Leiden University
Medical Center

Doc, what is my kidney function?
Cystatin C in daily practice

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DUTCH KIDNEY FOUNDATION

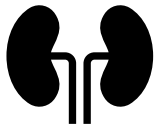
GFR: key parameter in diagnosis, staging, prognosis and management of CKD

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>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			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Medication eligibility, drug dosing



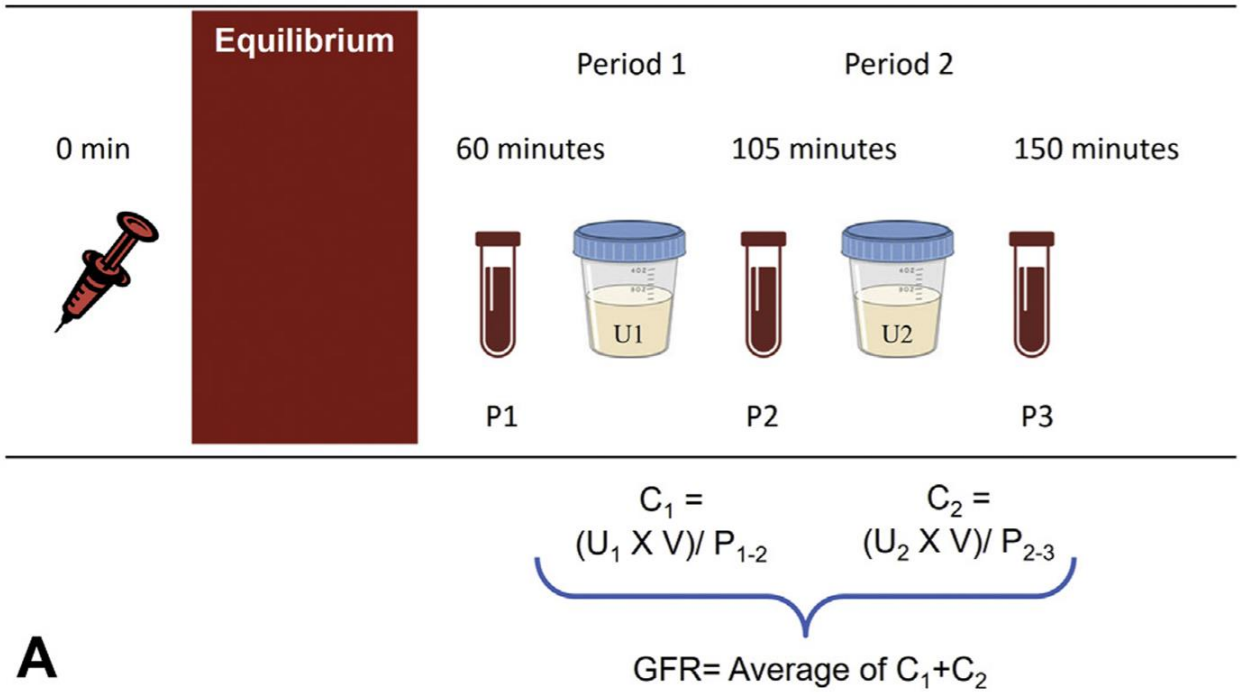
Kidney Transplant referral

Dialysis access placement

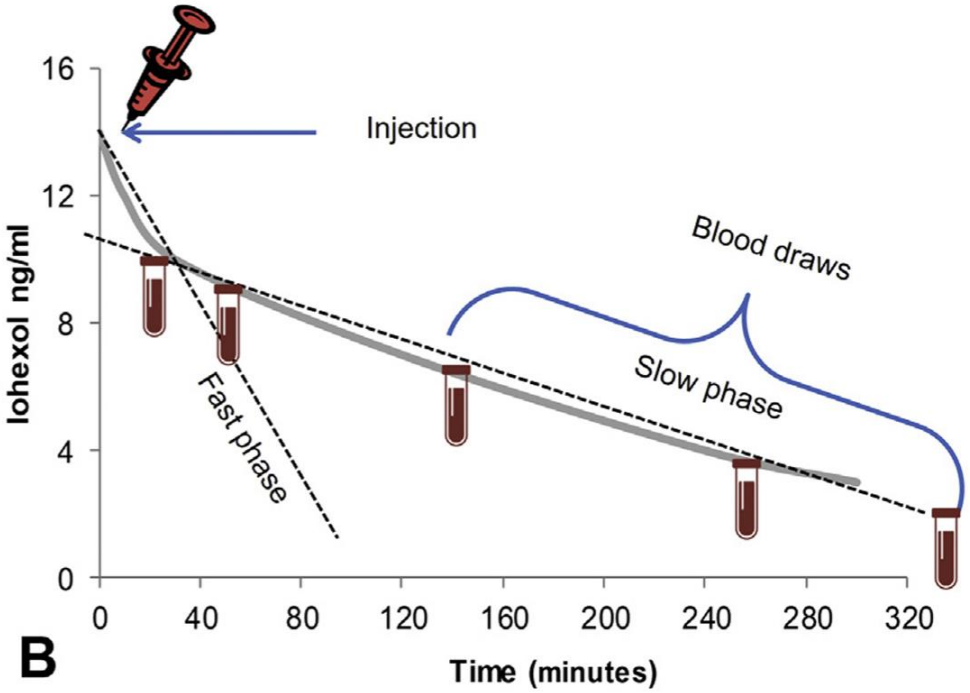
Nephrologist referral

Gold standard: urinary or plasma clearance exogenous substances

Urinary clearance (iothalamate)

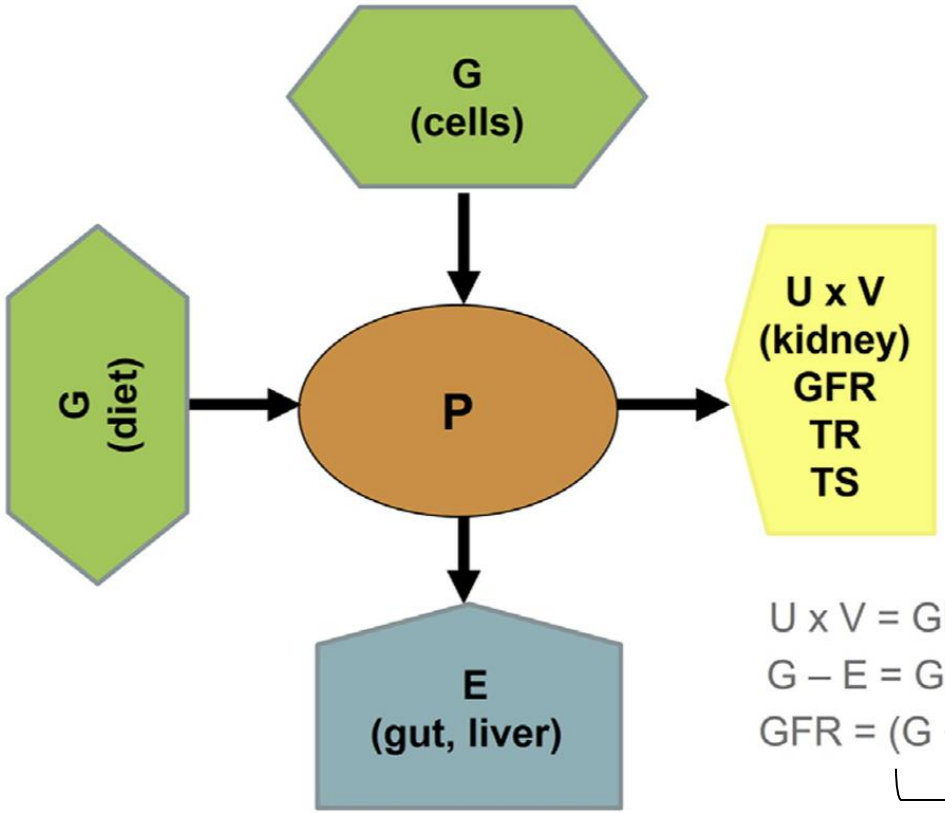


Plasma clearance (iohexol)



Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021
Inker, Lesley A. AJKD 78(5)

Using plasma concentration of endogenous substances



$$U \times V = GFR \times P - TR + TS$$
$$G - E = GFR \times P - TR + TS$$
$$GFR = (G + TR - TS - E) / P$$

Non-GFR determinants

$$mGFR \sim P\_creatinine + age + sex + race$$

Non-GFR determinants

Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021
Inker, Lesley A. AJKD 78(5)

