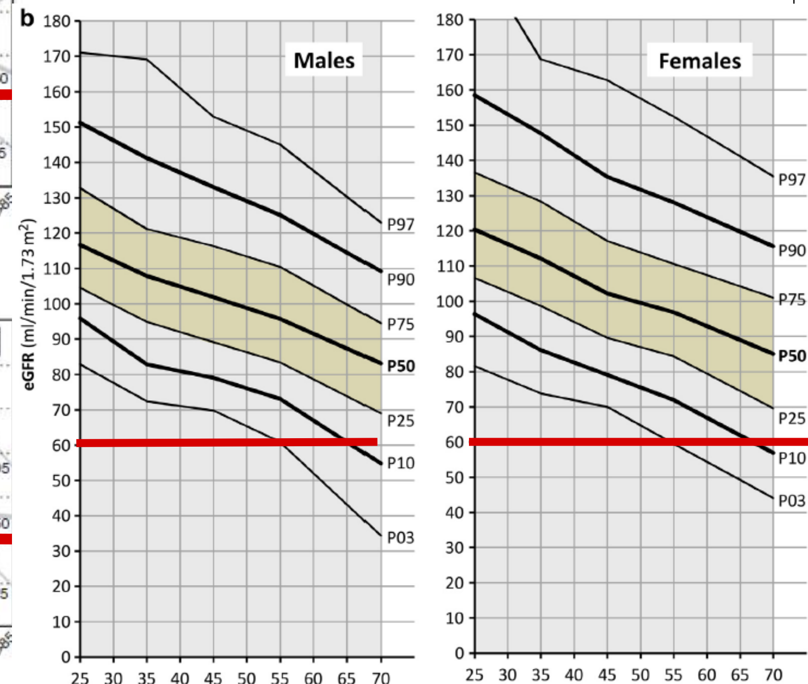


Figure 5 | Comparison of estimated GFR in two different cohorts. Mean, 5th, and 95th percentiles for expected eGFR by the re-expressed MDRD equation in living kidney donors (black lines) and eGFR by the re-expressed MDRD equation in subjects participating in the Nijmegen study[28] (gray lines) among different age groups for (a) men and (b) women.



The same in Japan…

The same in USA…

The same in Morocco…

Baba M, PlosOne, 2015

Poggio ED, Kidney Int, 2009

Benghanem Gharbi M, Kidney Int, 2016

- Concordant data worldwide
- eGFR is declining with aging
- A significant part of healthy subjects over 65 years have eGFR<60mL/min/1.73m^2

How to define a disease?

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ONLINE FIRST

Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

JAMA. 2012;308(22):2349-2360
Published online October 30, 2012. doi:10.1001/jama.2012.16817

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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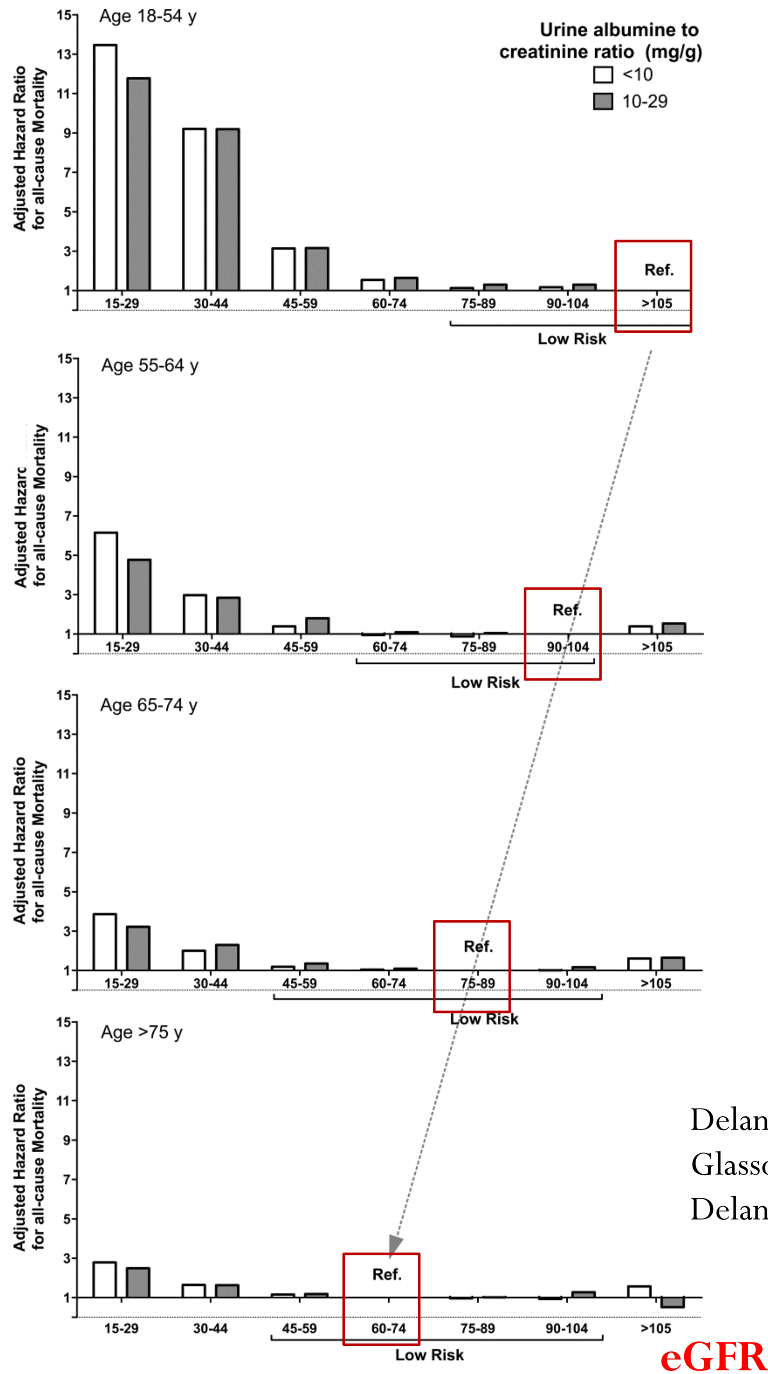
	G5	Kidney failure	<15			

