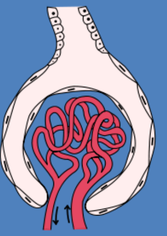
XXXIX NORDIC CONGRESS IN CLINICAL CHEMISTRY
17-20 SEPTEMBER 2024 STOCKHOLM

How to estimate GFR in 2024?



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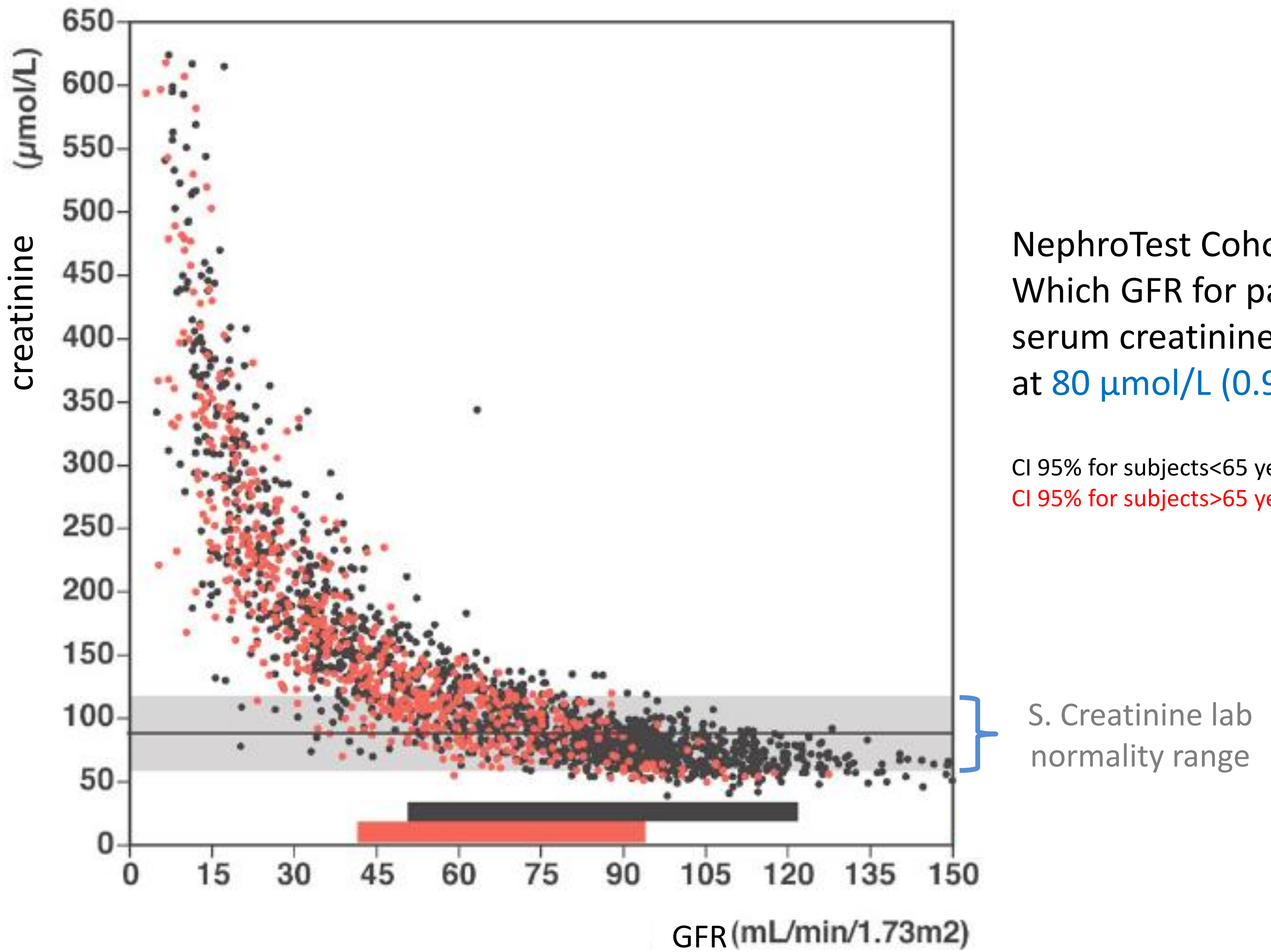
Category	Disclosure Information
Employer	Nothing to disclose.
Ownership Interest	Nothing to disclose.
Consultancy	IDS; Nephrolyx; Alentis Therapeutics; ARK Bioscience; Astellas
Research Funding	Nothing to disclose.
Honoraria	IDS; Fresenius Kabi; Fresenius Medical Care; Nephrolyx; Alentis Therapeutics; ARK Bioscience; AstraZeneca; Bayer
Patents or Royalties	Nothing to disclose.
Advisory or Leadership Role	Nothing to disclose.
Speakers Bureau	Nothing to disclose.
Other Interests or Relationships	Nothing to disclose.
Disclosure Updated Date	07/18/2023

- GFR is estimated with biomarkers
- Serum creatinine is one the most prescribed analysis
- The most important is probably to know the limitations…



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

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

With the kind permission of Marc Froissart

Other Limitations

Analytical

- Jaffe methods
- Enzymatic methods
- Jaffe and enzymatic methods gives slightly different results
- Pseudochromogen: glucose, fructose, ascorbate, proteins, urate, acetoacetate, acetone, pyruvate => false positive
- Bilirubins: false negative

Physiological: Tubular secretion

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

Physiological: Muscular mass

- Production (relatively) constant but muscular production => serum creatinine is dependent of muscualr mass, not only GFR (age? sex/gender? race/population?)
- Extra-renal production

Perrone RD, Clin Chem, 1992, 38, p1933
Delanaye P, Nephron, 2017, 136, p302

Creatinine: to the trash?

- Very cheap (0.04€ /Jaffe)
- Good specificty
- Good analytical CV, IDMS traceability

Creatinine clearance

- Not recommended (first line)
- Creatinine tubular secretion
- Lack of precision:

errors in urine collection

22 to 27% for « trained » patients

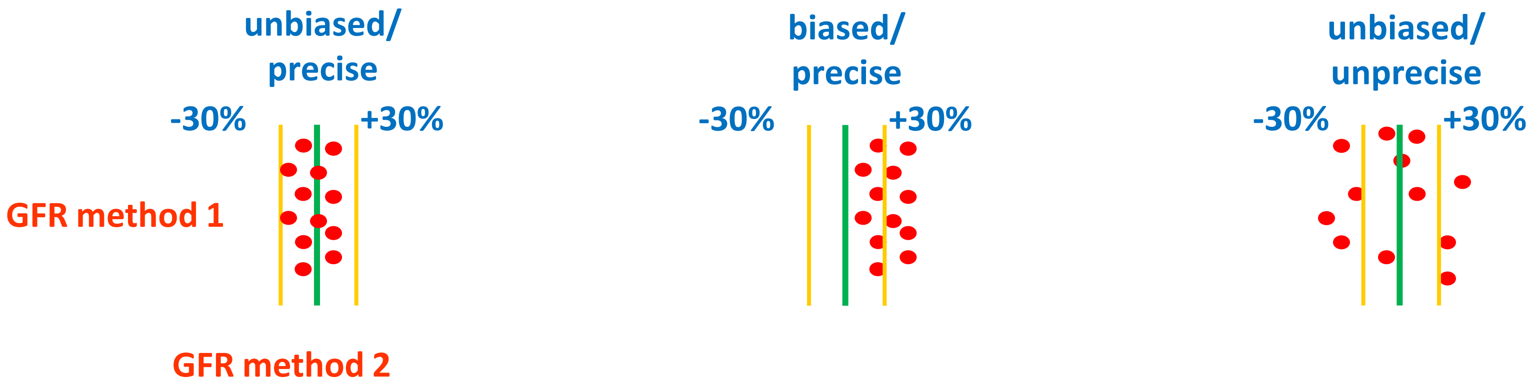
50 to 70 % for others

large intra-individual variability for creatinine excretion

KDIGO, Kidney Int, 2012, 3
Perrone RD, Clin Chem, 1992, 38, 1933

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



Bland JM, Altman DG, Lancet, 1986, 8476, 307
Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396

Which one?

- Cockcroft
- CKD-EPI
- EKFC

The Revised Lund Malmo equation

Jonas Björk

Ulf Nyman

Anders Grubb

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:	$X=2.56-0.926\times\ln(pCr/180)$

Generation of a New Cystatin C–Based Estimating Equation for Glomerular Filtration Rate by Use of 7 Assays Standardized to the International Calibrator

Anders Grubb,[1*†] Masaru Horio,[2] Lars-Olof Hansson,[3] Jonas Björk,[4] Ulf Nyman,[5] Mats Flodin,[3] Anders Larssson,[3] Arend Bökenkamp,[6] Yoshinari Yasuda,[2] Hester Blufpand,[6] Veronica Lindström,[1†] Ingrid Zegers,[7] Harald Althaus,[8†] Søren Blirup-Jensen,[1†] Yoshi Itoh,[9†] Per Sjöström,[10] Gunnar Nordin,[11] Anders Christensson,[12] Horst Klima,[13] Kathrin Sunde,[14] Per Hjort-Christensen,[15] David Armbruster,[16] and Carlo Ferrero[17]

Clinical Chemistry 60:7
974–986 (2014)

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

Which one?

- ~~Cockcroft~~
- CKD-EPI
- EKFC

The CKD-EPI equation

ARTICLE
Annals of Internal Medicine

A New Equation to Estimate Glomerular Filtration Rate

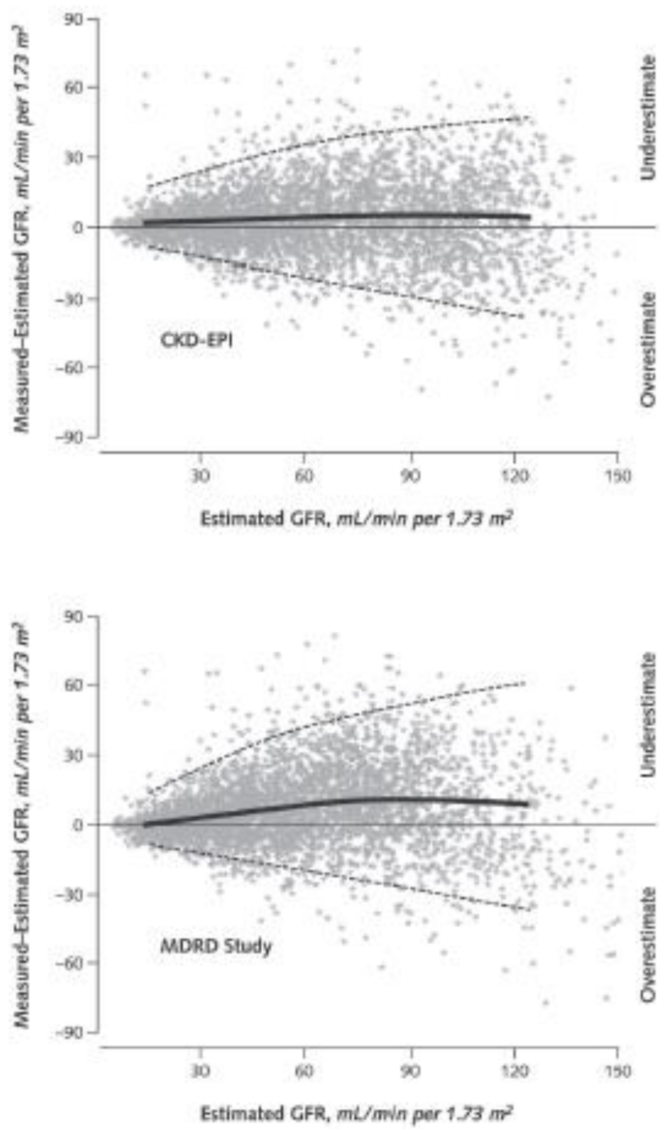
Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, MD, PhD, MHS, for the CKD-EPI (Chronic Kidney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



Levey AS, Ann Intern Med, 2009, p604

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

VOLUME 3 | ISSUE 1 | JANUARY 2013

http://www.kidney-international.org

Revised in 2024

CKD-EPI: What else?