Brief history of creatinine-based eGFR equations

	Cockcroft-Gault 1973
Study Design	Two measurements of 24h creatinine excretion per kg, n=236
Population	18-92 yrs All white men
Equations	CrCl = (140– age) x weight/72 x S_{Cr}
Race/Sex	Multiply by 0.85 if female No race variable
Limitations	Uses weight, needs adjustment for BSA and BMI >30

Brief history of creatinine-based eGFR equations

	Cockcroft-Gault 1973	MDRD 1999
Study Design	Two measurements of 24h creatinine excretion per kg, n=236	Cross sectional study, n=1628, estimation of GFR using serum Cr
Population	18-92 yrs All white men	Non-diabetic CKD population 18-70 yrs,~80% White
Equations	CrCl = (140– age) x weight/72 x S_{Cr}	eGFR = 186.3 x $(S_{Cr})^{-1.154}$ x $(Age)^{-0.203}$
Race/Sex	Multiply by 0.85 if female No race variable	Multiply by 0.742 if female Multiply by 1.21 if Black
Limitations	Uses weight, needs adjustment for BSA and BMI >30	Underestimates measured GFR at higher level

Brief history of creatinine-based eGFR equations

	Cockcroft-Gault 1973	MDRD 1999	CKD-EPI 2009
Study Design	Two measurements of 24h creatinine excretion per kg, n=236	Cross sectional study, n=1628, estimation of GFR using serum Cr	Cross sectional validation analysis, n=3896, estimation of GFR using Cr
Population	18-92 yrs All white men	Non-diabetic CKD population 18-70 yrs,~80% White	31.5% Black, median age 47, mGFR 67.6
Equations	$CrCl = (140 - age) \times weight/72 \times S_{Cr}$	$eGFR = 186.3 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203}$	$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.9929^{Age}$
Race/Sex	Multiply by 0.85 if female No race variable	Multiply by 0.742 if female Multiply by 1.21 if Black	Multiply by 1.018 if female Multiply by 1.159 if Black
Limitations	Uses weight, needs adjustment for BSA and BMI >30	Underestimates measured GFR at higher level	Limited no. of elderly, racial and ethnic minorities

An older Andrew Levy, US

Use of race in calculation of eGFRcr!

Brief history of creatinine-based eGFR equations

Lesley Inker, US

	Cockcroft-Gault 1973	MDRD 1999	CKD-EPI 2009	CKD-EPI 2021
Study Design	Two measurements of 24h creatinine excretion per kg, n=236	Cross sectional study, n=1628, estimation of GFR using serum Cr	Cross sectional validation analysis, n=3896, estimation of GFR using Cr	Cross sectional validation analysis, n=4050, estimation of GFR using Cr
Population	18-92 yrs All white men	Non-diabetic CKD population 18-70 yrs,~80% White	31.5% Black, median age 47, mGFR 67.6	14.3% black, 10 years older, 9 points higher mGFR than 2009 dataset
Equations	$CrCl = (140 - age) \times weight/72 \times S_{Cr}$	$eGFR = 186.3 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203}$	$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.9929^{Age}$	$eGFR = 142 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age}$
Race/Sex	Multiply by 0.85 if female No race variable	Multiply by 0.742 if female Multiply by 1.21 if Black	Multiply by 1.018 if female Multiply by 1.159 if Black	Multiply by 1.012 if female No race variable
Limitations	Uses weight, needs adjustment for BSA and BMI >30	Underestimates measured GFR at higher level	Limited no. of elderly, racial and ethnic minorities	Limited no. of Black patients with low GFR; using both CysC and Cr was more accurate

A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease

Recommend immediate implementation of the *CKD-EPI creatinine equation refit without the race variable* in all laboratories in the U.S.

The equation refit excludes race in the calculation and reporting, includes diversity in its development, is immediately available to all labs in the U.S., and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals.

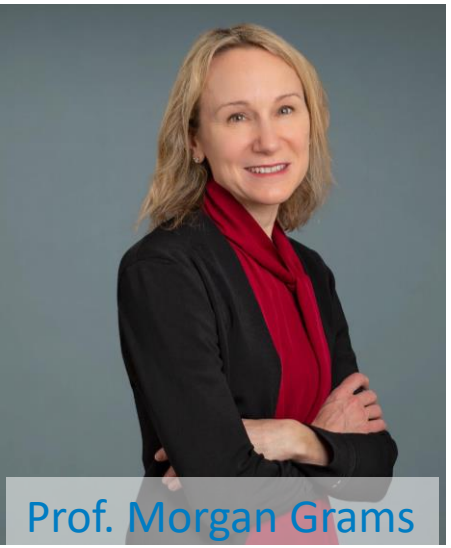
Encourage and fund research on GFR estimation with new endogenous filtration markers and on interventions to eliminate racial and ethnic disparities

The Task Force gathered input from diverse stakeholders and carefully reviewed the evidence to create these recommendations

Cynthia Delgado, Mukta Baweja, Deidra C. Crews, et al. *A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease.* *AJKD DOI:* 10.1053/j.ajkd.2021.08.003, *JASN DOI: 10.1681/ASN.2021070988*

Visual Graphic by Edgar Lerma, MD, FASN

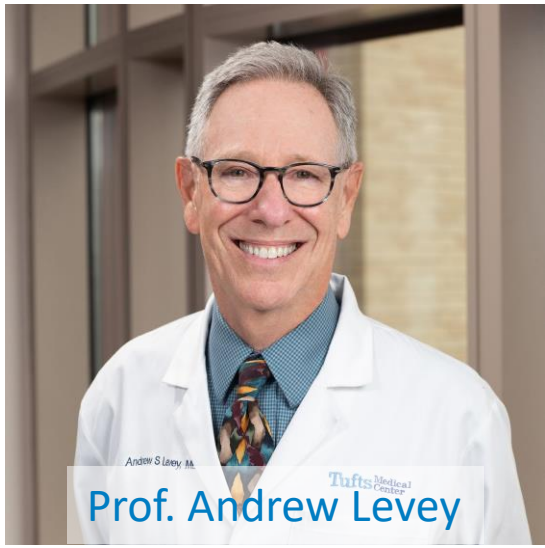
First paper in new research line


Prof. Morgan Grams

Nephrology Dialysis Transplantation (2023) 38: 119–128
https://doi.org/10.1093/ndt/gfac197
Advance Access publication date 11 June 2022

Removing race from the CKD-EPI equation and its impact on prognosis in a predominantly White European population

Edouard L. Fu[1,2,3], Josef Coresh[4], Morgan E. Grams[4,5], Catherine M. Clase[6], Carl-Gustaf Elinder[7], Julie Paik[2], Chava L. Ramspek[3], Lesley A. Inker[8], Andrew S. Levey[8], Friedo W. Dekker[3] and Juan J. Carrero[1]


Prof. Andrew Levey


Prof. Lesley Inker

- 1.6M adults undergoing routine serum creatinine measurements in Stockholm during 2007-2019
- We calculated changes in eGFR and reclassification across KDIGO GFR categories when changing from CKD-EPI 2009 to CKD-EPI 2021


Prof. Josef Coresh

Impact

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]

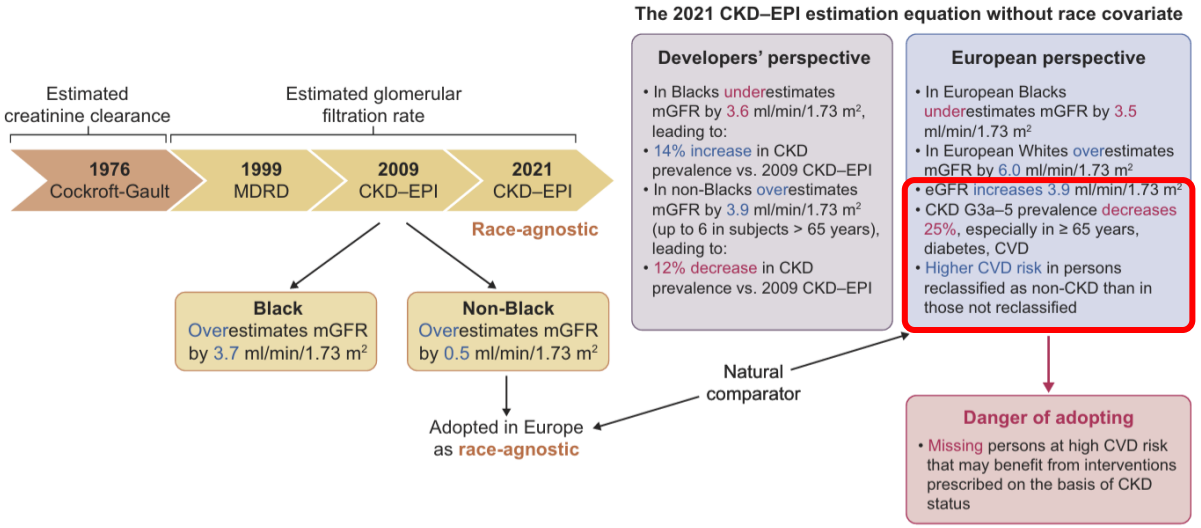


Figure 1: The development over time of the various GFR estimation equations, and their strengths and weaknesses.