Age 18-54 y =>

Age 55-64 y =>

Age 65-74 y =>

Age >75 y =>



Data from:

JAMA. 2012;308(22):2349-2360

Delanaye P, Clin Biochem Rev, 2016, p17
Glassock RJ, J Bras Nefrol, 2017, p59
Delanaye P, J Am Soc nephrol, 2019, p1785

J Am Soc Nephrol. 2019 Oct;30(10):1785-1805.

REVIEW www.jasn.org

CKD: A Call for an Age-Adapted Definition

Pierre Delanaye,[1] Kitty J. Jager,[2] Arend Bökenkamp,[3] Anders Christensson,[4] Laurence Dubourg,[5] Bjørn Odvar Eriksen,[6,7] François Gaillard,[8] Giovanni Gambaro,[9] Markus van der Giet,[10] Richard J. Glassock,[11] Olafur S. Indridason,[12] Marco van Londen,[13] Christophe Mariat,[14] Toralf Melsom,[6,7] Olivier Moranne,[15] Gunnar Nordin,[16] Runolfur Palsson,[12,17] Hans Pottel,[18] Andrew D. Rule,[19] Elke Schaeffner,[20] Maarten W. Taal,[21] Christine White,[22] Anders Grubb,[23] and Jan A. J. G. van den Brand[24]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

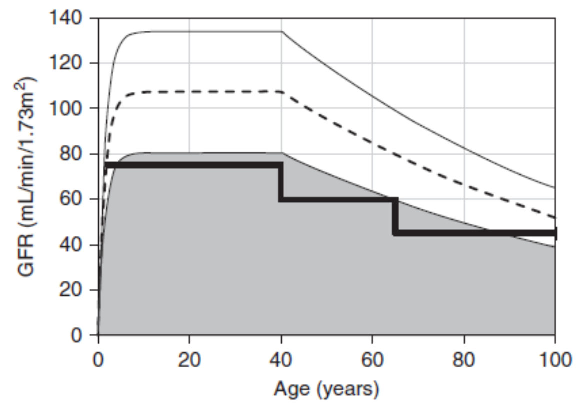


Figure 3. Age-specific thresholds in relation to age-specific GFR percentiles. GFR cut-off values and percentiles according to age (here percentiles of eGFR are calculated using the FAS equation). The bold line represents an age-adapted threshold for CKD: 75 ml/min per 1.73 m^2 for age below 40 years, 60 ml/min per 1.73 m^2 for age between 40 and 65 years, and 45 ml/min per 1.73 m^2 for age above 65 years. The dashed line represents the median (50th percentile) and the thin solid lines represent the 97.5th and 2.5th percentiles. The shaded zone is considered as below the normal reference intervals for GFR (<2.5th percentile).

The prevalence of chronic kidney disease in Iceland according to KDIGO criteria and age-adapted estimated glomerular filtration rate thresholds

Check for updates

see commentary on page 1090

Arnar J. Jonsson[1,2], Sigrun H. Lund[1], Bjørn O. Eriksen[3], Runolfur Palsson[1,2,4] and Olafur S. Indridason[2,4]

[1]*Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland;* [2]*Internal Medicine Services, Landspitali–The National University Hospital of Iceland, Reykjavik, Iceland;* [3]*Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; and* [4]*Division of Nephrology, Landspitali–The National University Hospital of Iceland, Reykjavik, Iceland*

Kidney International (2020) **98,** 1286–1295;