Ann Intern Med. 2021;174:183-191. doi:10.7326/M20-4366

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

Hans Pottel, PhD*; Jonas Björk, PhD*; Marie Courbebaisse, MD, PhD; Lionel Couzi, MD, PhD; Natalie Ebert, MD, MPH; Björn O. Eriksen, MD, PhD; R. Neil Dalton, PhD; Laurence Dubourg, MD, PhD; François Gaillard, MD, PhD; Cyril Garrouste, MD; Anders Grubb, MD, PhD; Lola Jacquemont, MD, PhD; Magnus Hansson, MD, PhD; Nassim Kamar, MD, PhD; Edmund J. Lamb, PhD; Christophe Legendre, MD; Karin Littmann, MD; Christophe Mariat, MD, PhD; Toralf Melsom, MD, PhD; Lionel Rostaing, MD, PhD; Andrew D. Rule, MD; Elke Schaeffner, MD, PhD, MSc; Per-Ola Sundin, MD, PhD; Stephen Turner, MD, PhD; Arend Bökenkamp, MD; Ulla Berg, MD, PhD; Kajsa Åsling-Monemi, MD, PhD; Luciano Selistre, MD, PhD; Anna Åkesson, BSc; Anders Larsson, MD, PhD; Ulf Nyman, MD, PhD†; and Pierre Delanaye, MD, PhD†

Measured GFR and IDMS traceable creatinine
N=11,251 in the development and internal validation dataset
N=8,378 in the external validation dataset
N=1,254 between 2 and 18 years
7+6 cohorts
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.

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DE GRUYTER Clin Chem Lab Med 2022; 60(3): 401–407

Pierre Delanaye*, François Gaillard, Jessica van der Weijden, Geir Mjøen, Ingela Ferhman-Ekholm, Laurence Dubourg, Natalie Ebert, Elke Schaeffner, Torbjörn Åkerfeldt, Karolien Goffin, Lionel Couzi, Cyril Garrouste, Lionel Rostaing, Marie Courbebaisse, Christophe Legendre, Maryvonne Hourmant, Nassim Kamar, Etienne Cavalier, Laurent Weekers, Antoine Bouquegneau, Martin H. de Borst, Christophe Mariat, Hans Pottel and Marco van Londen

Age-adapted percentiles of measured glomerular filtration in healthy individuals: extrapolation to living kidney donors over 65 years

Before 40 y: mGFR = 107 mL/min/1.73m²
…and it seems universal…

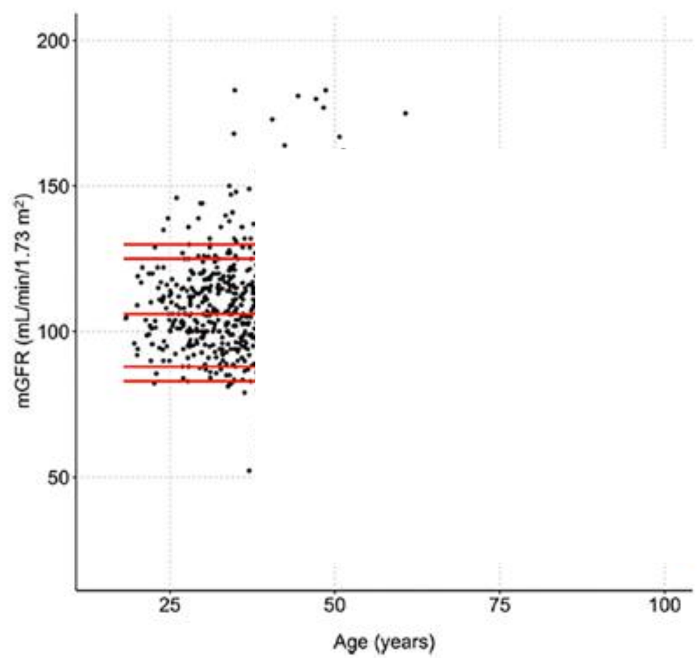

Figure 3: mGFR according to age in the development (dark dots) and external validation cohort (n=329) (gray dots). Red lines are percentiles 5, 10, 50, 90 and 95, calculated from kidney donors younger than 65 years and extrapolated for ages >65 years.

Pierre Delanaye*, François Gaillard, Jessica van der Weijden, Geir Mjøen, Ingela Ferhman-Ekholm, Laurence Dubourg, Natalie Ebert, Elke Schaeffner, Torbjörn Åkerfeldt, Karolien Goffin, Lionel Couzi, Cyril Garrouste, Lionel Rostaing, Marie Courbebaisse, Christophe Legendre, Maryvonne Hourmant, Nassim Kamar, Etienne Cavalier, Laurent Weekers, Antoine Bouquegneau, Martin H. de Borst, Christophe Mariat, Hans Pottel and Marco van Londen

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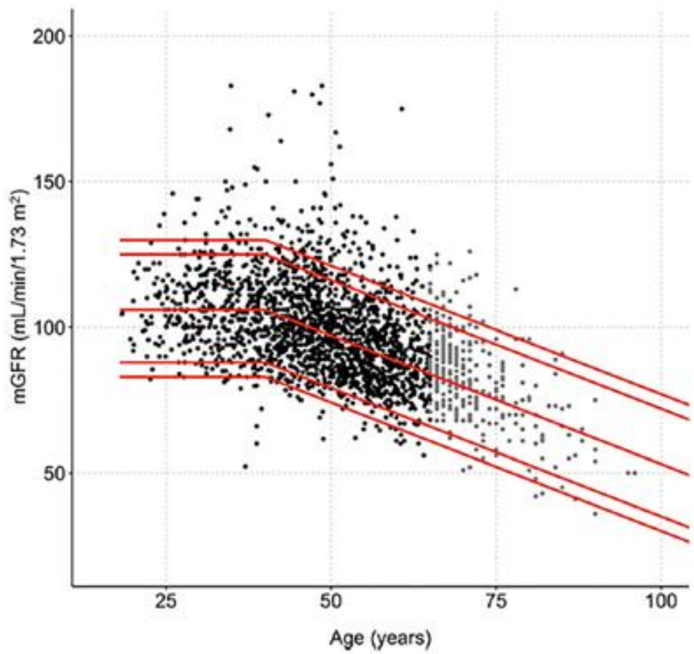

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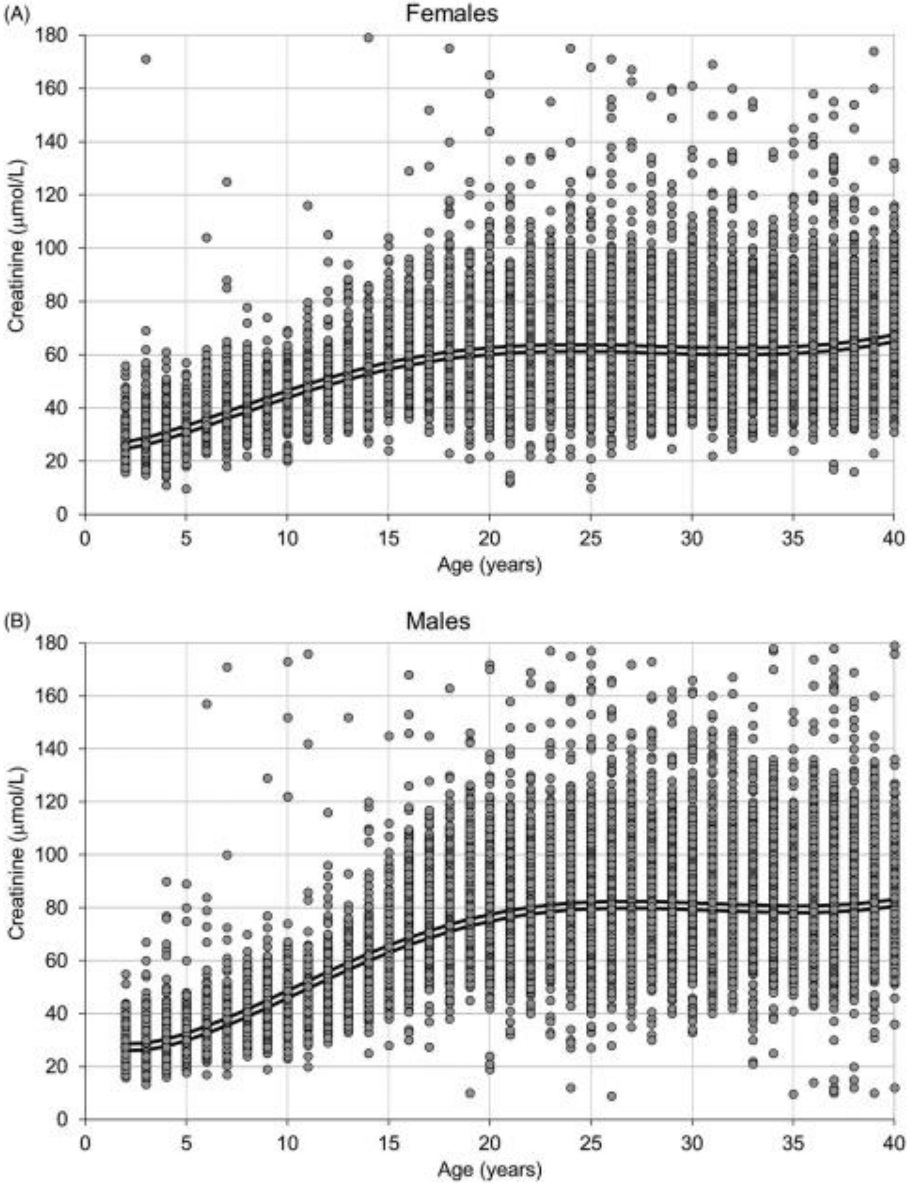

N=83,257 from three labs (Sweden, Belgium)

62 µmol/L= 0,70 mg/dL

80 µmol/L= 0,90 mg/dL

Bjork J, Scand J Clin Lab Invest, 2020, 80, p456

Figure 1. The new EKFC equation.