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)

Cystatin C and its eGFR equations

Acta Med Scand 1985; 218: 499–503

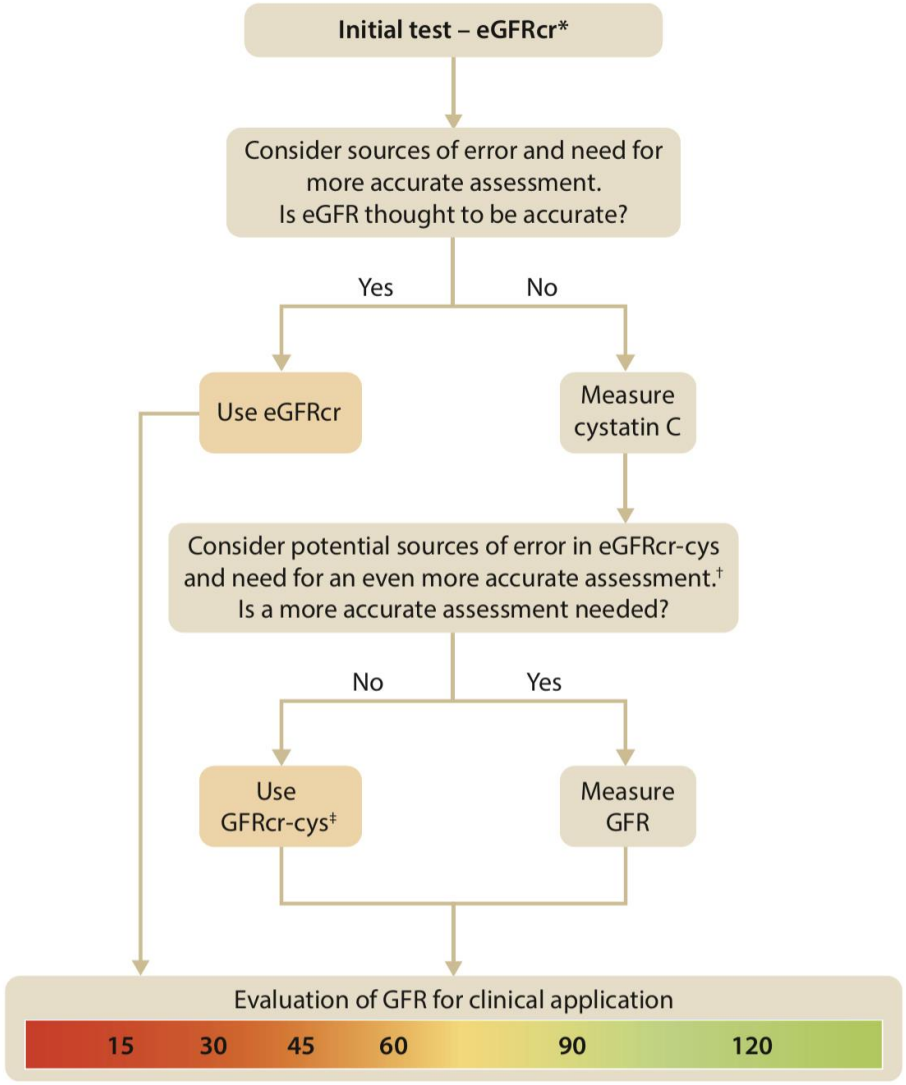
Serum Concentration of Cystatin C, Factor D and β_2-Microglobulin as a Measure of Glomerular Filtration Rate

A. GRUBB, O. SIMONSEN, G. STURFELT, L. TRUEDSSON and H. THYSELL

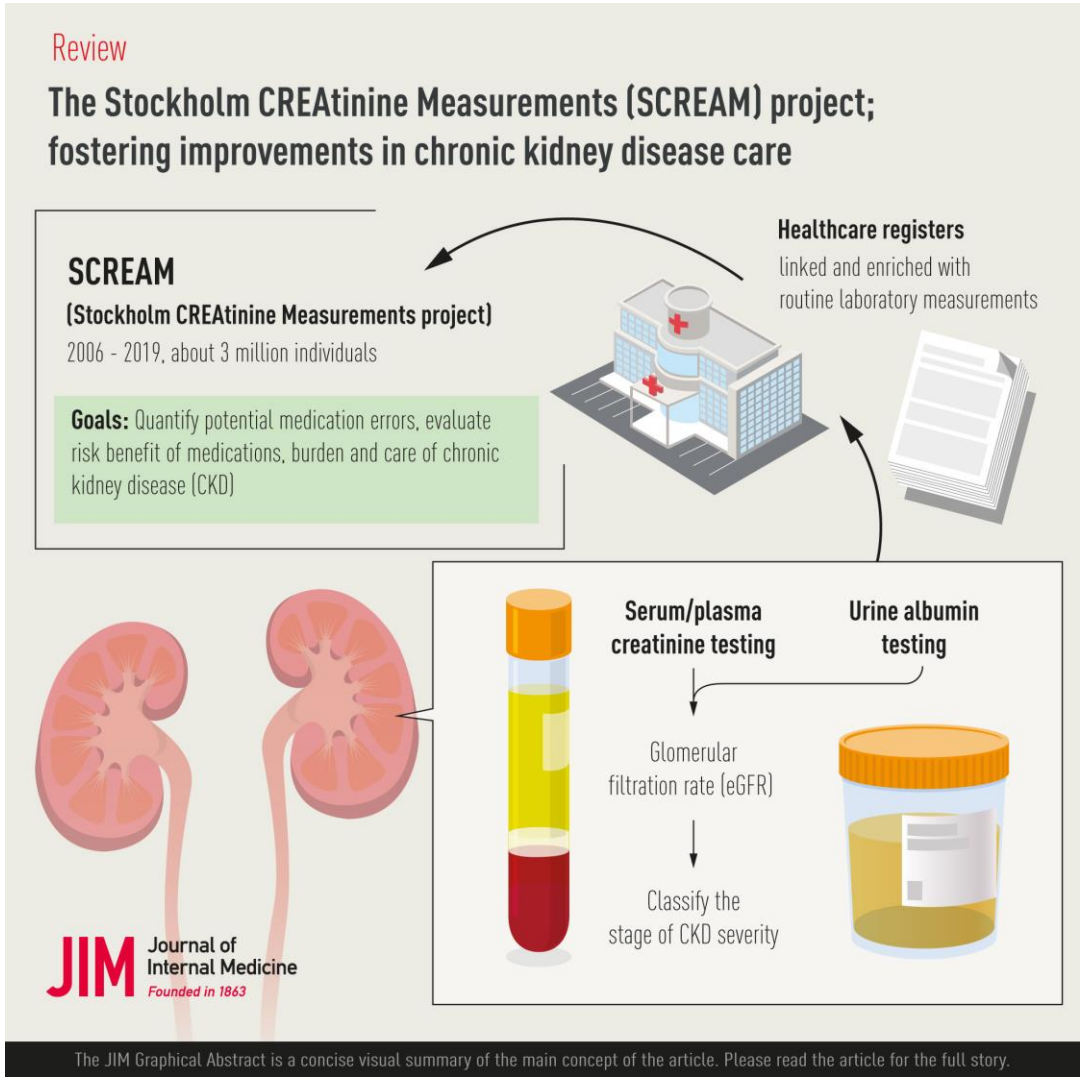
From the Department of Clinical Chemistry, Malmö General Hospital, Malmö, and Departments of Nephrology and Immunology, University Hospital, Lund, Sweden