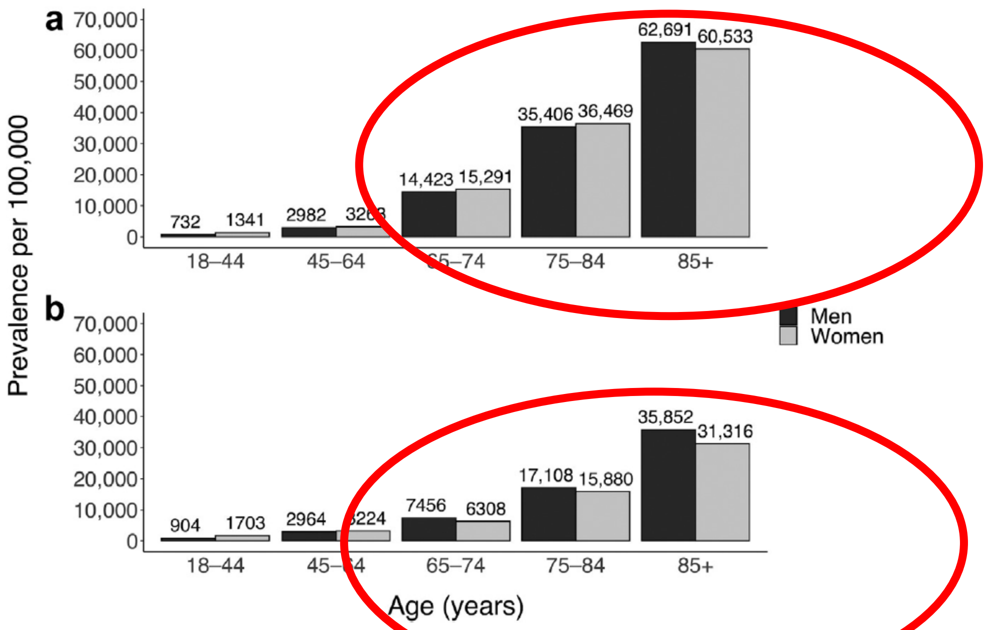


Figure 2 | Mean annual prevalence of chronic kidney disease stages 1–5 by age group and sex, using (a) the Kidney Disease: Improving Global Outcomes (KDIGO) definition and (b) age-adapted estimated glomerular filtration rate (eGFR) thresholds.

- Normal function

- How to estimate GFR?

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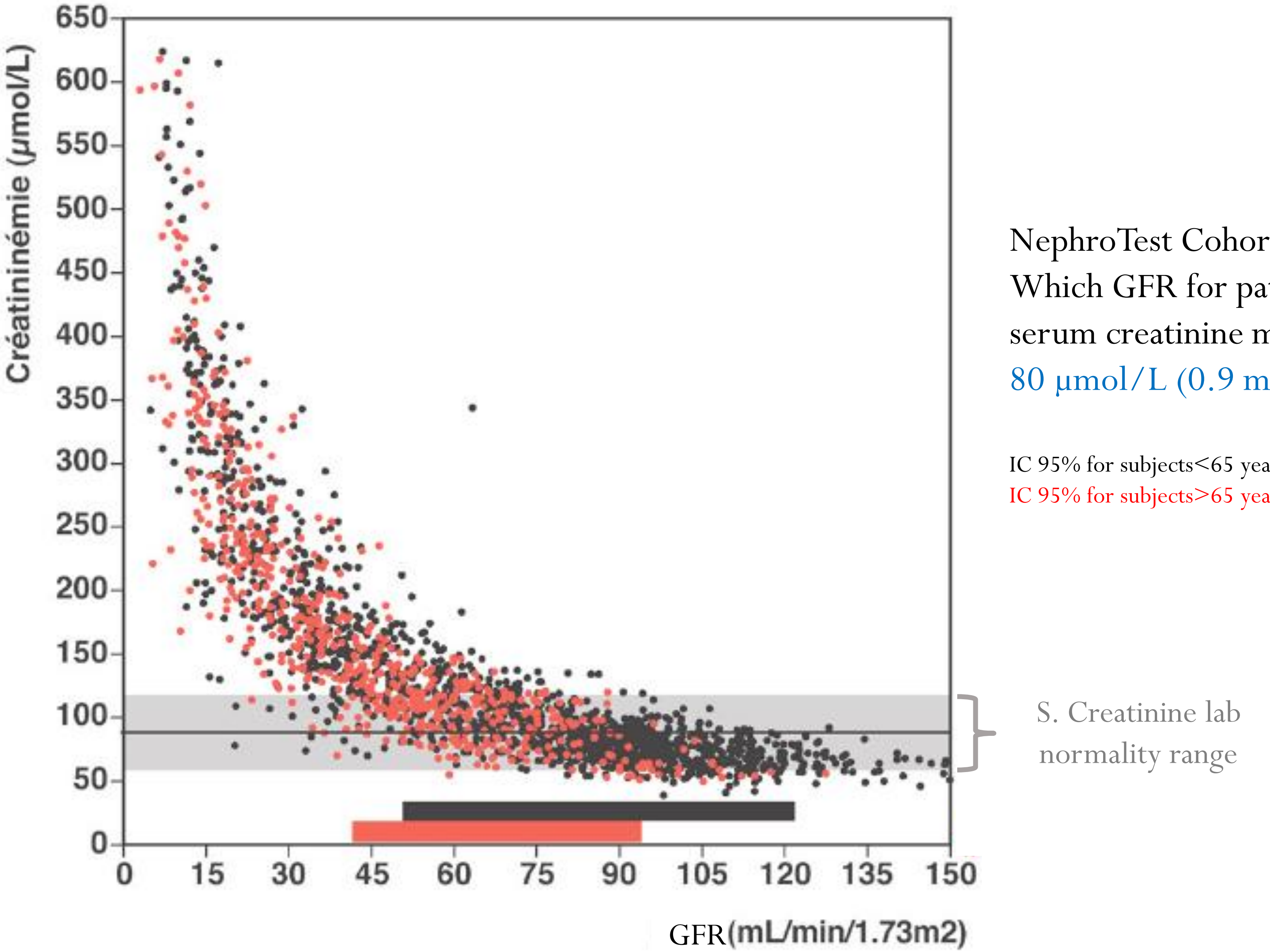

NephroTest Cohort (France)
Which GFR for patients with serum creatinine measured at 80 µmol/L (0.9 mg/dL)?