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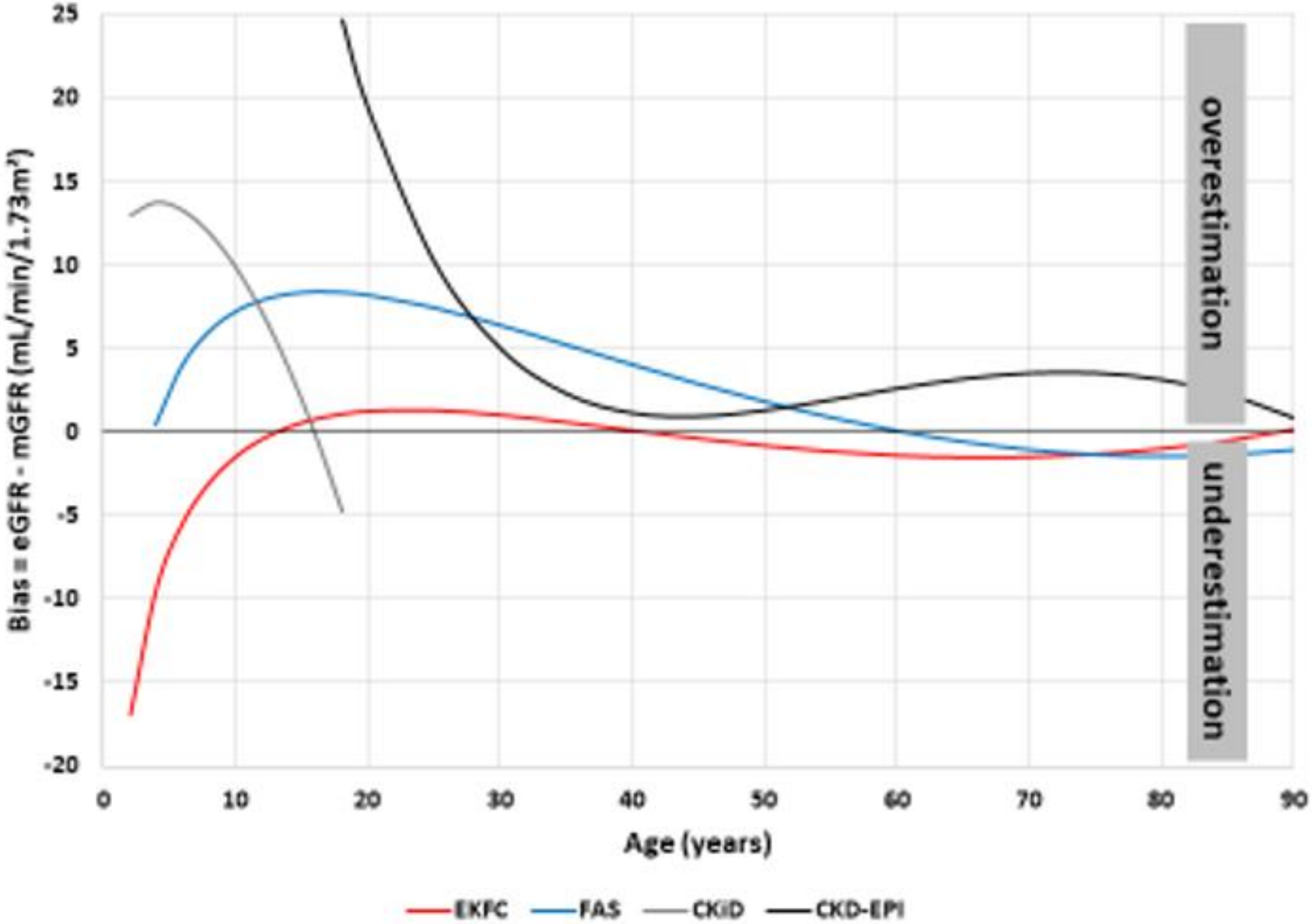

Bias = eGFR - mGFR (mL/min/1.73m²)
25
20
15
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
60
70
80
90
Age (years)
overestimation
underestimation
EKFC
FAS
CKiD
CKD-EPI

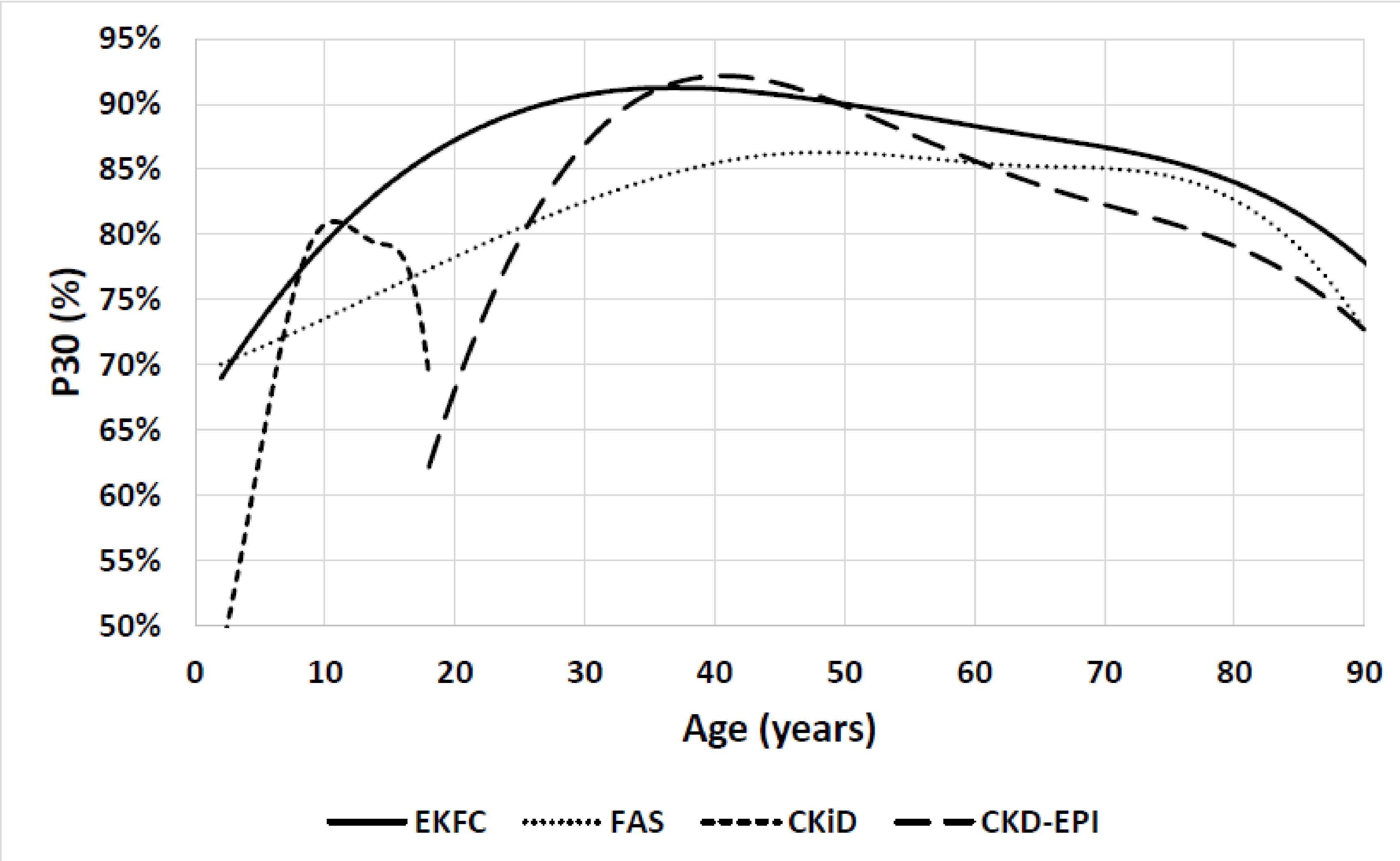

Figure S8. P30-accuracy against age for the EKFC, FAS, CKiD and CKD-EPI equation in the external validation dataset. P30 (%) was graphically presented across the age spectrum using cubic splines with two free knots and using 3rd degree polynomials.

EKFC: added value

- Better performance (not more expensive)
- More « physiological»: correction at the serum creatinine level (sex, race), age better conceptualized, « Q » specific to specific populations
- Valid from 2y to old ages
- Children: no need for height
- No implausible jump at transition adolescence/young adults

Debate on the race factor in USA

Semantic remark

Serum creatinine is different between Black and non-Black people in USA (and we don’t know why!)

(normal) mGFR is not different

The race coefficient in the CKD-EPI$_{2009}$ was considered as a source of discrimination

Eneanya N, Nat Rev Nephrol, 2022, 18, p84
Hsu CY, N Engl J med, 2021, p1750

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart, M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson, E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew, S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

› N Engl J Med. 2021 Nov 4;385(19):1737-1749.

Table 3. Accuracy of Current and New Approaches for GFR Estimation as Compared with Measured GFR in the Validation Data Set.

Filtration Marker and Equation*	Black Participants	Non-Black Participants	Difference between Black Participants and Non-Black Participants (95% CI)†
	Bias: Median Difference between Measured GFR and eGFR (95% CI)‡		
		milliliters per minute per 1.73 square meters	
Creatinine			
eGFRcr(ASR), current	−3.7 (−5.4 to −1.8)	−0.5 (−0.9 to 0.0)	−3.2 (−5.0 to −1.3)
eGFRcr(ASR-NB), new	7.1 (5.9 to 8.8)	−0.5 (−0.9 to 0.0)	7.6 (6.1 to 9.0)
eGFRcr(AS), new	3.6 (1.8 to 5.5)	−3.9 (−4.4 to −3.4)	7.6 (5.6 to 9.5)
Creatinine			
eGFRcr(ASR), current	85.1 (82.2 to 87.9)	89.5 (88.5 to 90.4)	−4.4 (−7.6 to −1.2)
eGFRcr(ASR-NB), new	86.4 (83.4 to 89.1)	89.5 (88.5 to 90.4)	−3.1 (−6.2 to 0)
eGFRcr(AS), new	87.2 (84.5 to 90.0)	86.5 (85.4 to 87.6)	0.7 (−2.4 to 3.8)

NKF and ASN Release New Way to Diagnose Kidney Diseases

Both Organizations Recommend Race-Free Approach to Estimate GFR

Sept. 23, 2021, New York, NY - Today, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases has released its final report, which outlines a new race-free approach to diagnose kidney disease. In the report, the NKF-ASN Task Force recommends the adoption of the new **eGFR 2021 CKD EPI creatinine equation that estimates kidney function without a race variable. The task force also recommended increased use of cystatin C combined with serum (blood) creatinine, as a confirmatory assessment of GFR or kidney function.**

Ethnic/race factor in Europe/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

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

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Check for updates

Hindawi
International Journal of Nephrology
Volume 2020, Article ID 2141038, 9 pages
https://doi.org/10.1155/2020/2141038