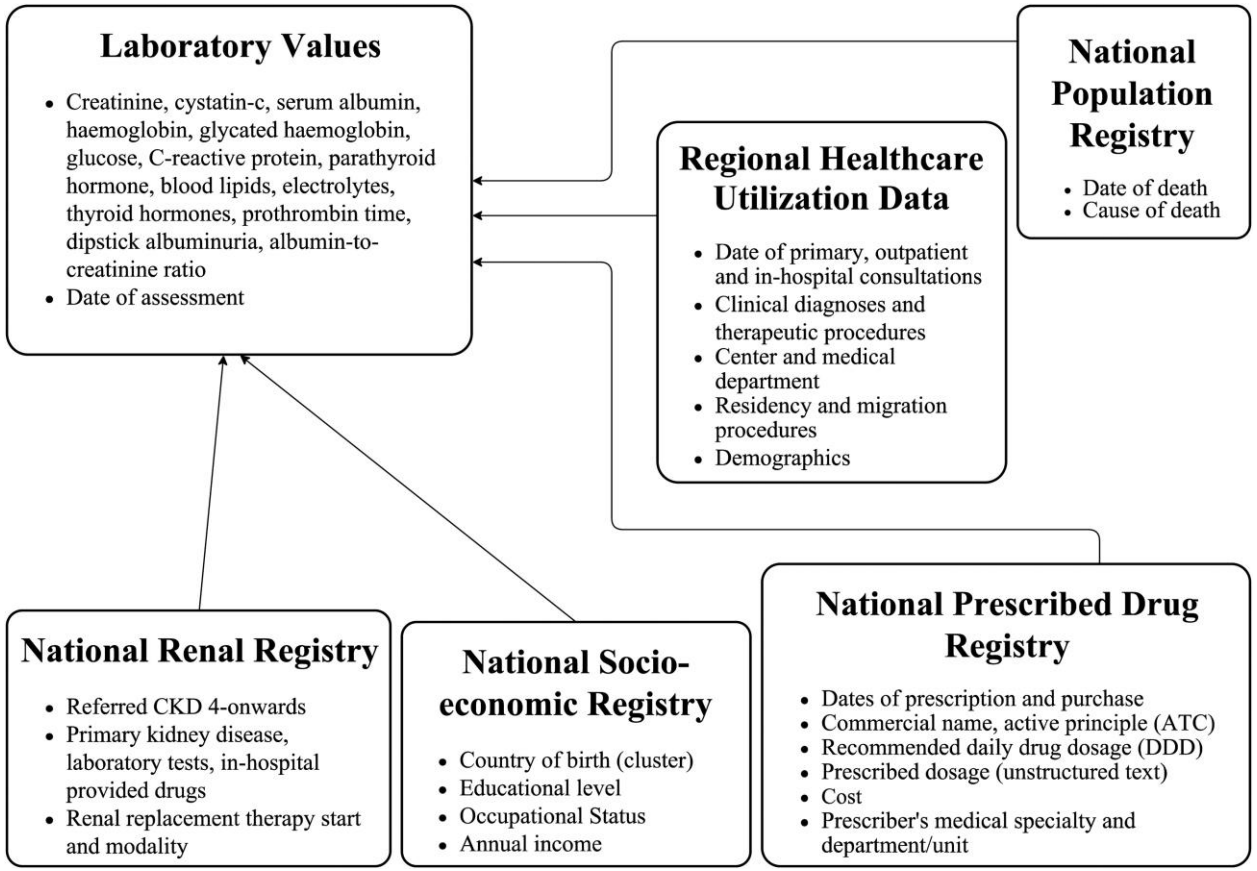
- NOT AFFECTED by creatinine non-GFR determinants: diet, muscle mass
- AFFECTED by other non-GFR determinants, like inflammation, obesity or hyperthyroidism
- Less affected by “race”, so cystatin C equations did not include race coefficient

KDIGO 2024


Initial test – eGFRcr*
Consider sources of error and need for more accurate assessment. Is eGFR thought to be accurate?
Yes
No
Use eGFRcr
Measure cystatin C
Consider potential sources of error in eGFRcr-cys and need for an even more accurate assessment.† Is a more accurate assessment needed?
No
Yes
Use GFRcr-cys‡
Measure GFR
Evaluation of GFR for clinical application
15
30
45
60
90
120

Data source

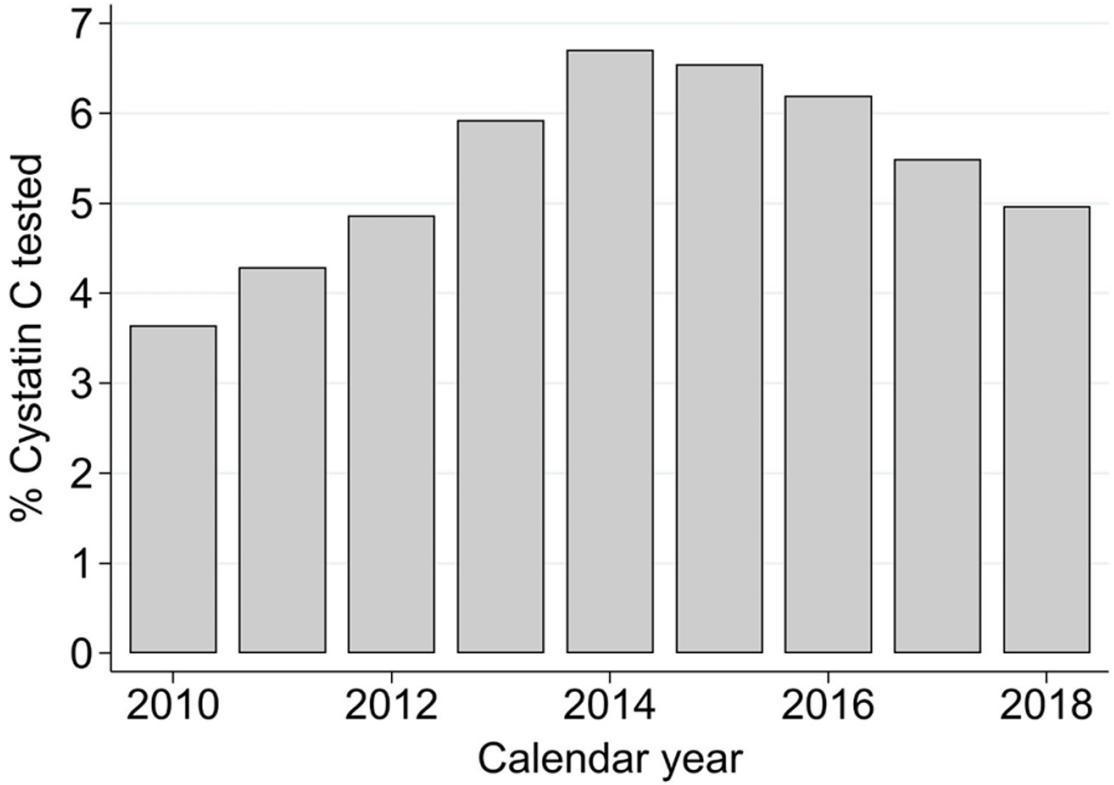

Review
The Stockholm CREAtinine Measurements (SCREAM) project; fostering improvements in chronic kidney disease care
SCREAM
(Stockholm CREAtinine Measurements project)
2006 - 2019, about 3 million individuals
Goals: Quantify potential medication errors, evaluate risk benefit of medications, burden and care of chronic kidney disease (CKD)
Healthcare registers
linked and enriched with routine laboratory measurements
Serum/plasma creatinine testing
Urine albumin testing
Glomerular filtration rate (eGFR)
Classify the stage of CKD severity
JIM Journal of Internal Medicine
Founded in 1863
The JIM Graphical Abstract is a concise visual summary of the main concept of the article. Please read the article for the full story.


Laboratory Values
• Creatinine, cystatin-c, serum albumin, haemoglobin, glycated haemoglobin, glucose, C-reactive protein, parathyroid hormone, blood lipids, electrolytes, thyroid hormones, prothrombin time, dipstick albuminuria, albumin-to-creatinine ratio
• Date of assessment
National Population Registry
• Date of death
• Cause of death
Regional Healthcare Utilization Data
• Date of primary, outpatient and in-hospital consultations
• Clinical diagnoses and therapeutic procedures
• Center and medical department
• Residency and migration procedures
• Demographics
National Renal Registry
• Referred CKD 4-onwards
• Primary kidney disease, laboratory tests, in-hospital provided drugs
• Renal replacement therapy start and modality
National Socio-economic Registry
• Country of birth (cluster)
• Educational level
• Occupational Status
• Annual income
National Prescribed Drug Registry
• Dates of prescription and purchase
• Commercial name, active principle (ATC)
• Recommended daily drug dosage (DDD)
• Prescribed dosage (unstructured text)
• Cost
• Prescriber's medical specialty and department/unit

Incorporation of Cystatin C Testing in Clinical Practice: Real World Experience in Sweden

KI REPORTS
KIReports.org

Shoshana H. Ballew[1,2], Yingying Sang[1], Josef Coresh[1,2], Edouard L. Fu[3,4], Dorothea Nitsch[5], Juan Jesus Carrero[4,6,8] and Morgan E. Grams[7,8]



year	N*	Creatinine only	Creatinine and cystatin C	% cystatin C tested
2010	529,996	510,679	19,317	3.64
2011	562,036	537,929	24,107	4.29
2012	518,709	493,470	25,239	4.87
2013	534,151	502,500	31,651	5.93
2014	552,909	515,809	37,100	6.71
2015	560,570	523,862	36,708	6.55
2016	568,561	533,323	35,238	6.20
2017	579,278	547,475	31,803	5.49
2018	536,958	510,267	26,691	4.97
Overall	1,369,183	1,216,514	152,669	11.15

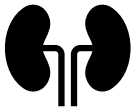
*Total number of individuals with any creatinine measured within the year.