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

With the kind permission of Marc Froissart

Which one?

- Cockcroft
- MDRD
- CKD-EPI
- Others

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

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.

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

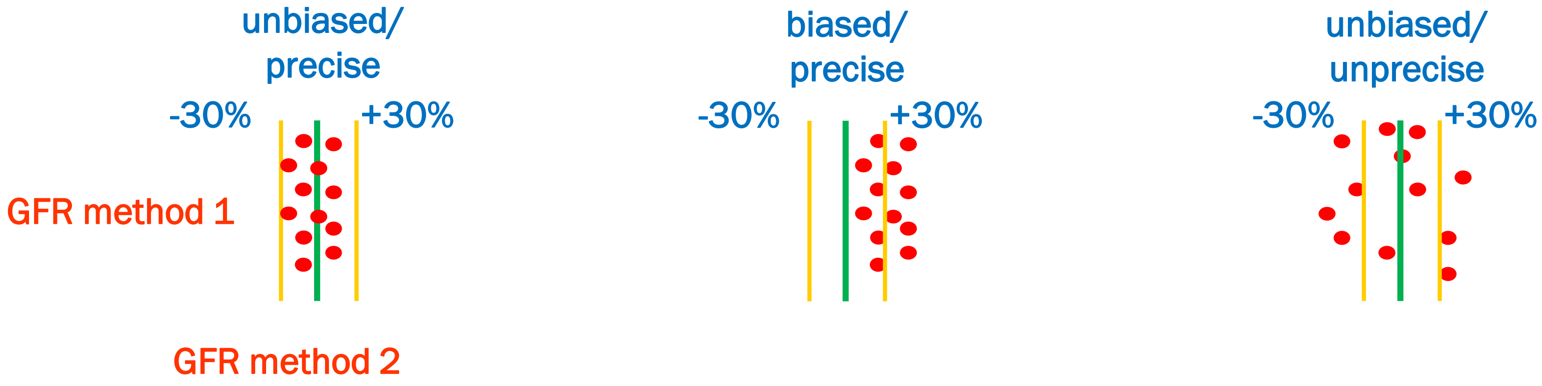


Table 1. MDRD study equations and Cockcroft equation commonly used for GFR estimation

Cockcroft and Gault

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

4-Variable MDRD study equation (IDMS traceable)

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

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.

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)*

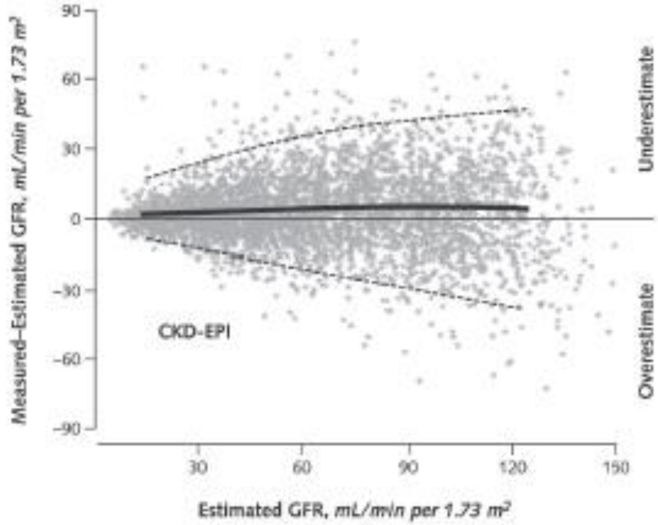
Ann Intern Med. 2009;150:604-612.

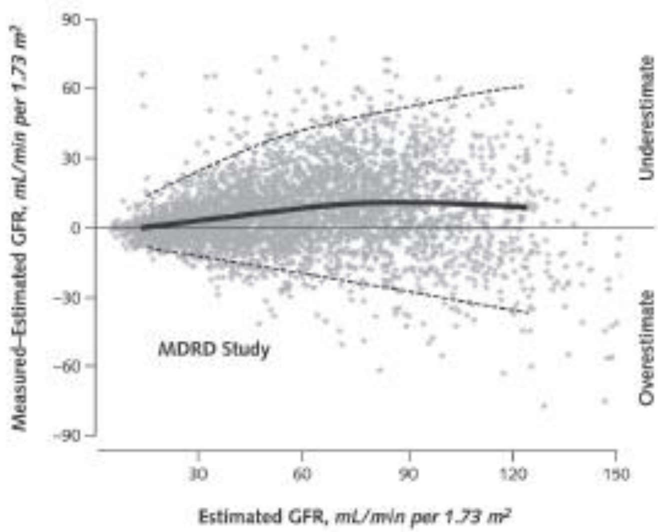
Table 2. **The CKD-EPI Equation for Estimating GFR on the Natural Scale***

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.