Hindawi

Research Article

No Race-Ethnicity Adjustment in CKD-EPI Equations Is Required for Estimating Glomerular Filtration Rate in the Brazilian Population

ARTICLE IN PRESS

www.kidney-international.org   clinical investigation

Performance of creatinine- or cystatin C–based equations to estimate glomerular filtration rate in sub-Saharan African populations

Justine B. Bukabau[1,7], Eric Yayo[2,7], Appolinaire Gnionsahé[3], Dagui Monnet[2], Hans Pottel[4], Etienne Cavalier[5], Aliocha Nkodila[1], Jean Robert R. Makulo[1], Vieux M. Mokoli[1], François B. Lepira[1], Nazaire M. Nseka[1], Jean-Marie Krzesinski[6], Ernest K. Sumaili[1,7] and Pierre Delanaye[6,7]

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Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa

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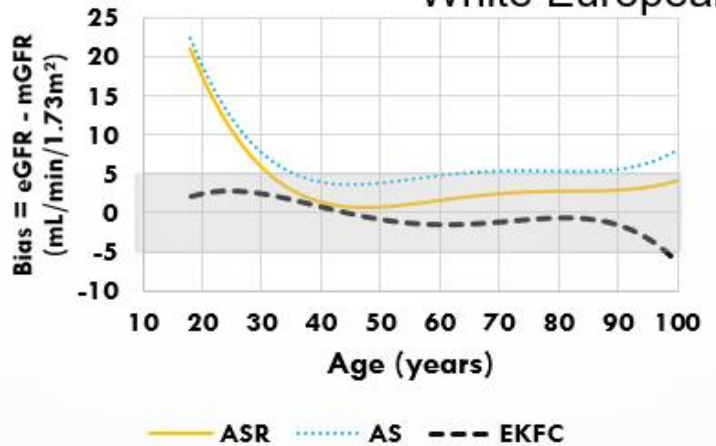
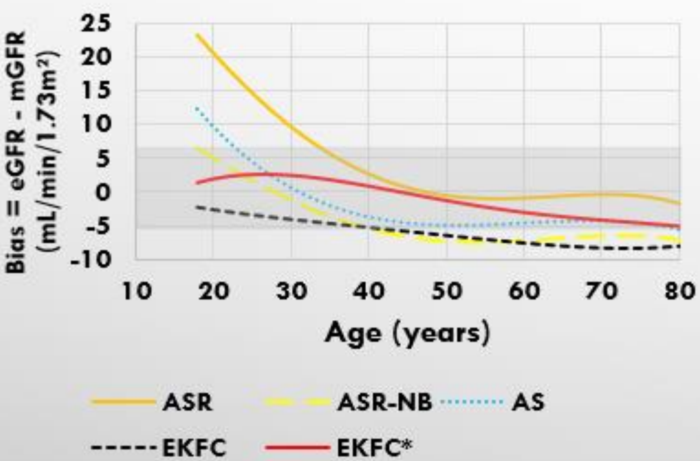
Methods

- Adults, measured GFR, IDMS creatinine
- EKFC consortium: 11 cohorts from Europe (n=17,321)
- Data from Paris (n=4,429, among them 964 Black Europeans)
- Data from Africa (RDC and Côte d'Ivoire, n=508)

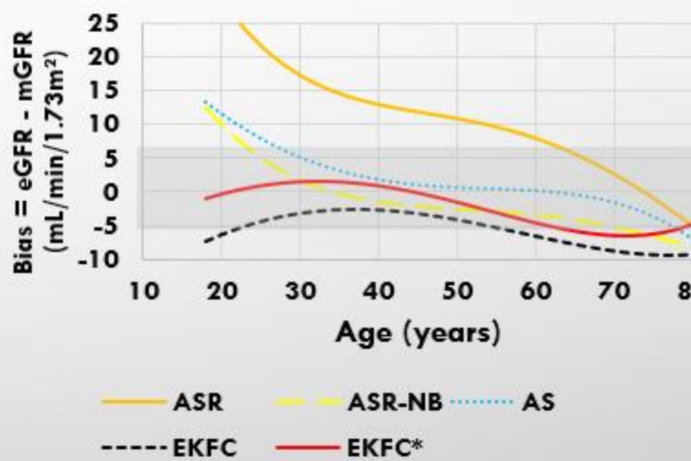
White Europeans (n=17,321)



Black Europeans (n=964)



Black Africans (n=508)



Americentrism in estimation of glomerular filtration rate equations

Kidney International (2022) **101**, 856–858; https://doi.org/10.1016/j.kint.2022.02.022

KEYWORDS: glomerular filtration rate; race; serum creatinine

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Clin Chem Lab Med 2023; 61(1): 44–47

DE GRUYTER

EFLM Paper

Pierre Delanaye, Elke Schaeffner, Mario Cozzolino, Michel Langlois, Mario Plebani, Tomris Ozben and Etienne Cavalier*, on behalf of the Board members of the EFLM Task Group Chronic Kidney Diseases

The new, race-free, Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation to estimate glomerular filtration rate: is it applicable in Europe? A position statement by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM)

Nephrol Dial Transplant (2023) 38: 1–6
https://doi.org/10.1093/ndt/gfac254
Advance Access publication date 7 September 2022

What should European nephrology do with the new CKD-EPI equation?

Ron T. Gansevoort[1], Hans-Joachim Anders[2], Mario Cozzolino[3], Danilo Fliser[4], Denis Fouque[5], Alberto Ortiz[6,7], Maria José Soler[8] and Christoph Wanner[9]

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Performance of the European Kidney Function Consortium (EKFC) creatinine-based equation in United States cohorts

Check for updates

see commentary on page 445

Pierre Delanaye[1,2,16], Andrew D. Rule[3,16], Elke Schaeffner[4,16], Etienne Cavalier[5,16], Junyan Shi[6,7], Andrew N. Hoofnagle[7,8,9,10], Ulf Nyman[11,16], Jonas Björk[12,13,15,16] and Hans Pottel[14,15,16]

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Kidney International (2024) **105,** 629–637;

Validation of EKFC in US populations

Cohorts	Sample Size	Age (years)	Measured GFR (mL/min/1.73m²)	% of women	% of Black subjects	Proportion of individuals with urinary clearance data available
All	*12,854*	*56.0 [22.1]*	*57 [46]*	*44.3*	*21.7*	*93.2*
AASK	1,844	54.5 [16.0]	57 [35]	35.9	100	100
ALTOLD	381	43.3 [19.0]	97 [18]	65.1	1.8	0
CRIC	1,194	59.0 [17.7]	48 [28]	44.4	44.7	100
CRISP	217	34.0 [13.0]	93 [34]	59.0	11.1	100
DCCT/EDIC	809	31.0 [9.0]	119 [25]	47.8	1.4	100
GENOA/ECAC	1,093	66.1 [12.1]	80 [27]	56.6	0	100
Mayo Clinic	5,069	59.0 [21.0]	50 [40]	44.6	2.0	100
MDRD	1,756	51.0 [21.0]	36 [29]	39.5	12.4	100
PERL	491	52.0 [15.0]	70 [25]	33.6	10.8	0

Results are expressed in % or Median [interquartile range].
GFR: glomerular filtration rate

Q-values could be population specific

Q-values determined in different populations

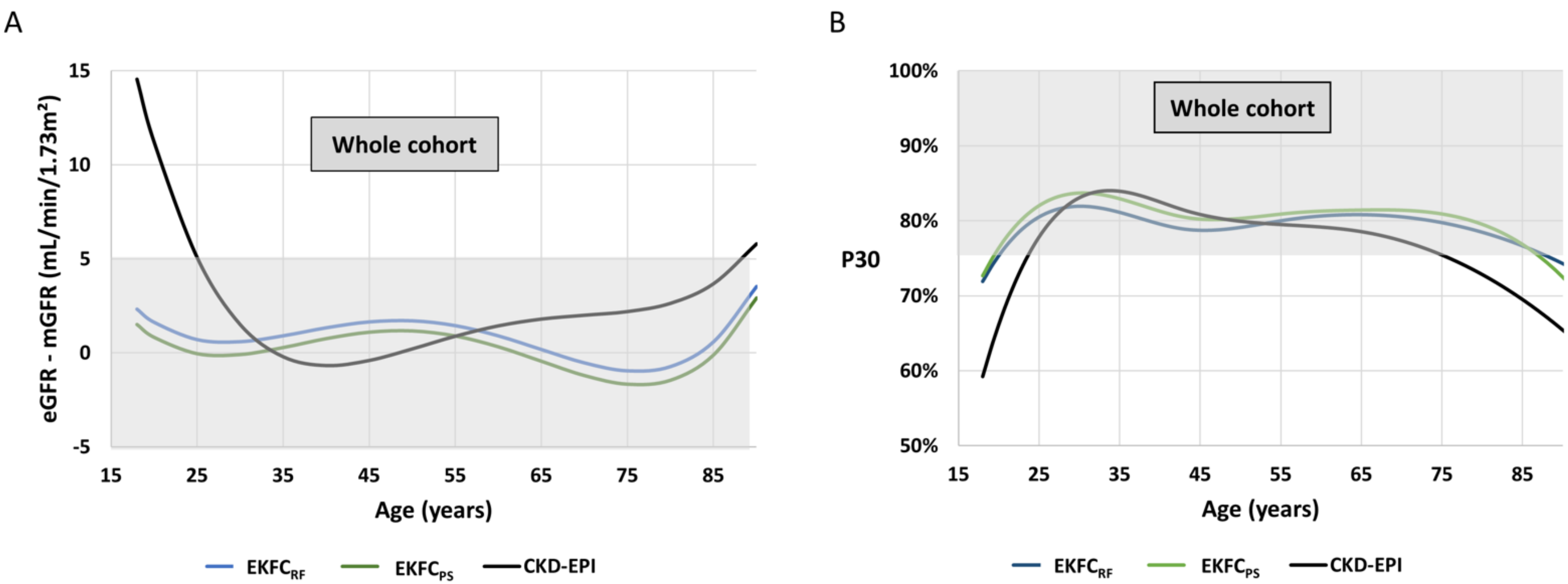
	Q value in women	Q value in men	Origine
White European	0.70	0.90	Large data from laboratories in Sweden and Belgium
Black European	0.74	1.02	Living kidney donors in Paris
Black Africans (Central Africa)	0.72	0.96	Healthy people in Congo
White US population-specific	0.73	0.93	Large data from laboratories from University of Washington Medicine System
Black US population-specific	0.73	1.00	Large data from laboratories from University of Washington Medicine System
White US population-specific	0.70	0.94	National Health and Nutrition Examination Survey
Black US population-specific	0.72	1.03	National Health and Nutrition Examination Survey
US race-free	0.73	0.97	Large data from laboratories from University of Washington Medicine System
China	0.62	0.88	27,830 healthy people