Who gets tested in Sweden?

Table 1. Characteristics of individuals tested for creatinine and/or cystatin C in 2014

Characteristics	Overall	Cystatin C and creatinine tested	Only creatinine tested
N	552909	37100	515809
eGFRcr (SD), ml/min per 1.73m^2	90 (22)	75 (27)	91 (21)
eGFRcys (SD), ml/min per 1.73m^2	69 (32)	69 (32)	
KDIGO G-stage by eGFRcr, %			
eGFR 90 + ml/min per 1.73m^2	55	33	57
eGFR 60–89 ml/min per 1.73m^2	36	38	36
eGFR 45–59 ml/min per 1.73m^2	5.6	14	5.1
eGFR 30–44 ml/min per 1.73m^2	2.3	9.5	1.8
eGFR <30 ml/min per 1.73m^2	1.0	6.3	0.64
Any urine protein measured, %	26	47	24
ACR/PCR measured, %	13	34	11
Dipstick measured, %	13	13	13
ACR/PCR[a] (IQI), mg/g	14 (4–69)	16.8 (4.4–110.6)	8.0 (2.7–23.9)
Dipstick + and above, %	6.1	8.2	5.9
Age (SD), yr	58 (19)	63 (18)	57 (19)
Female, %	55	46	55
Hypertension, %	47	68	45
Hypertension medication use, %	44	64	42
RAAS inhibitor use, %	30	45	28
Diuretics, %	19	34	18
Diabetes, %	13	23	13
Statin, %	19	29	18
History of coronary heart disease, %	6.7	12	6.3
History of cerebrovascular disease, %	5.7	9.8	5.4
History of heart failure, %	5.5	13	5.0
History of peripheral artery disease, %	1.2	2.7	1.04
History of atrial fibrillation, %	8.0	15.8	7.4
Liver disease, %	2.4	3.7	2.3
Recent cancer, %	12	17	11
Chronic obstructive pulmonary disease, %	4.1	6.8	3.9
Potassium >5 mmol/l, %	0.28	1.1	0.22
Anemia by hemoglobin,[b] %	4.3	9.1	4.0

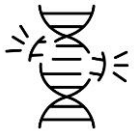
↑ Age



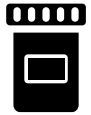
↓ $eGFR_{cr}$ ↑UACR

↑ coronary heart disease, heart failure

↑ diabetes



↑ cancer



↑ medications

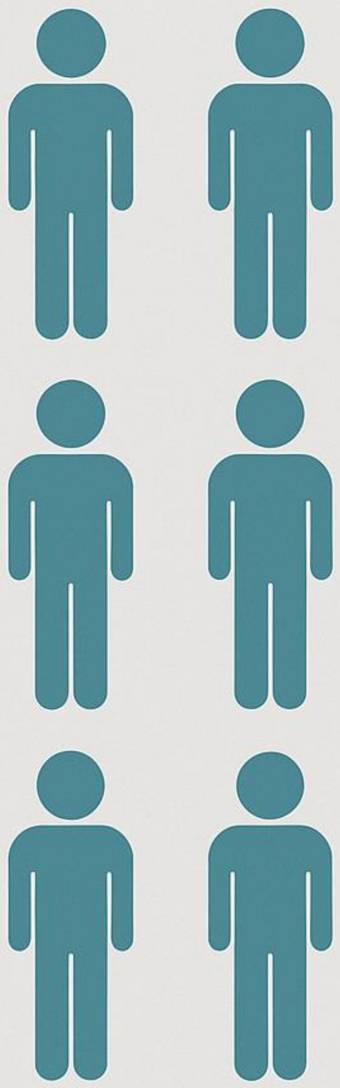
Nephrol Dial Transplant, 2024, **39**, 694–706

https://doi.org/10.1093/ndt/gfad219

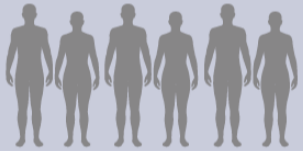
Advance access publication date: 9 October 2023

Accuracy of GFR estimating equations based on creatinine, cystatin C or both in routine care

Edouard L. Fu[1,2,3], Andrew S. Levey[4], Josef Coresh[5], Morgan E. Grams[6], Anne-Laure Faucon[2,7], Carl-Gustaf Elinder[8], Friedo W. Dekker[3], Pierre Delanaye[9,10], Lesley A. Inker[4] and Juan-Jesus Carrero[2,11]



Remarques statistiques.
MER GLACIALE
OCÉAN ATLANTIQUE
Mer du Nord
MER MÉDITERRANÉE
Mer Noire
EUROPE
Suite des Remarques statistiques.



6174 adults referred for single-point plasma clearance of iohexol, 9579 observations

Creatinine and cystatin C

SCREAM, Stockholm, Sweden
Routine referrals 2011–2021

56 years

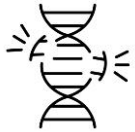
40% female

Comorbid conditions were common:

30% cardiovascular disease

28% liver disease

26% diabetes



26% cancer

Table 2: Bias, IQR, P_{30} and correct classification of different GFR estimating equations compared with single-point plasma iohexol clearance.

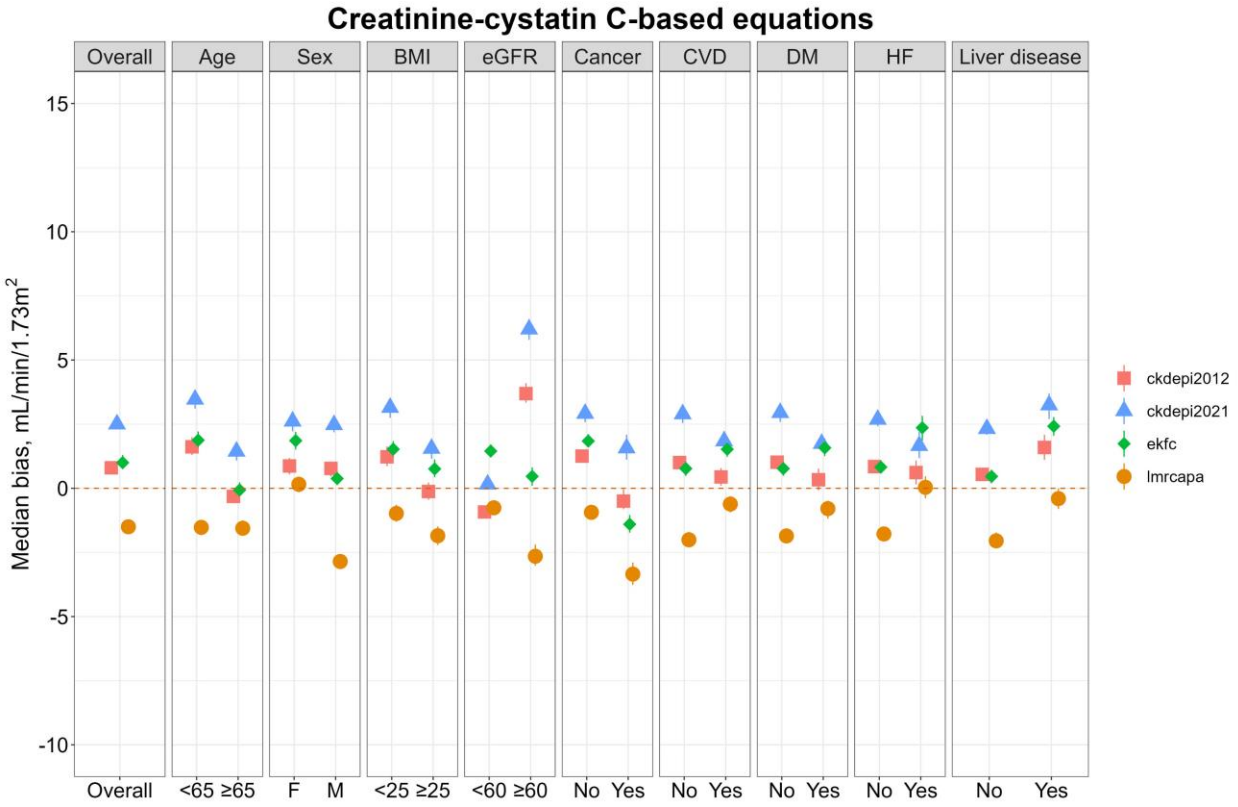
	Bias, mL/min/1.73 m^2 (95% CI)[a]	IQR, mL/min/1.73 m^2 (Q1, Q3)[b]	P_{30}, % (95% CI)[c]	Correct classification, % (95% CI)[d]
Creatinine-based equations				
CKD-EPI 2009	5.6 (5.3 to 6.0)	17.6 (−2.3 to 15.3)	74.1 (73.2 to 75.0)	56.4 (55.4 to 57.4)
CKD-EPI 2021	9.1 (8.8 to 9.5)	18.6 (0.6 to 19.2)	68.1 (67.2 to 69.1)	51.8 (50.9 to 52.8)
EKFC 2021	2.7 (2.5 to 3.0)	15.6 (−4.6 to 11.0)	79.5 (78.7 to 80.3)	58.9 (57.9 to 59.9)
RLM 2011	0.2 (−0.2 to 0.4)	15.6 (−7.7 to 7.9)	82.2 (81.4 to 82.9)	58.6 (57.6 to 59.5)
Cystatin C–based equations				
CKD-EPI 2012	−2.6 (−2.9 to −2.3)	15.0 (−10.4 to 4.6)	82.5 (81.7 to 83.3)	58.3 (57.4 to 59.3)
EKFC 2023	−1.1 (−1.4 to −0.9)	14.6 (−11.5 to 3.1)	84.5 (83.8 to 85.2)	60.8 (59.8 to 61.7)
CAPA 2014			83.2 (82.5 to 84.0)	58.1 (57.2 to 59.1)
Creatinine–cystatin C–based equations				
CKD-EPI 2012			89.1 (88.4 to 89.7)	66.7 (65.7 to 67.6)
CKD-EPI 2021			87.6 (86.9 to 88.2)	66.3 (65.3 to 67.2)
Mean of EKFC eGFRcr and EKFC eGFRcys			88.5 (87.9 to 89.2)	66.8 (65.8 to 67.7)
Mean of RLM and CAPA			90.8 (90.2 to 91.4)	65.8 (64.8 to 66.7)