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:

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

- n=610, iohexol, IDMS traceable enzymatic method
- Mean = 52 mL/min/1,73 m^2

Ann Intern Med. 2012;157:471-481

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×(150−pCr)
Female	pCr≥150 µmol/L:	X=2.50−0.926×ln(pCr/150)
Male	pCr<180 µmol/L:	X=2.56+0.00968×(180−pCr)
Male	pCr≥180 µmol/L:	X=2.56−0.926×ln(pCr/180)

- Lund-Malmo
- n=3495 (by 2847 subjects), iohexol, IDMS serum creatinine
- Mean GFR = 60 mL/min/1,73 m²

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

An estimated glomerular filtration rate equation for the full age spectrum

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

$$\mathrm{FAS-eGFR} = \frac{107.3}{(\mathrm{SCr}/Q)} \quad \text{for } 2 \le \text{age} \le 40 \text{ years}$$

$$\mathrm{FAS-eGFR} = \frac{107.3}{(\mathrm{SCr}/Q)} \times 0.988^{(\mathrm{Age}-40)} \quad \text{for age} > 40 \text{ years}$$

N=6870, including 735 children

Ann Intern Med. 2020 Nov 10. doi: 10.7326/M20-4366. Online ahead of print.

Annals of Internal Medicine ORIGINAL RESEARCH

Development and Validation of a Modified Full Age Spectrum Creatinine-Based Equation to Estimate Glomerular Filtration Rate

A Cross-sectional Analysis of Pooled Data

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- Subjects with measured GFR and standardized creatinine
- 11,251 development and internal validation
- 8,378 external validation
- 1,254 aged between 2 to 18 years
- 7 + 6 cohorts
- Only White people

Figure 1. The new EKFC equation.

Age	SCr/Q	Equation
2–40 y	<1	$107.3 \times (SCr/Q)^{-0.322}$
	≥1	$107.3 \times (SCr/Q)^{-1.132}$
>40 y	<1	$107.3 \times (SCr/Q)^{-0.322} \times 0.990^{(Age - 40)}$
	≥1	$107.3 \times (SCr/Q)^{-1.132} \times 0.990^{(Age - 40)}$

Q Values

For ages 2–25 y:

Males:

$\ln(Q) = 3.200 + 0.259 \times Age - 0.543 \times \ln(Age) - 0.00763 \times Age^2 + 0.0000790 \times Age^3$

Females:

$\ln(Q) = 3.080 + 0.177 \times Age - 0.223 \times \ln(Age) - 0.00596 \times Age^2 + 0.0000686 \times Age^3$

For ages >25 y:

Males:

Q = 80 μmol/L (0.90 mg/dL)

Females:

Q = 62 μmol/L (0.70 mg/dL)

SCr and Q in μmol/L (to convert to mg/dL, divide by 88.4)

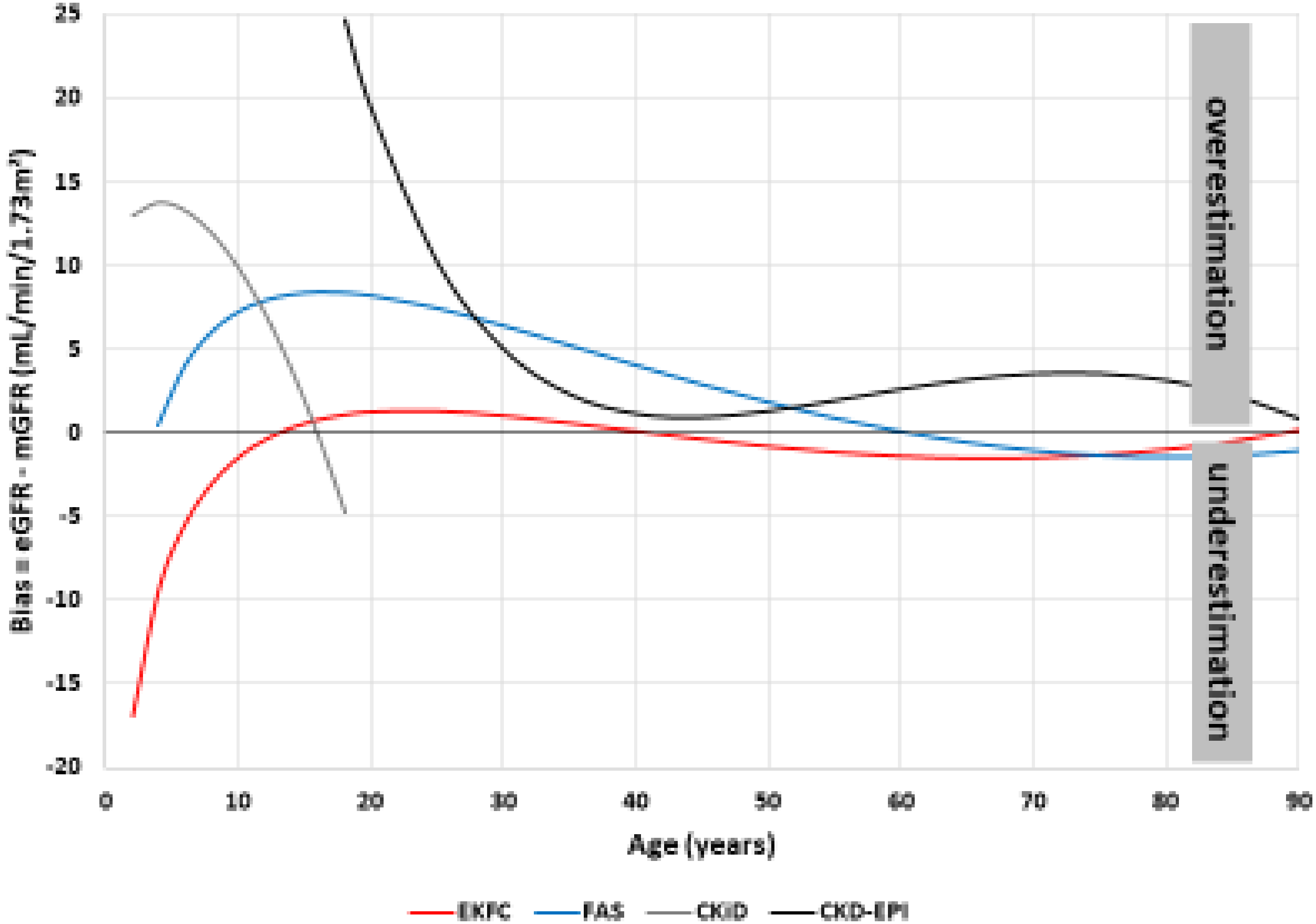
Q values (in μmol/L or mg/dL) correspond to the median SCr values for the age- and sex-specific populations. EKFC = European Kidney Function Consortium; SCr = serum creatinine.