All results are expressed in mg/dL

Shi J, Clin Chim Acta, 2021, 520, p16

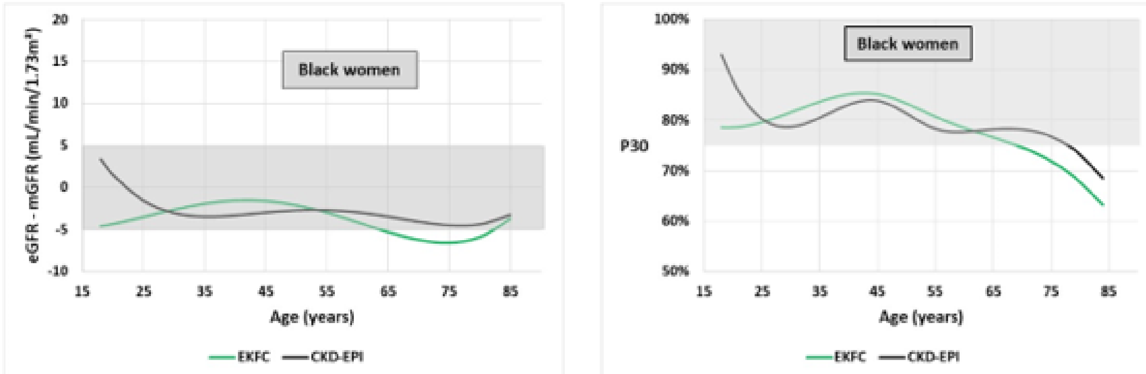
A

B



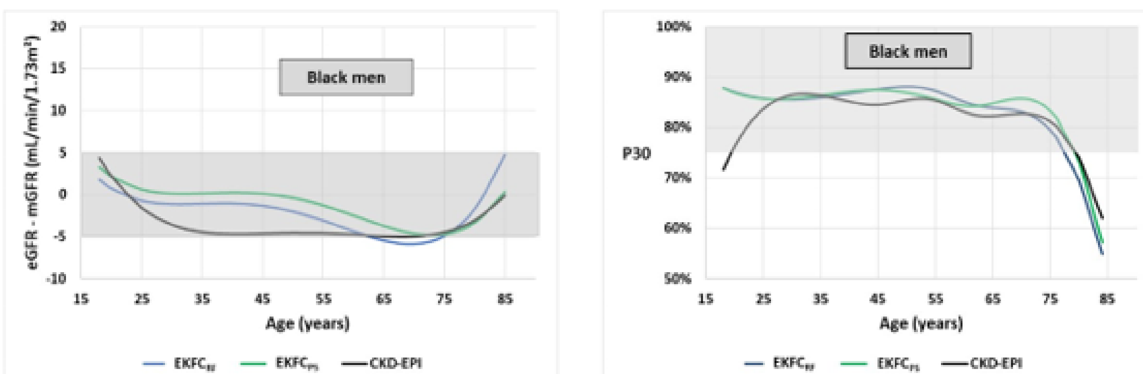
A
Whole cohort
eGFR - mGFR (mL/min/1.73m²)
15
10
5
0
-5
15
25
35
45
55
65
75
85
Age (years)
EKFC_RF
EKFC_PS
CKD-EPI
B
Whole cohort
P30
100%
90%
80%
70%
60%
50%
15
25
35
45
55
65
75
85
Age (years)
EKFC_RF
EKFC_PS
CKD-EPI

Bias (A) and accuracy within 30% (P30) (B) for the CKD-EPI$_{2021}$ and the EKFC in Black women (n=1,087) according to age.



Legend: CKD-EPI$_{2021}$: race-free Chronic Kidney Disease Epidemiology, EKFC$_{RF}$: European Kidney Function Consortium with race-free Q-values. EKFC$_{PS}$: European Kidney Function with population specific Q-values

Bias (A) and accuracy within 30% (P30) (B) for the CKD-EPI$_{2021}$, the EKFC$_{RF}$ and EKFC$_{PS}$ in Black men (n=1,703) according to age.



Legend: CKD-EPI$_{2021}$: race-free Chronic Kidney Disease Epidemiology, EKFC$_{RF}$: European Kidney Function Consortium with race-free Q-values. EKFC$_{PS}$: European Kidney Function with population specific Q-values

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China	0.62	0.88	27,830 healthy people

All results are expressed in mg/dL

Nephron

Clinical Practice: Mini-Review

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Glomerular Filtration Rate Estimation in Adults: Myths and Promises

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- The main advantage of EKFC is its flexibility
- Q can be adapted to every population
- Including a mixed "racial" population or a "race-free"
- Q can be obtained from large or very specific database
- Q can be obtained in every hospital (true "local" Q)

Q is population-based concept

Q is population-based concept

Q is population-based concept

- eGFR is a population-based concept

Q is population-based concept

- eGFR is a population-based concept
- What if a different Q-value is applied at the individual level?
- each change in Q value of 0.01 (for a male person with Q of 0.90 mg/dL) is corresponding change in eGFR of 0.75 mL/min/1.73 m2 (around the threshold of 60 mL/min/1.73 m2)

Q from 0,90 to 0,97 (race-free): EKFC moves from 60 to 55 mL/min/173m²

Cystatin C…a Swedish biomarker

The blood serum concentration of **cystatin** C (gamma-trace) as a measure of the glomerular filtration rate.

Simonsen O, Grubb A, Thysell H.

Scand J Clin Lab Invest. 1985 Apr;45(2):97-101. doi: 10.3109/00365518509160980.

PMID: 3923607

The calculated values of the glomerular elimination rate for creatinine and **cystatin** C were normally distributed in contrast to those for beta 2-microglobulin. The calculated glomerular elimination rate of **cystatin** C was not correlated to age, sex, type of disorder ...

Serum concentration of **cystatin** C, factor D and beta 2-microglobulin as a measure of glomerular filtration rate.

Grubb A, Simonsen O, Sturfelt G, Truedsson L, Thysell H.

Acta Med Scand. 1985;218(5):499-503. doi: 10.1111/j.0954-6820.1985.tb08880.x.

PMID: 3911736

The calculated glomerular elimination rates of creatinine, **cystatin** C and factor D were normally distributed, in contrast to those of beta 2-microglobulin. According to data presented so far, **cystatin** C seems to be the LMW protein of first choice when GFR is to be e ...

CAPA equation, standardization of cystatin C measurement, Shrunken pore syndrome etc etc etc

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

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

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

Basis of Equation and Sex	Serum Creatinine†	Serum Cystatin C	Equation for Estimating GFR
	mg/dl	*mg/liter*	
CKD-EPI creatinine equation‡			
Female	≤0.7		$144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$ [× 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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cystatin C–Based Equation to Estimate GFR without the Inclusion of Race and Sex

H. Pottel, J. Björk, A.D. Rule, N. Ebert, B.O. Eriksen, L. Dubourg, E. Vidal-Petiot, A. Grubb, M. Hansson, E.J. Lamb, K. Littmann, C. Mariat, T. Melsom, E. Schaeffner, P.-O. Sundin, A. Åkesson, A. Larsson, E. Cavalier, J.B. Bukabau, E.K. Sumaili, E. Yayo, D. Monnet, M. Flamant, U. Nyman, and P. Delanaye

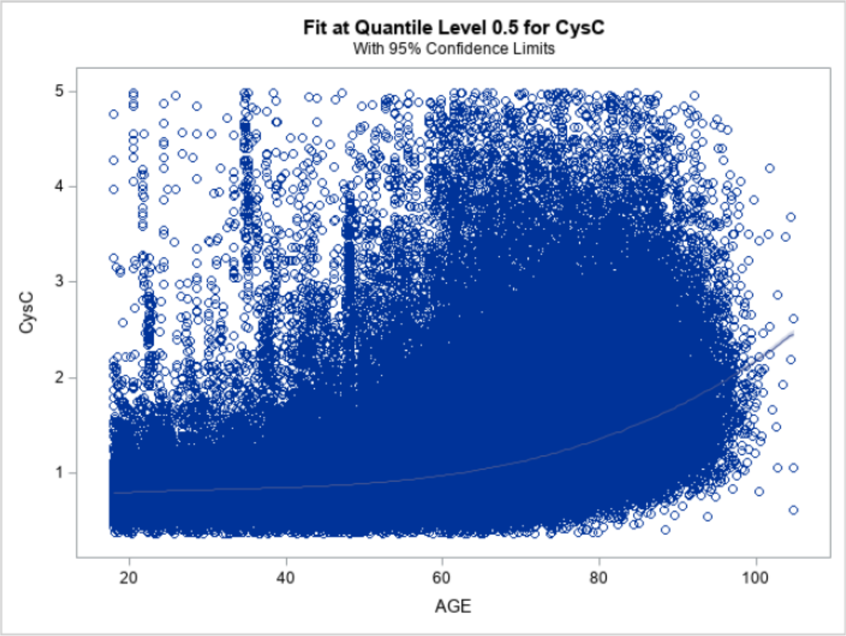
ABSTRACT

N Engl J Med 2023;388:333-43.

First step: cystatin C and age

Laboratory data from Sweden
N=227,643
♀ 95,469
♂ 132,174

Figure S3. Cystatin C versus age and the median quantile line for the 227,643 included subjects.

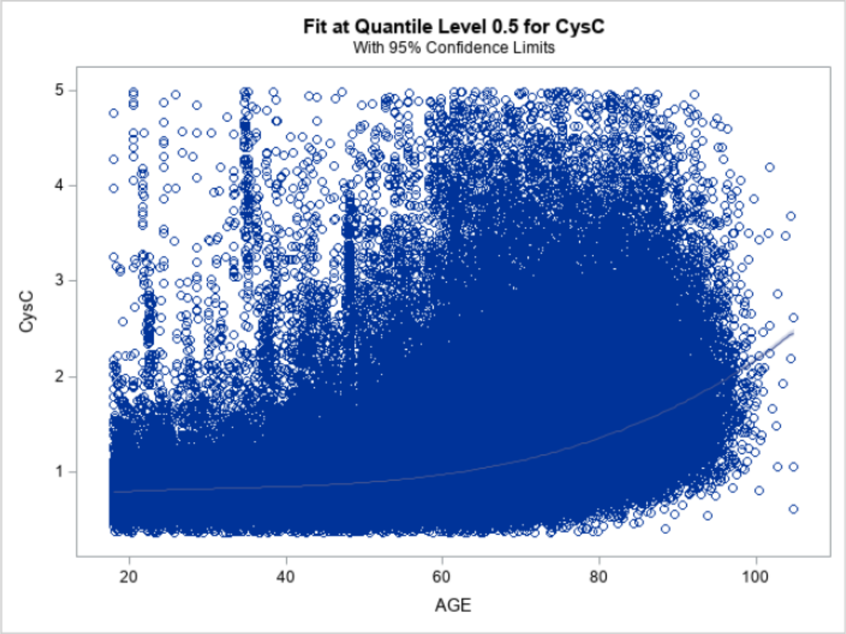


♀ Q' = 0.79 mg/L until 50 y,
Q' = 0.79 + 0.005 x (Age – 50)
♂ Q' = 0.86 mg/L until 50 y
Q' = 0.86 + 0.005 x (Age – 50)