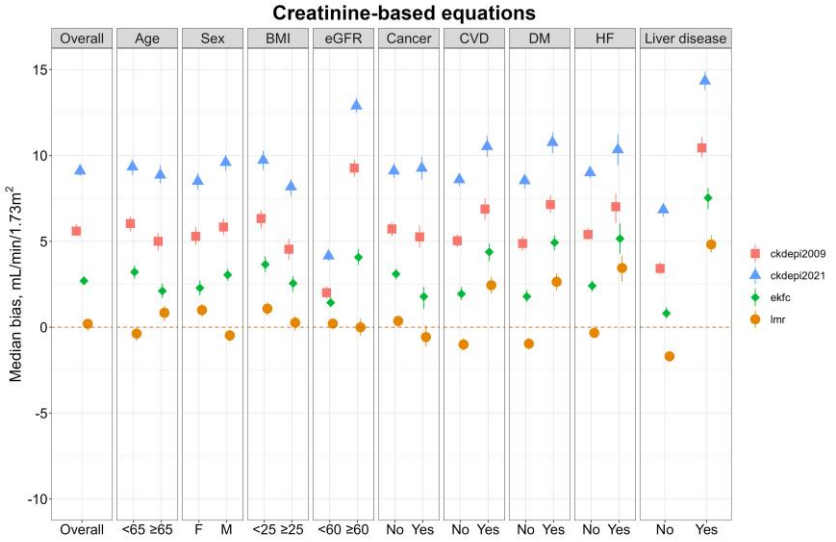
Even with the best equation
Only 2/3 correct classification

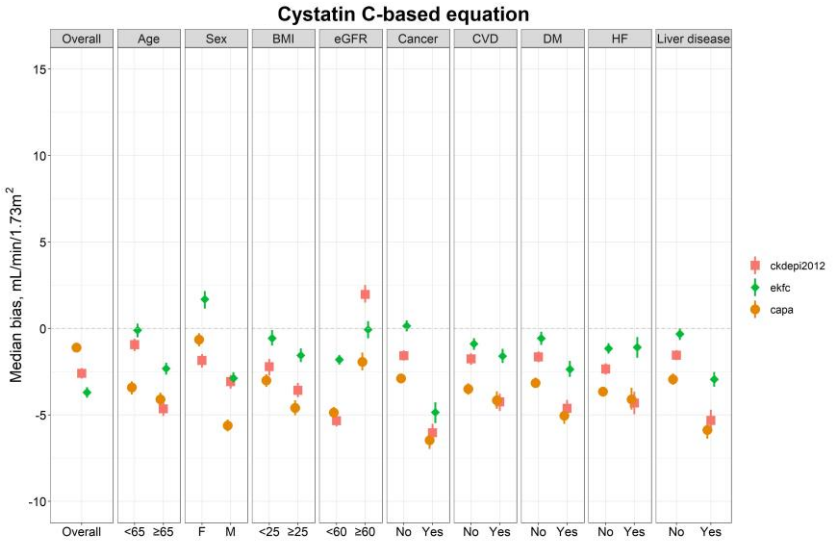
10% of patients have eGFR outside 30% of mGFR

[a]Bias was expressed as the median difference in eGFR minus mGFR (95% CI). A negative bias indicates underestimation of the mGFR, and a positive bias indicates overestimation of the mGFR.
[b]IQR is defined as the IQR and a measure of precision (the dispersion of individual errors around the bias).
[c]P_{30} was defined as the percentage of individuals with eGFRs within 30% of mGFR (95% CI).
[d]Correct classification of GFR categories was defined as agreement of eGFR and mGFR categories using the KDIGO GFR categories (<15, 15–29, 30–44, 45–59, 60–89 and ≥90 mL/min/1.73 m^2).

Subgroup analyses







Conclusion

Best filtration marker award

GFR estimated with *both* creatinine and cystatine C

- $eGFR_{cr-cys}$ was superior to $eGFR_{cr}$ or $eGFR_{cys}$ regardless of specific equation used, with small bias and high P_{30}
- all $eGFR_{cys}$ and $eGFR_{cr-cys}$ equations had more homogeneous performance than $eGFR_{cr}$

Best creatinine equation award

EKFC or RLM

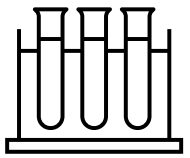
- Worse performance of CKD-EPI compared with EKFC and RLM may reflect differences in population characteristics and mGFR methods
- Implementing $eGFR_{cr}$ equations will require trade-off between accuracy and uniformity across regions

CLINICAL EPIDEMIOLOGY www.jasn.org

Accuracy of GFR Estimating Equations in Patients with Discordances between Creatinine and Cystatin C-Based Estimations

Edouard L. Fu,[1,2,3] Andrew S. Levey,[4] Josef Coresh,[5] Carl-Gustaf Elinder,[6] Joris I. Rotmans,[7] Friedo W. Dekker,[3] Julie M. Paik,[1] Peter Barany,[6] Morgan E. Grams,[7] Lesley A. Inker,[4] and Juan-Jesus Carrero[2]

Rationale



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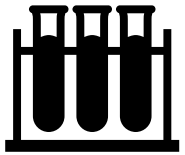
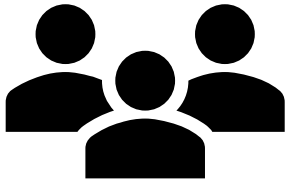


$eGFR_{cr}$ $eGFR_{cys}$

Which eGFR is most accurate and should be used for decision making when discordances occur?