Excel calculator: send me an email!

	EKFC	FAS	CKD-EPI
Adults aged ≥65 y			
Median bias (95% CI), *mL/min/1.73 m²*			
All (*n* = 2567)	-1.2 (-1.0 to -1.6)	-1.1 (-1.5 to -0.6)	3.0 (2.5 to 3.6)
eGFR <45 mL/min/1.73 m² (*n* = 852)	-0.5 (-0.9 to -0.1)	0.7 (0.2 to 1.2)	0.5 (0.1 to 0.9)
eGFR ≥45 mL/min/1.73 m² (*n* = 1715)	-2.0 (-2.6 to -1.3)	-2.9 (-3.7 to -2.4)	5.1 (4.3 to 6.0)
Imprecision, SD (P25-P75)			
All (*n* = 2567)	12.1 (-7.6 to 5.0)	14.3 (-8.5 to 5.3)	12.5 (-2.9 to 10.2)
eGFR <45 mL/min/1.73 m² (*n* = 852)	7.1 (-4.3 to 3.8)	7.2 (-3.5 to 5.1)	7.2 (-2.9 to 5.1)
eGFR ≥45 mL/min/1.73 m² (*n* = 1715)	13.9 (-9.6 to 6.1)	16.7 (-10.8 to 5.8)	14.3 (-2.9 to 13.1)
Accuracy P30 (95% CI), %			
All (*n* = 2567)	85.3 (83.9 to 86.7)	83.6 (82.1 to 85.0)	80.7 (79.2 to 82.2)
eGFR <45 mL/min/1.73 m² (*n* = 852)	76.8 (73.9 to 79.6)	73.9 (71.0 to 76.9)	69.6 (65.5 to 73.7)
eGFR ≥45 mL/min/1.73 m² (*n* = 1715)	89.6 (88.1 to 91.0)	88.4 (86.9 to 89.9)	83.7 (81.9 to 85.4)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CKiD = Chronic Kidney Disease in Children Study; eGFR = estimated glomerular filtration rate; EKFC = European Kidney Function Consortium; FAS = full age spectrum; P25–P75 = interquartile range; P30 = accuracy within 30% of measured GFR.

* For children (aged 2 to <18 y) and adults in age subgroups 18 to <40 y, 40 to <65 y, and ≥65 y, according to the age-adapted thresholds for EKFC eGFR: 75, 60, and 45 mL/min/1.73 m², respectively.



25
20
15
10
5
0
-5
-10
-15
-20
Bias = eGFR - mGFR (mL/min/1.73m²)
0
10
20
30
40
50
60
70
80
90
Age (years)
overestimation
underestimation
EKFC
FAS
CKiD
CKD-EPI

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		$144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$ [× 1.159 if black]
Female	>0.7		$144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
Male	≤0.9		$141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$ [× 1.159 if black]
Male	>0.9		$141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
CKD-EPI cystatin C equation§			
Female or male		≤0.8	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age}$ [× 0.932 if female]
Female or male		>0.8	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age}$ [× 0.932 if female]
CKD-EPI creatinine–cystatin C equation¶			
Female	≤0.7	≤0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Female	>0.7	≤0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Male	≤0.9	≤0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Male	>0.9	≤0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 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:

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

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

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

Cystatin C

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

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.

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

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-EPI_{Cr}	$MEAN_{LMR+CAPA}$	FAS_{Cr+Cys}	CKD-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.