First step: cystatin C and sex

Laboratory data from Sweden
N=227,643
♀ 95,469
♂ 132,174

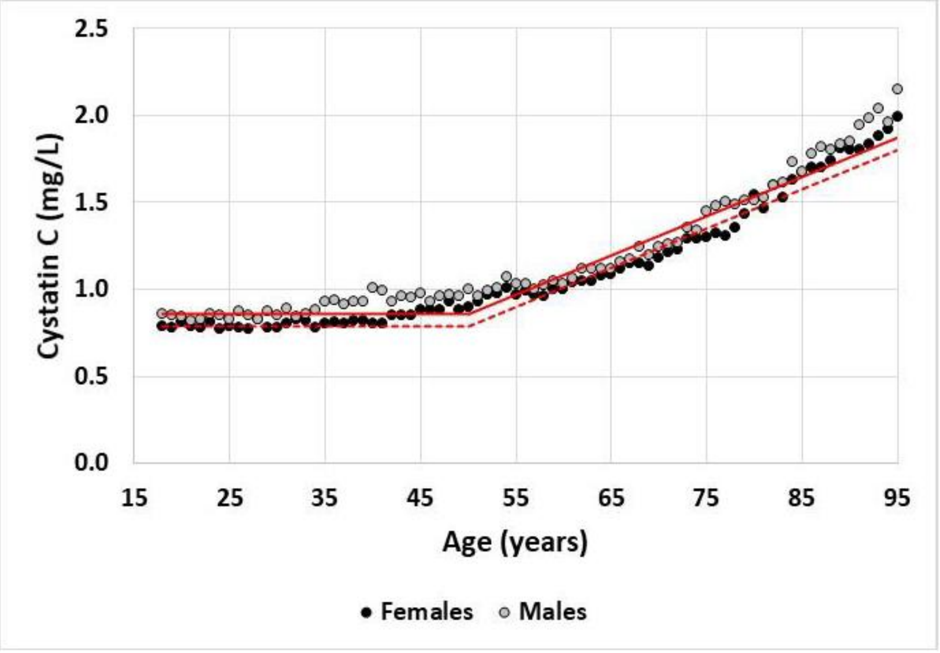
Figure S3. Cystatin C versus age and the median quantile line for the 227,643 included subjects.



♀ Q' = 0.79 mg/L until 50 y,
Q' = 0.79 + 0.005 x (Age – 50)
♂ Q' = 0.86 mg/L until 50 y
Q' = 0.86 + 0.005 x (Age – 50)

Second step: cystatin C and sex

Figure S4. Median plasma cystatin C in one-year intervals against age for men and women. A mathematical model to define Q'-values is proposed (red solid line): for adults Q' = 0.79 mg/L (women, dashed line) and 0.86 mg/L (men, solid line) until 50 years and a linear increasing model thereafter.



Q' = 0.83 mg/L until 50 years
Q' = 0.83 + 0.005 x (Age – 50)

Third step: Cystatin C and race

- Data from the same center in France
- Same method for GFR (Cr-EDTA), creatinine and cystatin C measurements
- Black and White people

Table S3. Patient characteristics of the entire cohorts used for the matching analysis (mean ± SD)

Ethnicity/Sex	N	Age (years)	BMI (kg/m^2)	mGFR ($mL/min/1.73m^2$)	SCr (mg/dL)	CysC (mg/L)
White Men	1296 (57%)	53.0 ± 14.6	26.2 ± 4.9	61.8 ± 26.0	1.52 ± 0.73	1.52 ± 0.68
Black Men	436 (63%)	50.7 ± 13.1	26.3 ± 4.5	62.0 ± 22.1	1.73 ± 0.81	1.41 ± 0.61
White Women	966 (43%)	52.5 ± 15.2	25.8 ± 6.2	62.8 ± 26.8	1.16 ± 0.61	1.38 ± 0.73
Black Women	261 (37%)	51.9 ± 15.2	27.4 ± 5.8	59.1 ± 25.6	1.40 ± 0.79	1.46 ± 0.76

Third step: Cystatin C and race

Matched analysis 1:1 for

- sex
- BMI (±2,5 kg/m²)
- Measured GFR (±3 mL/min/1.73m²)
- age (± 3 y)

Table S4. Demographic and renal characteristics of the matched White and Black subjects (mean ± SD)

Sex	N	Age (years)	BMI (kg/m²)	mGFR (mL/min/1.73m²)	SCr (mg/dL)	CysC (mg/L)
White Men	377	51.1 ± 12.2	25.7 ± 3.4	63.8 ± 21.0	1.43 ± 0.62	1.41 ± 0.56
Black Men	377	50.8 ± 12.3	25.8 ± 3.5	63.6 ± 21.0	1.65 ± 0.64	1.37 ± 0.59
White Women	200	53.4 ± 11.9	26.1 ± 4.6	59.7 ± 23.2	1.16 ± 0.53	1.40 ± 0.69
Black Women	200	53.3 ± 11.9	26.2 ± 4.6	59.8 ± 23.1	1.33 ± 0.61	1.41 ± 0.64

Fourth Step:
Validation of the new equation

$$\text{EKFC} - \text{eGFR} = 107.3/[\text{Biomarker}/Q]^{\alpha} \times [0.990^{(\text{Age}-40)} \text{ if age} > 40 \text{ years}],$$

with $\alpha = 0.322$ when biomarker/Q is less than 1 and $\alpha = 1.132$ when biomarker/Q is 1 or more.

Adults
Measured GFR, IDMS traceable creatinine, calibrated cystatin C
N=12,832

11 cohorts
White Europeans: n=7,727
White Europeans from Paris: n=2,646
White US: n=1,093
Black Europeans from Paris: n=858
Black Africans: n=508

Table 1. Performance of Single Biomarker (Serum Creatinine or Cystatin C)–Based Equations to Estimate the Glomerular Filtration Rate.*

Variable	Serum Creatinine–Based Equations		
	CKD-EPI eGFRcr(ASR)	CKD-EPI eGFRcr(AS)	EKFC eGFRcr
EKFC cohort, 7727 White patients			
Median bias (95% CI) — ml/min/1.73 m^2†	3.96 (3.67 to 4.32)	7.40 (7.02 to 7.76)	0.58 (0.32 to 0.86)
IQR of estimated GFR− measured GFR— ml/min/1.73 m^2‡	15.5 (−3.0 to 12.5)	16.3 (0.0 to 16.3)	14.5 (−6.5 to 8.0)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	14.8 (14.4 to 15.2)	16.3 (15.9 to 16.6)	13.1 (12.8 to 13.4)
P_{10} — % (95% CI)¶	40.3 (39.2 to 41.4)	34.7 (33.6 to 35.8)	43.3 (42.2 to 44.4)
P_{30} — % (95% CI)‖	81.6 (80.8 to 82.5)	75.7 (74.8 to 76.7)	85.8 (85.0 to 86.5)

7.40 (7.02 to 7.76)	0.58 (0.32 to 0.86)
16.3 (0.0 to 16.3)	14.5 (−6.5 to 8.0)
16.3 (15.9 to 16.6)	13.1 (12.8 to 13.4)
34.7 (33.6 to 35.8)	43.3 (42.2 to 44.4)
75.7 (74.8 to 76.7)	85.8 (85.0 to 86.5)

Table 1. Performance of Single Biomarker (Serum Creatinine or Cystatin C)–Based Equations to Estimate the Glomerular Filtration Rate.*

Variable	Cystatin C–Based Equations	
	CKD-EPI eGFRcys	EKFC eGFRcys without Sex
EKFC cohort, 7727 White patients		
Median bias (95% CI) — ml/min/1.73 m²†	0.28 (−0.02 to 0.64)	0.00 (−0.37 to 0.27)
IQR of estimated GFR− measured GFR— ml/min/1.73 m²‡	19.1 (−7.9 to 11.2)	14.4 (−7.9 to 6.5)
Root-mean-square error (95% CI) — ml/min/1.73 m²¶	15.8 (15.5 to 16.1)	13.5 (12.9 to 14.1)
P_{10} — % (95% CI)¶	32.0 (31.0 to 33.0)	41.7 (40.6 to 42.8)
P_{30} — % (95% CI)‖	80.8 (79.9 to 81.7)	86.2 (85.4 to 87.0)

Cystatin C–Based Equations	
CKD-EPI eGFRcys	EKFC eGFRcys without Sex
0.28 (−0.02 to 0.64)	0.00 (−0.37 to 0.27)
19.1 (−7.9 to 11.2)	14.4 (−7.9 to 6.5)
15.8 (15.5 to 16.1)	13.5 (12.9 to 14.1)
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Table 1. Performance of Single Biomarker (Serum Creatinine or Cystatin C)–Based Equations to Estimate the Glomerular Filtration Rate.*

Variable	Serum Creatinine–Based Equations			Cystatin C–Based Equations	
	CKD-EPI eGFRcr(ASR)	CKD-EPI eGFRcr(AS)	EKFC eGFRcr	CKD-EPI eGFRcys	EKFC eGFRcys without Sex
EKFC cohort, 7727 White patients					
Median bias (95% CI) — ml/min/1.73 m²†	3.96 (3.67 to 4.32)	7.40 (7.02 to 7.76)	0.58 (0.32 to 0.86)	0.28 (−0.02 to 0.64)	0.00 (−0.37 to 0.27)
IQR of estimated GFR− measured GFR— ml/min/1.73 m²‡	15.5 (−3.0 to 12.5)	16.3 (0.0 to 16.3)	14.5 (−6.5 to 8.0)	19.1 (−7.9 to 11.2)	14.4 (−7.9 to 6.5)
Root-mean-square error (95% CI) — ml/min/1.73 m²¶	14.8 (14.4 to 15.2)	16.3 (15.9 to 16.6)	13.1 (12.8 to 13.4)	15.8 (15.5 to 16.1)	13.5 (12.9 to 14.1)
P_{10} — % (95% CI)¶	40.3 (39.2 to 41.4)	34.7 (33.6 to 35.8)	43.3 (42.2 to 44.4)	32.0 (31.0 to 33.0)	41.7 (40.6 to 42.8)
P_{30} — % (95% CI)‖	81.6 (80.8 to 82.5)	75.7 (74.8 to 76.7)	85.8 (85.0 to 86.5)	80.8 (79.9 to 81.7)	86.2 (85.4 to 87.0)

Table 2. Performance of Combined Serum Creatinine– and Cystatin C–Based Equations to Estimate GFR.*