6185 adults

47% → $eGFR_{cys} < eGFR_{cr}$ (**>20% lower**)

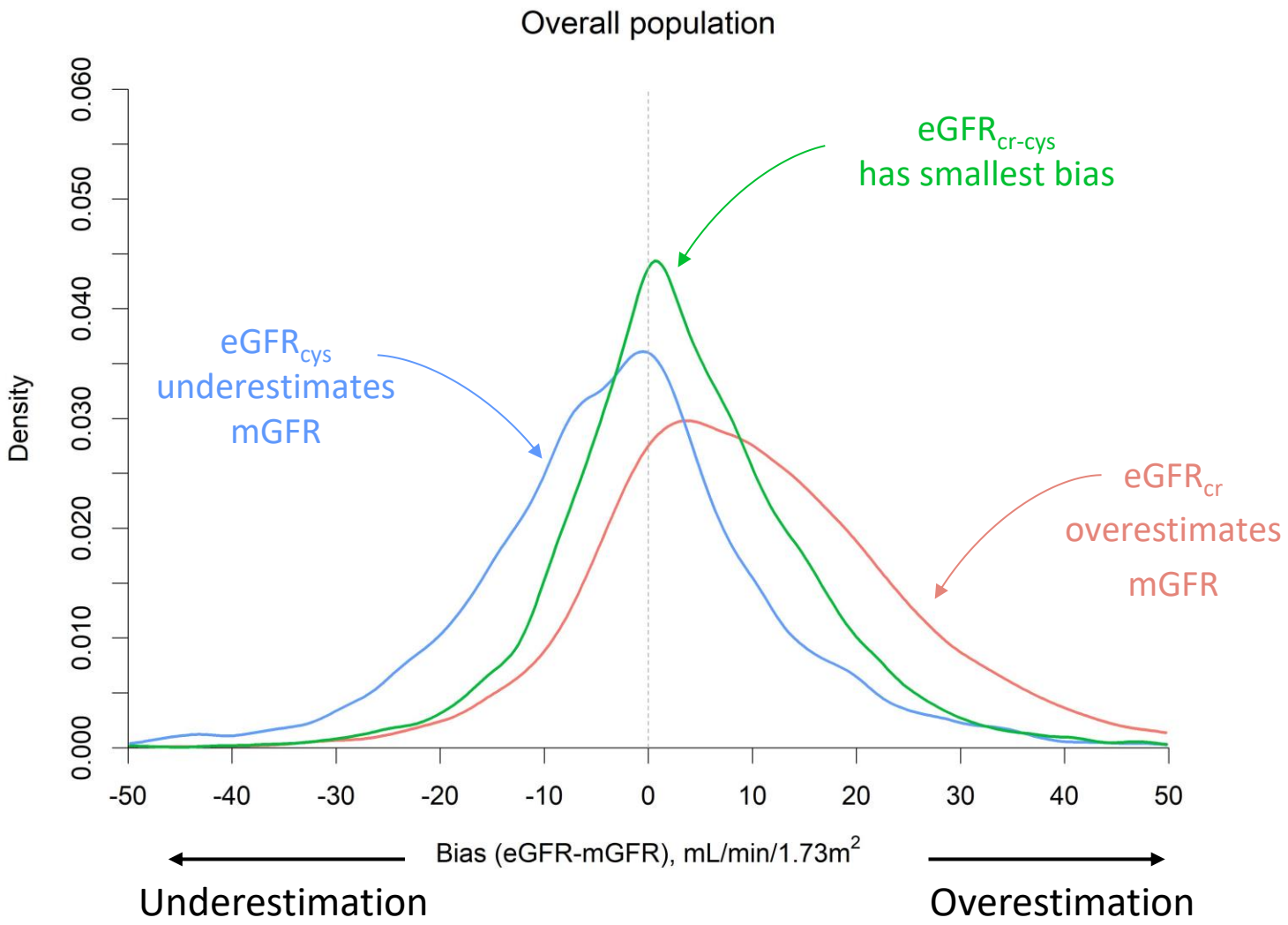
45% → $eGFR_{cys} \approx eGFR_{cr}$ (**within 20%**)

8% → $eGFR_{cys} > eGFR_{cr}$ (**>20% higher**)

In each stratum performance:

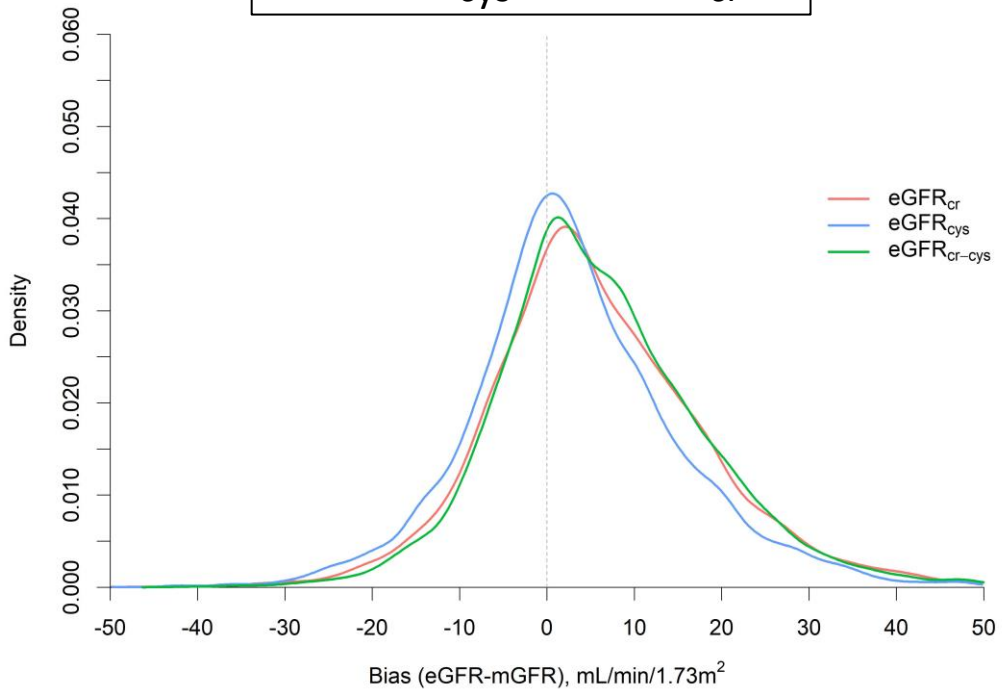
1. $eGFR_{cr}$ (CKD-EPI 2021)
2. $eGFR_{cys}$ (CKD-EPI 2012)
3. $eGFR_{cr\text{-}cys}$ (CKD-EPI 2021)