N=804, from 74 to 93 years old

DE GRUYTER Clin Chem Lab Med 2017; aop

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

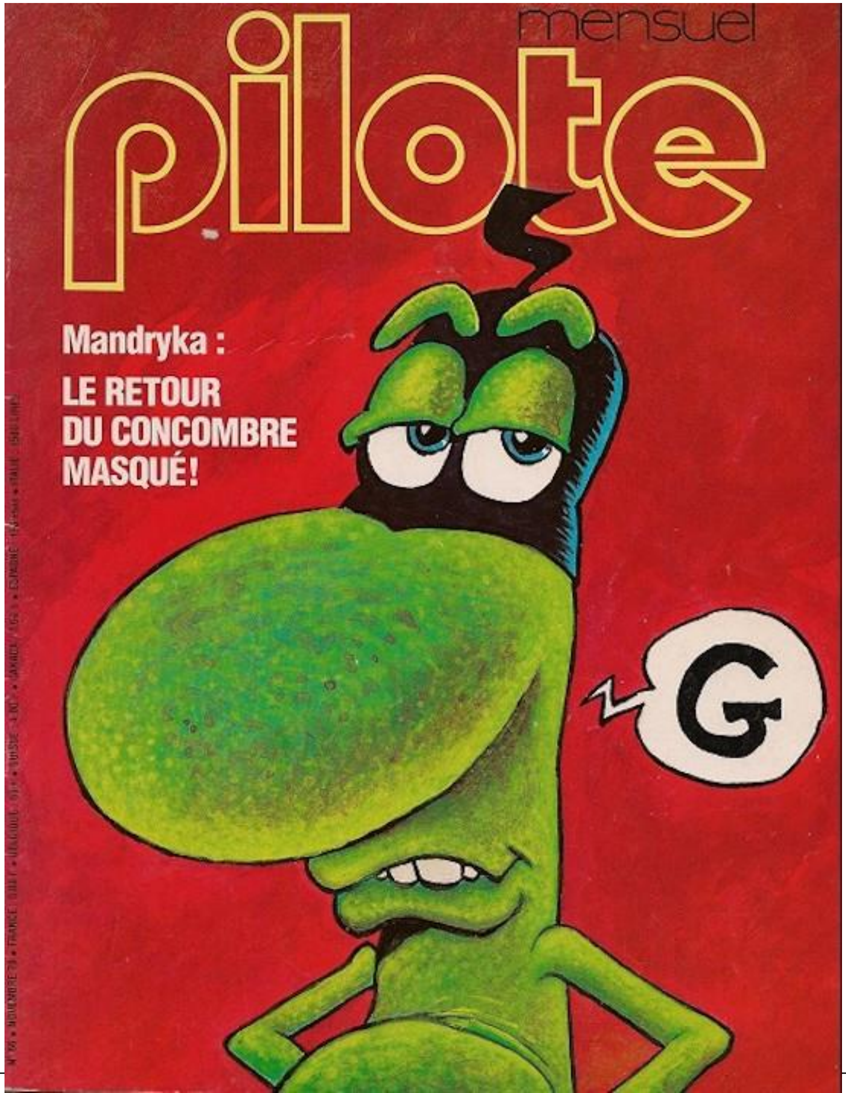
LM+CAPA slightly better

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).

Cockcroft : the come back…
(drug dosage adaptation and geriatry)



Why ?

- Safer in the old
- « History »
- Volume of distribution

« Safer » doses in the elderly

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doi:10.1093/ndt/gfm289
Advance Access publication 16 June 2007

NDT Nephrology Dialysis Transplantation

Original Article

Use of GFR equations to adjust drug doses in an elderly multi-ethnic group—a cautionary tale

Jagbir Gill, Rhonda Malyuk, Ognjenka Djurdjev and Adeera Levin

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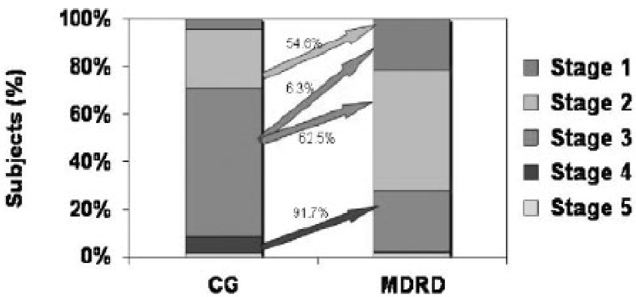


Fig. 2. Impact of MDRD on CG-based stages of CKD. In general, MDRD classified the majority of subjects into a different stage of CKD than CG. A 54.6% of subjects classified as stage 2 CKD by CG, were reclassified as stage 1 by MDRD. A 6.3% of patients classified as stage 3 CKD by CG were reclassified as stage 1 by MDRD and 62.5% were reclassified to stage 2 by MDRD. A 91.7% of patients classified as stage 4 by CG, were reclassified to stage 3 by MDRD.

Decrease in DIGOXINE dosage:

MDRD: 46/179

Cockcroft: 104/179

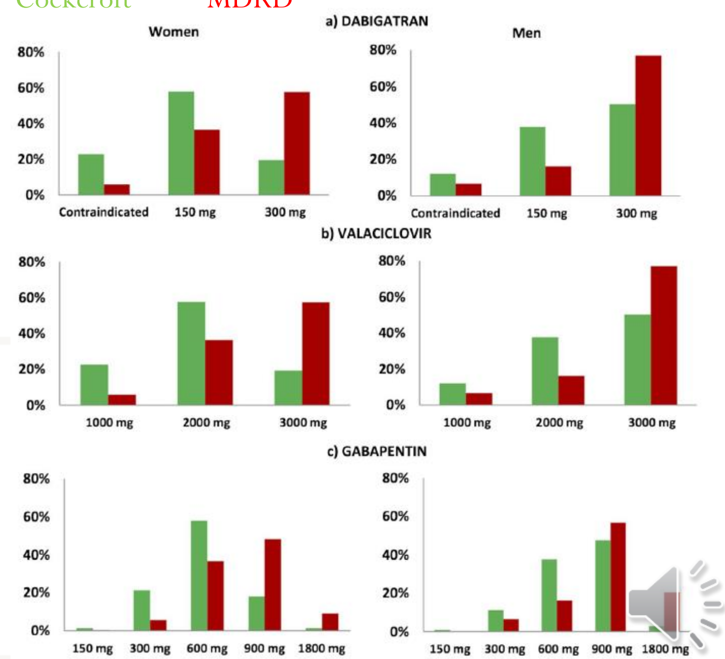
Open Access Research

BMJ open

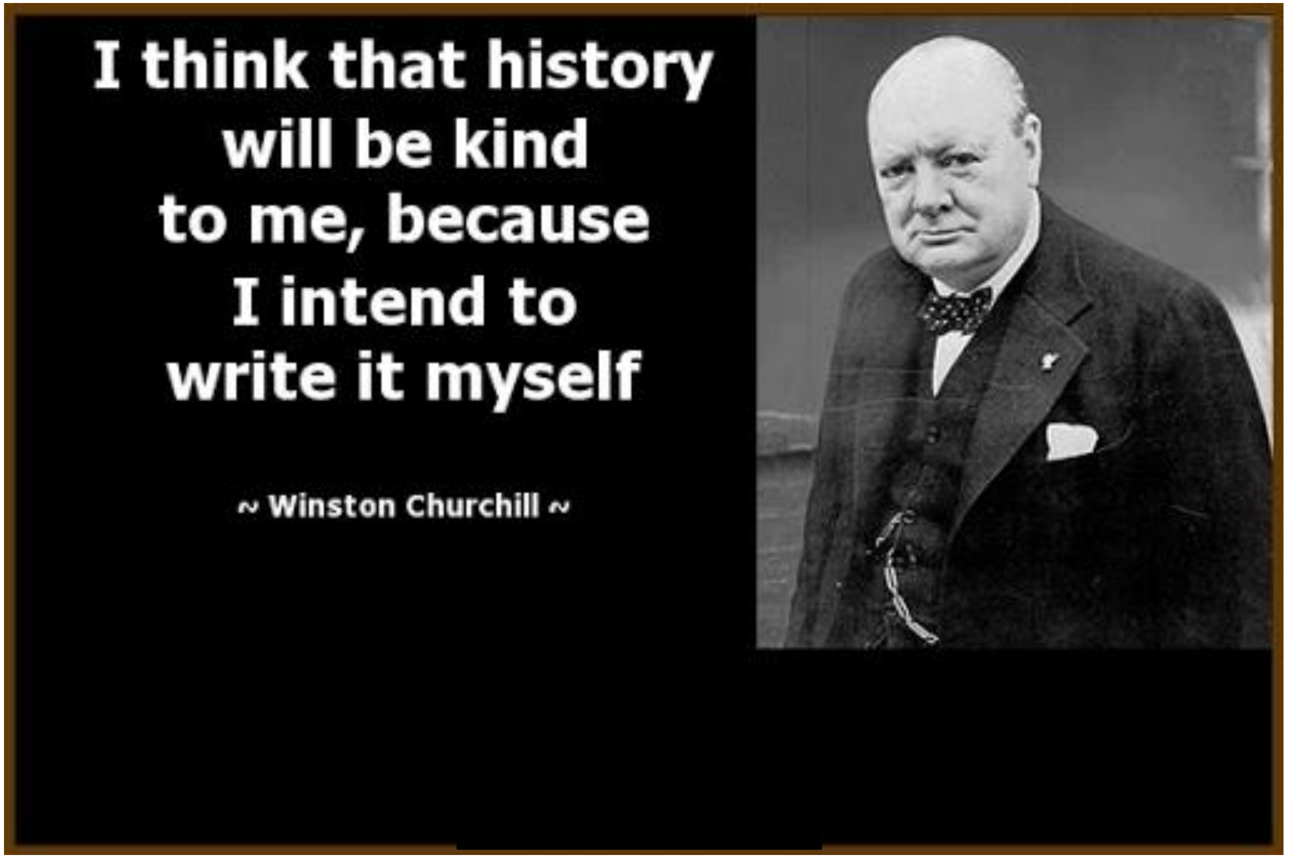
Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly

Anders Helldén,[1] Ingegerd Odar-Cederlöf,[1] Göran Nilsson,[2] Susanne Sjöviker,[3] Anders Söderström,[4] Mia von Euler,[1,5] Gunnar Öhlén,[6] Ulf Bergman[1,7,8]

Cockcroft MDRD



Cockcroft and History



Cockcroft and volume of distibution

- Volume of distribution is important for drug dosage adaptation
- Weight is a proxy for volume of distribution

What about guidelines?

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

They don't take position

Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or (CDER) Lei Zhang, 301-796-1635.

Either the C-G or MDRD equation can be used to assign subjects to a renal impairment group or stage, and PK results should be shown for both C-G estimates of creatinine clearance and eGFR. Creatinine clearance calculated using timed urine collections (e.g., 24 hours) is not suitable for routine clinical practice or clinical trials and in many settings does not improve estimates of GFR over that provided by prediction equations.

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)

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
- Clinical research, EMA
- No definitive proof…

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CKJ REVIEW

Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol?

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European Kidney Function Consortium (EKFC)

Conclusions

- GFR is physiologically declining with age
- The threshold for « normality » in the elderly could be 45 mL/min/1.73m²
- Estimating GFR in the elderly is difficult…and still subject of debate
- New EKFC equation
- Interest of cystatin C (combined equations)
- Measuring GFR in very specific populations/indications

Thank you for your attention!

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