Variable	CKD-EPI eGFRcr-cys(ASR)	CKD-EPI eGFRcr-cys(AS)	EKFC eGFRcr-cys without Sex
EKFC cohort, 7727 White patients			
Median bias (95% CI) — ml/min/1.73 m^2†	2.50 (2.17 to 2.76)	5.04 (4.69 to 5.36)	0.37 (0.14 to 0.66)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	14.8 (−3.6 to 11.2)	16.7 (−1.8 to 14.9)	12.0 (−5.9 to 6.1)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	13.1 (12.8 to 13.4)	14.7 (14.4 to 15.0)	11.3 (11.0 to 11.6)
P_{10} — % (95% CI)¶	41.5 (40.4 to 42.6)	37.2 (36.2 to 38.3)	48.9 (47.8 to 50.0)
P_{30} — % (95% CI)‖	88.3 (87.6 to 89.0)	84.2 (83.4 to 85.0)	90.4 (89.8 to 91.1)
Paris cohort, 2646 White patients			
Median bias (95% CI) — ml/min/1.73 m^2†	−1.35 (−1.82 to −0.97)	0.64 (0.16 to 1.15)	−0.65 (−1.06 to −0.23)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	13.4 (−7.5 to 5.8)	14.1 (−5.8 to 8.3)	12.4 (−6.8 to 5.6)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	12.1 (11.6 to 12.7)	12.6 (12.0 to 13.1)	11.8 (11.2 to 12.4)
P_{10} — % (95% CI)¶	43.9 (42.0 to 45.8)	42.3 (40.4 to 44.1)	45.8 (43.9 to 47.7)
P_{30} — % (95% CI)‖	89.7 (88.5 to 90.8)	89.2 (88.0 to 90.4)	92.1 (91.1 to 93.1)
U.S. cohort, 1093 White patients			
Median bias (95% CI) — ml/min/1.73 m^2†	9.23 (8.45 to 10.10)	13.9 (13.1 to 14.9)	0.97 (0.01 to 2.12)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	18.4 (0.5 to 18.8)	18.1 (5.1 to 23.3)	17.4 (−8.2 to 9.2)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	18.1 (17.1 to 19.1)	21.0 (20.1 to 22.0)	15.5 (14.3 to 16.7)
P_{10} — % (95% CI)¶	37.1 (34.3 to 40.0)	28.1 (25.4 to 30.8)	45.7 (42.7 to 48.6)
P_{30} — % (95% CI)‖	79.5 (77.1 to 81.9)	72.1 (69.4 to 74.8)	88.7 (86.9 to 90.6)
Paris cohort, 858 Black patients			
Median bias (95% CI) — ml/min/1.73 m^2†	−0.37 (−1.06 to 0.57)	−2.08 (−2.71 to −1.32)	−0.65 (−1.23 to 0.11)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	15.2 (−6.4 to 8.8)	14.0 (−7.9 to 6.1)	12.4 (−6.2 to 6.2)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	13.3 (11.9 to 14.6)	12.6 (11.2 to 13.9)	11.6 (10.0 to 13.0)
P_{10} — % (95% CI)¶	38.7 (35.4 to 42.0)	38.9 (35.7 to 42.2)	48.3 (44.9 to 51.6)
P_{30} — % (95% CI)‖	87.9 (85.7 to 90.1)	89.0 (87.0 to 91.1)	92.0 (90.1 to 93.8)
African cohort, 508 Black patients			
Median bias (95% CI) — ml/min/1.73 m^2†	8.55 (6.87 to 10.30)	4.08 (2.37 to 5.78)	0.42 (−1.03 to 1.51)
IQR of estimated GFR – measured GFR — ml/min/1.73 m^2‡	24.7 (−4.5 to 20.1)	22.0 (−7.4 to 14.7)	17.1 (−7.2 to 10.0)
Root-mean-square error (95% CI) — ml/min/1.73 m^2§	19.7 (18.2 to 21.1)	17.2 (15.8 to 18.5)	14.7 (13.3 to 16.0)
P_{10} — % (95% CI)¶	28.7 (24.8 to 32.7)	34.3 (30.1 to 38.4)	43.5 (39.2 to 47.8)
P_{30} — % (95% CI)‖	75.0 (71.2 to 78.8)	77.6 (73.9 to 81.2)	84.3 (81.1 to 87.4)

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ORIGINAL ARTICLE

Extending the cystatin C based EKFC-equation to children – validation results from Europe

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Cystatin C/EKFC

- Cystatin C allows an eGFR without race nor sex
- EKFC is mathematically the same as EKFC creatinine, only Q is changing
- Continuum between children and adults for $EKFC_{crea}$
- Equations based on cystatin C are not better than equations based on creatinine
- EKFC equations are slightly better than corresponding CKD-EPI equations => good alternative to CKD-Epi in Europe and Africa
- Combined equations are better (P30 +5-10%)
- Standardisation
- More costly
- How to manage discrepant results?
- Place of EKFC and/or cystatin C in the next KDIGO?

https://ekfccalculator.pages.dev/

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

Recommendation 1.1.2.1:	**In adults at risk for CKD, we recommend using creatinine-based estimated glomerular filtration rate (eGFRcr). If cystatin C is available, the GFR category should be estimated from the combination of creatinine and cystatin C (creatinine and cystatin C–based estimated glomerular filtration rate [eGFRcr-cys]) *(1B)*.**

1.2.4 Selection of GFR estimating equations

Recommendation 1.2.4.1: We recommend using a validated GFR estimating equation to derive GFR from serum filtration markers (eGFR) rather than relying on the serum filtration markers alone (*1D*).

Practice Point 1.2.4.1: Use the same equation within geographical regions (as defined locally [e.g., continent, country, and region] and as large as possible). Within such regions, equations may differ for adults and children.

Practice Point 1.2.4.2: Use of race in the computation of eGFR should be avoided.

Special considerations

Pediatric considerations

Practice Point 1.2.4.3: Estimate GFR in children using validated equations that have been developed or validated in comparable populations.

Table 14 | Validated GFR estimating equations

Marker	Equation name and year	Age	Variables	Development populations
Creatinine	CKD-EPI 2009[238]	≥18; modification CKD-EPI 40 for pediatric available	Developed using A, S, R but reported not using the Black race coefficient, A, S, R (NB)	8254 Black and NB individuals from 10 studies in the United States and Europe[a]
	CKiD U25 2021[239]	1–25	A, S, height	928 children with CKD in the United States and Canada
	CKD-EPI 2021[147]	≥18	A, S	8254 Black and NB individuals from 10 studies in the United States and Europe[a]
	EKFC 2021[240]	2–100	A, S, European Black and NB specific Q-value; separate Q-values for Africa vs. Europe	mGFR vs. SCr (11,251 participants in 7 studies in Europe and 1 study from the United States) Normal GFR from 5482 participants in 12 studies of kidney donor candidates (100% Caucasian) European NB Q from 83,157 laboratory samples (age 2–40 years) in 3 European hospital clinical laboratories; European Black Q-value (N = 90 living kidney donors from Paris); African Black Q-value (N = 470 healthy individuals from République Démocratique de Congo); All Q-values developed in cohorts independent for EKFC development and validation
	Lund Malmö Revised 2014[241]		A, S	3495 GFR examinations from 2847 adults from Sweden referred for measurement of GFR
	CKD-EPI 2009 Modified for China 2014[b,242]	≥18	A, S	589 people with diabetes from the Third Affiliated Hospital of Sun Yat-sen University, China
	CKD-EPI 2009 Modified for Japan 2016[b,83]	≥18	A, S	413 hospitalized Japanese people in 80 medical centers
	CKD-EPI 2009 Modified for Pakistan 2013[b,235]	≥18	A, S	542 randomly selected low- to middle-income communities in Karachi and 39 people from the kidney clinic
Cystatin C	CKD-EPI 2012[148]	≥18	A, S	5352 Black and NB individuals from 13 studies in the United States and Europe
	EKFC 2023[91]	18–100	A	mGFR vs. SCys (assumed to be the same as mGFR vs. SCr) Normal GFR (same as for the SCr equation) Q from laboratory samples from 227,643 (42% female) laboratory samples from Uppsala University Hospital, Sweden
	CAPA 2014[243]		A, S	4690 individuals within large subpopulations of children and Asian and Caucasian adults
Creatinine-cystatin C	CKD-EPI 2012[148]	≥18	Developed using A, S, R but reported not using the Black race coefficient, A, S, R (NB)	5352 Black and NB individuals from 13 studies in the United States and Europe
	CKD-EPI 2021[147]	≥18	A, S	5352 Black and NB individuals from 13 studies in the United States and Europe
	Average of EKFC cr and cys[240]	≥2	A, S, European race specific Q-value; separate Q-values for Africa vs. Europe	See above for EKFC creatinine and cystatin C

Limitations of equations = creatinine

Specific populations:
Equations are not magic!
Keep our clinical feeling!!

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

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

ICU (Delanaye P, BMC Nephrology, 2014, 15, 9)

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

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

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

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

Do not over-interpet an eGFR result…

All equations remain estimation…

Good at the population level

Lack of precision at the individual level

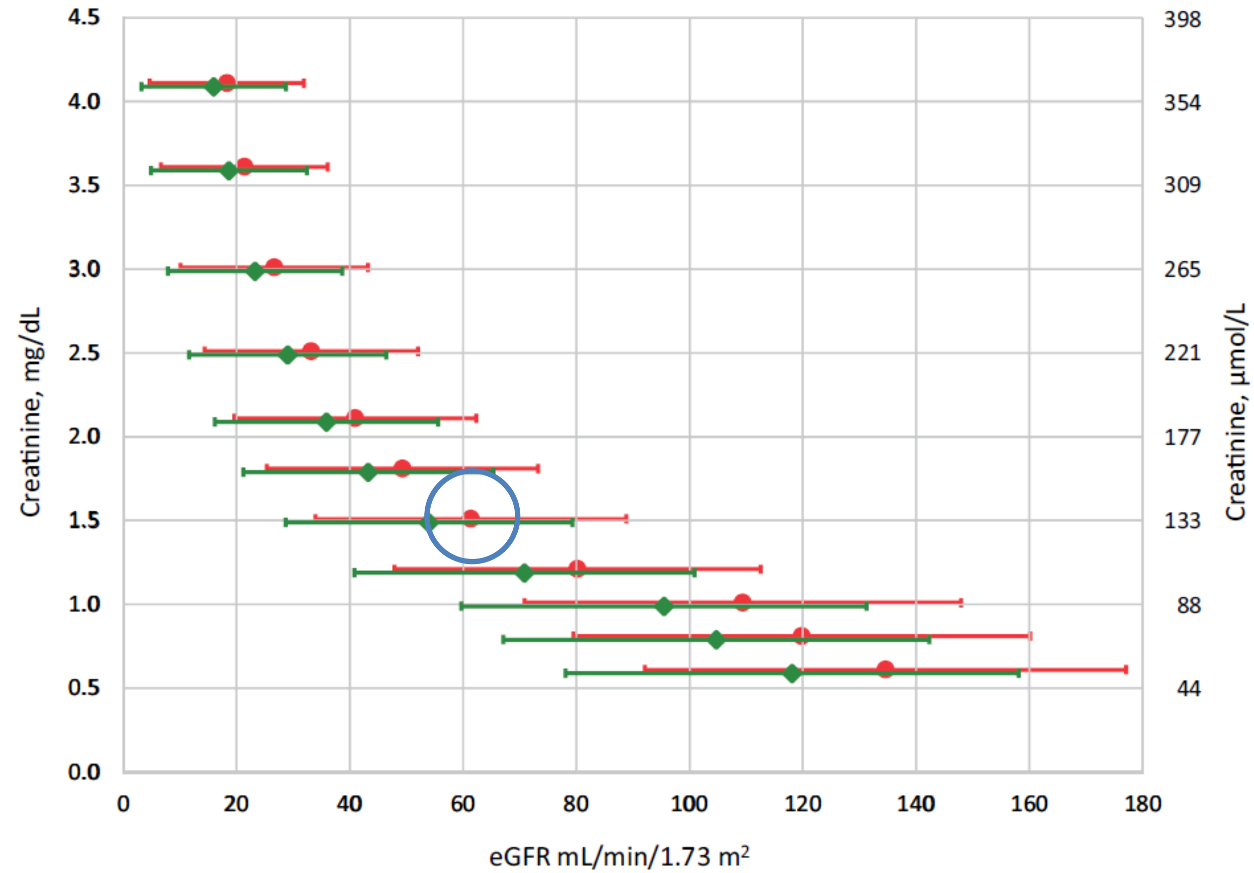

Fig. 1. Uncertainty of eGFR calculated using the CKD-EPI equations for African-Americans and non-African-Americans at various creatinine concentrations for a 50-year-old male. Circles (red, larger values) indicate African-American and diamonds (green, lower values) indicate non-African-American equations. Plot symbols are the eGFR values and error bars represent the 95% CI for each eGFR value.

eGFR = 60,25 ml/min/1.73m²

Miller WG, Clin Chem, 2021, p693 and p820

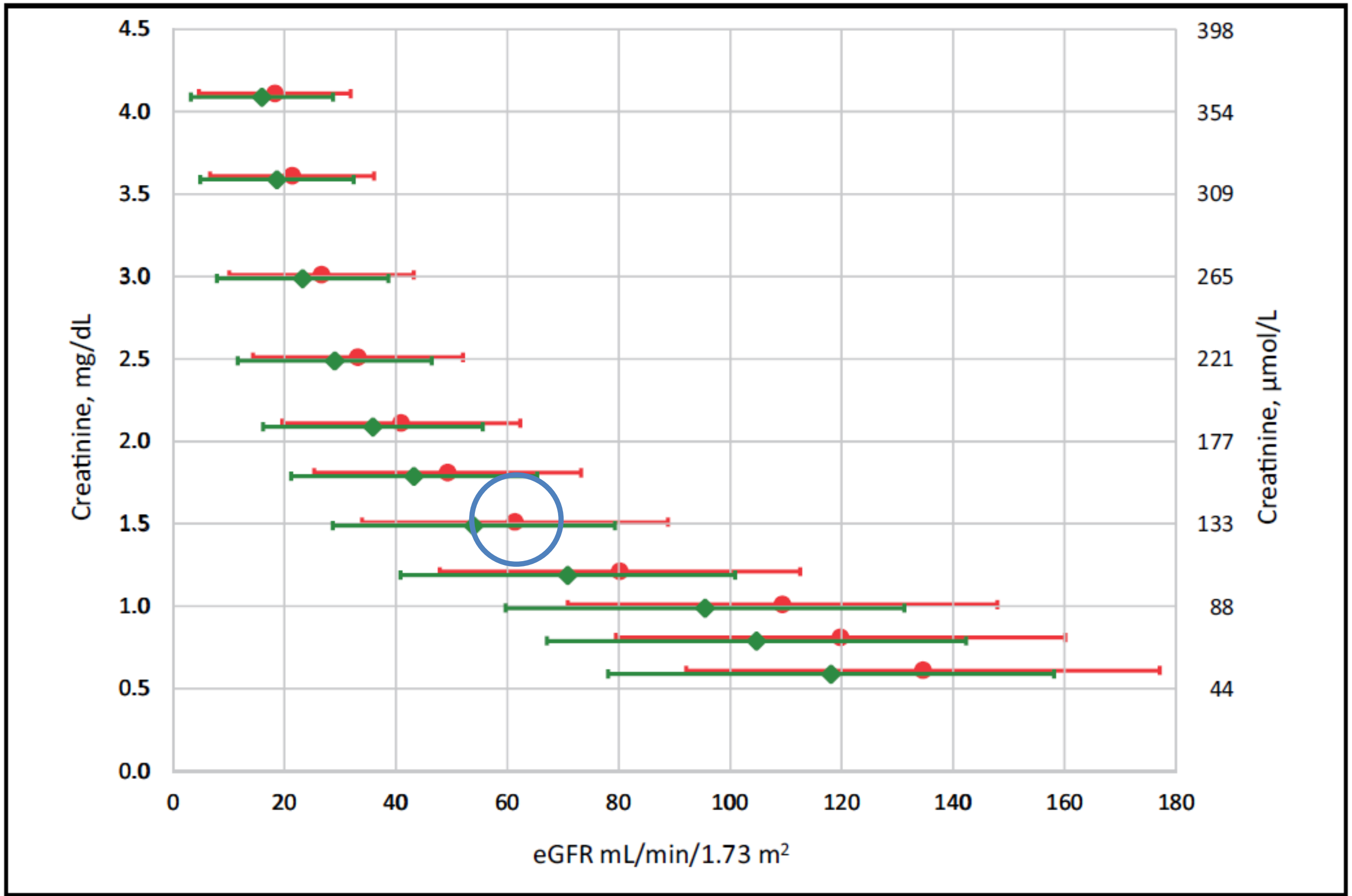

Fig. 1. Uncertainty of eGFR calculated using the CKD-EPI equations for African-Americans and non-African-Americans at various creatinine concentrations for a 50-year-old male. Circles (red, larger values) indicate African-American and diamonds (green, lower values) indicate non-African-American equations. Plot symbols are the eGFR values and error bars represent the 95% CI for each eGFR value.

eGFR ~~= 60,25 ml/min/1.73m²~~

= 60 ml/min/1.73m² (CI 95%: 33-87)

Miller WG, Clin Chem, 2021, p693 and p820

Variable	CKD-EPI eGFRcr-cys(ASR)	CKD-EPI eGFRcr-cys(AS)	EKFC eGFRcr-cys without Sex
EKFC cohort, 7727 White patients			
Median bias (95% CI) — ml/min/1.73 m²†	2.50 (2.17 to 2.76)	5.04 (4.69 to 5.36)	0.37 (0.14 to 0.66)
IQR of estimated GFR – measured GFR — ml/min/1.73 m²‡	14.8 (−3.6 to 11.2)	16.7 (−1.8 to 14.9)	12.0 (−5.9 to 6.1)
Root-mean-square error (95% CI) — ml/min/1.73 m²§	13.1 (12.8 to 13.4)	14.7 (14.4 to 15.0)	11.3 (11.0 to 11.6)
P_{10} — % (95% CI)¶	41.5 (40.4 to 42.6)	37.2 (36.2 to 38.3)	48.9 (47.8 to 50.0)
P_{30} — % (95% CI)‖	88.3 (87.6 to 89.0)	84.2 (83.4 to 85.0)	90.4 (89.8 to 91.1)

REVIEWS

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

GO BACK to MEASURED GFR

Delanaye P, Nature Rev Nephrol, 2013, 9, p513
Ebert N, Clin Kidney J, 2021, 14, p1861
Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Shafi T, Ann Intern Med, 2022, 175, p1073

Iohexol plasma clearance

Not so cumbersome

Not so costly

ARTICLE IN PRESS

www.kidney-international.org review

Iohexol plasma clearance measurement protocol standardization for adults: a consensus paper of the European Kidney Function Consortium

OPEN

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LABORATORY ANALYSIS

Practice Point 1.2.2.2: Where more accurate ascertainment of GFR will impact treatment decisions, measure GFR using plasma or urinary clearance of an exogenous filtration marker (Table 9).

Sweden is the best !

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Diagnostic standard: assessing glomerular filtration rate

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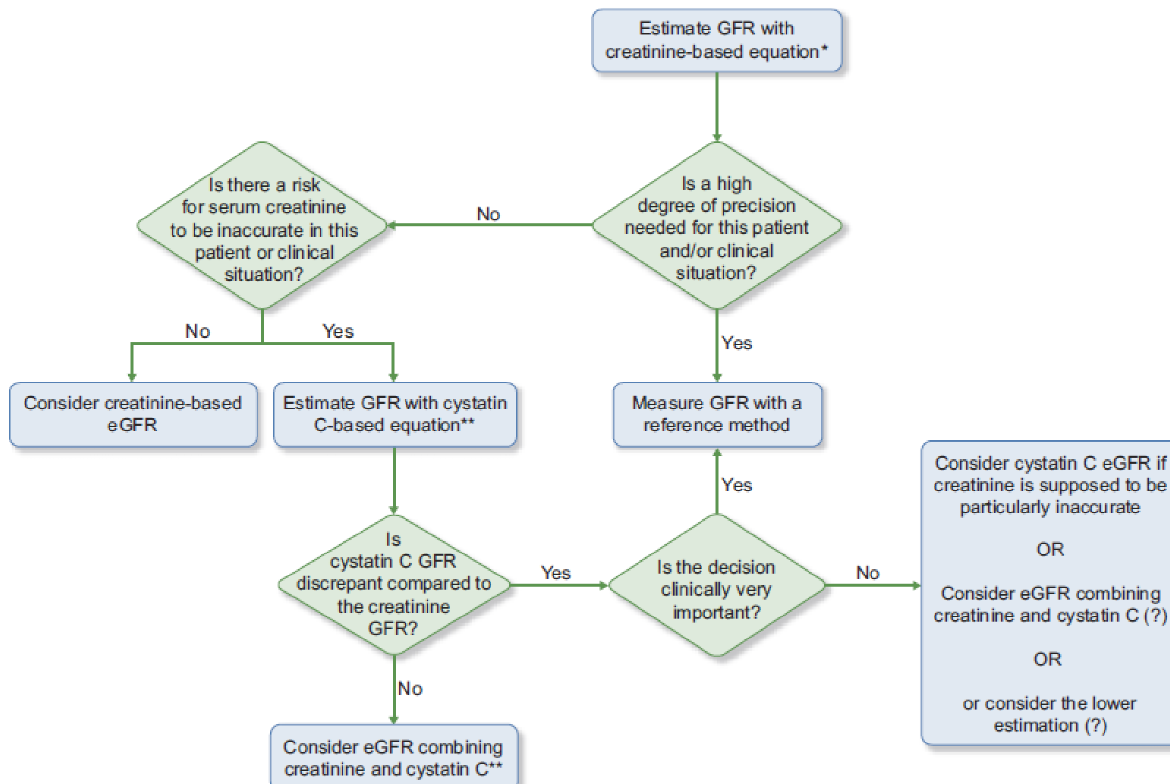

Figure 1: Estimation of GFR in Nephrology, in clinical practice and at the individual level. *Using the best validated equation in your region and/or population. **Using the cystatin C or combined equation corresponding to the creatinine-based equation used at the first step.

Thanks for your attention