Distribution of bias in the overall population

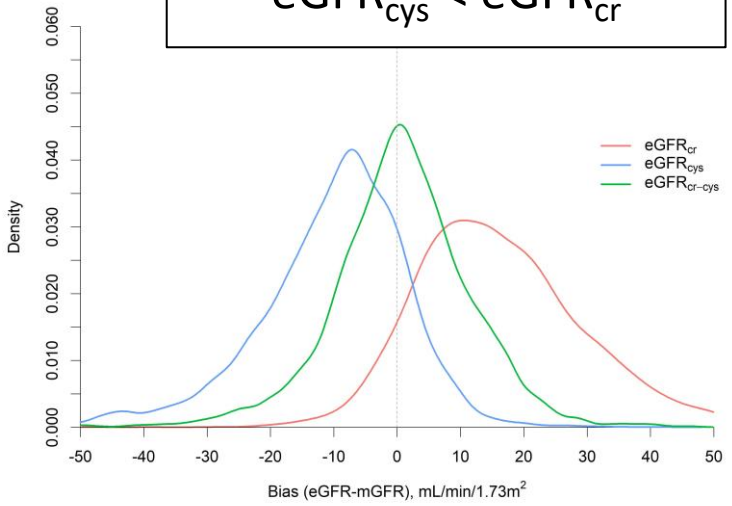


Distribution of bias stratified by discordance

$eGFR_{cys} \approx eGFR_{cr}$



$eGFR_{cys} < eGFR_{cr}$



$eGFR_{cys} > eGFR_{cr}$

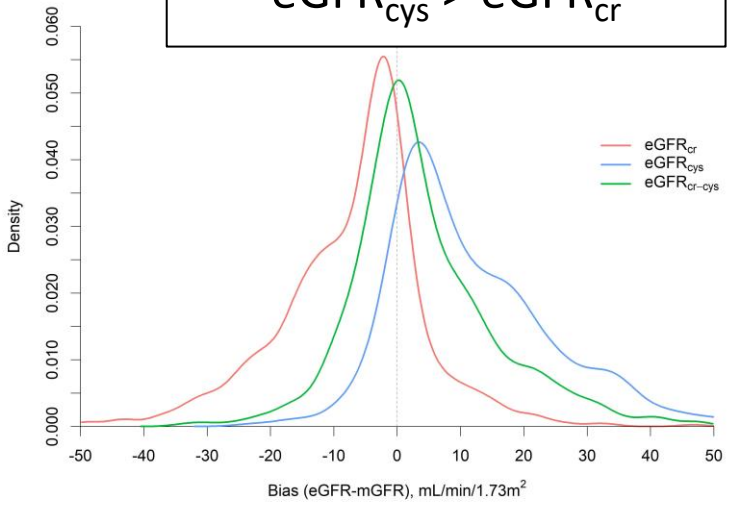


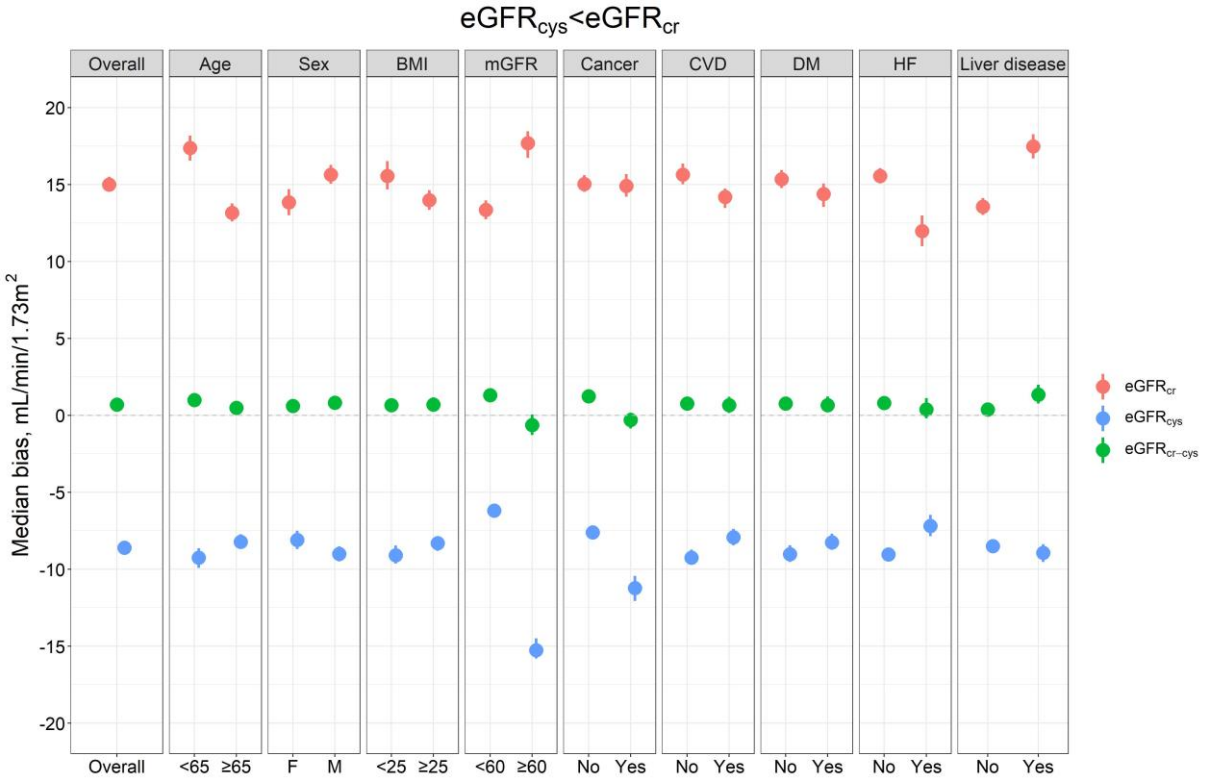
Table 2. Bias, P_{30}, interquartile range and correct classification of different Chronic Kidney Disease Epidemiology Collaboration eGFR equations, overall and stratified by the magnitude and direction of the discordance between $eGFR_{cr}$ and $eGFR_{cys}$

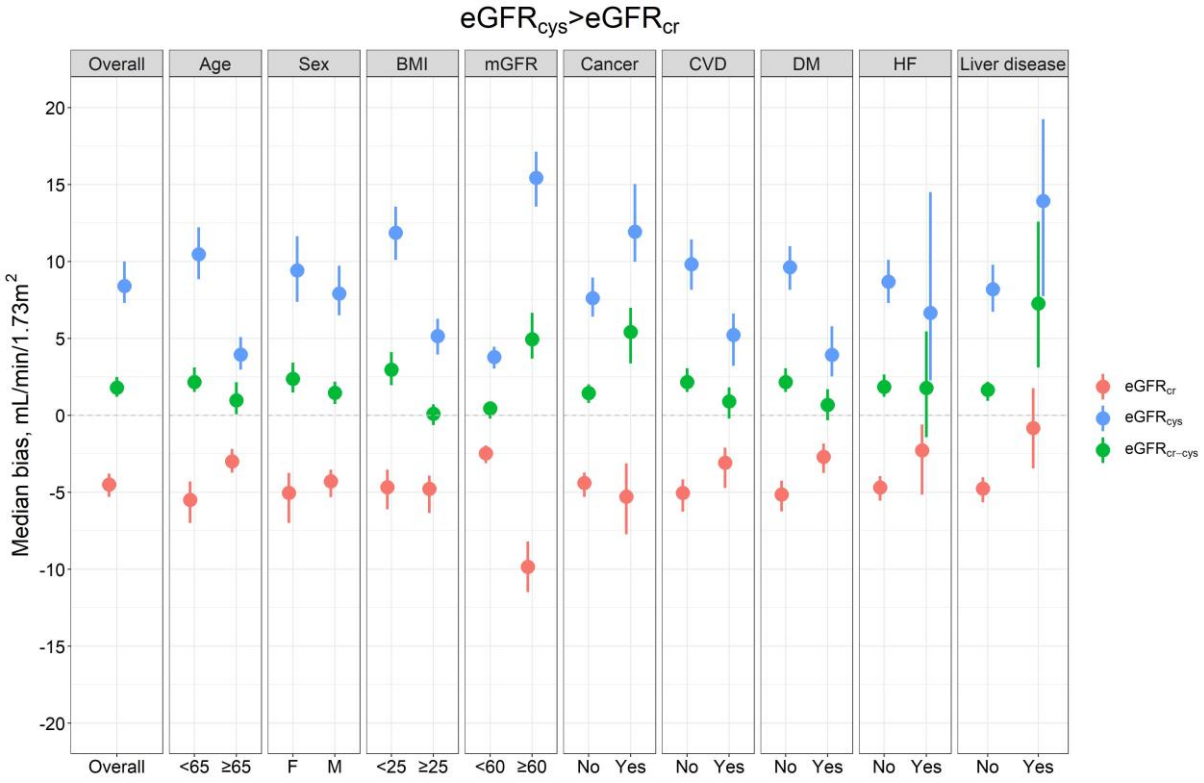
Metrics	Total Population	$eGFR_{cys}$<$eGFR_{cr}$	$eGFR_{cys}$≈$eGFR_{cr}$	$eGFR_{cys}$>$eGFR_{cr}$
		$eGFR_{cys}$ >20% Lower Than $eGFR_{cr}$	$eGFR_{cys}$ Within 20% of $eGFR_{cr}$	$eGFR_{cys}$ >20% Higher Than $eGFR_{cr}$
$eGFR_{cr}$				
Bias, ml/min per 1.73 m^2	8.7 (8.4–9.0)	15.0 (14.6–15.5)	4.5 (4.1–4.8)	−4.5 (−5.3 to −3.8)
P_{30} (%)	68.8 (67.8–69.7)	49.7 (48.3–51.2)	86.0 (84.9–87.0)	85.9 (83.2–88.3)
IQR, ml/min per 1.73 m^2	18.6 (0.2–18.8)	17.5 (7.0–24.5)	15.1 (−2.0 to 13.1)	12.3 (−13.0 to −0.7)
Correct classification (%)	52.6 (51.6–53.6)	38.1 (36.7–39.5)	66.5 (65.1–67.9)	61.9 (58.3–65.4)
$eGFR_{cys}$				
Bias, ml/min per 1.73 m^2	−2.3 (−2.6 to −2.0)	−8.6 (−9.0 to −8.3)	2.1 (1.7–2.4)	8.4 (7.3–10.0)
P_{30}	80.7 (79.9–81.5)	72.9 (71.6–74.2)	90.4 (89.5–91.3)	71.8 (68.4–75.1)
IQR, ml/min per 1.73 m^2	15.6 (−10.5 to 5.1)	14.2 (−16.5 to −2.3)	13.8 (−4.0 to 9.9)	16.5 (2.5–19.0)
Correct classification	57.4 (56.4–58.4)	45.4 (43.9–46.8)	69.2 (67.8–70.5)	62.9 (59.4–66.6)
$eGFR_{cr-cys}$				
Bias, ml/min per 1.73 m^2	2.5 (2.2–2.7)	0.7 (0.4–1.0)	5.0 (4.6–5.4)	1.8 (1.2–2.5)
P_{30}	86.4 (85.7–87.1)	84.3 (83.2–85.4)	88.3 (87.3–89.3)	87.8 (85.4–90.2)
IQR, ml/min per 1.73 m^2	13.6 (−3.5–10.0)	12.6 (−5.5–7.1)	14.5 (−1.4–13.2)	12.3 (−2.6–9.6)
Correct classification	65.4 (64.5–66.4)	61.6 (60.2–63)	68.4 (67–69.7)	71.9 (68.6–75.2)

Reclassification

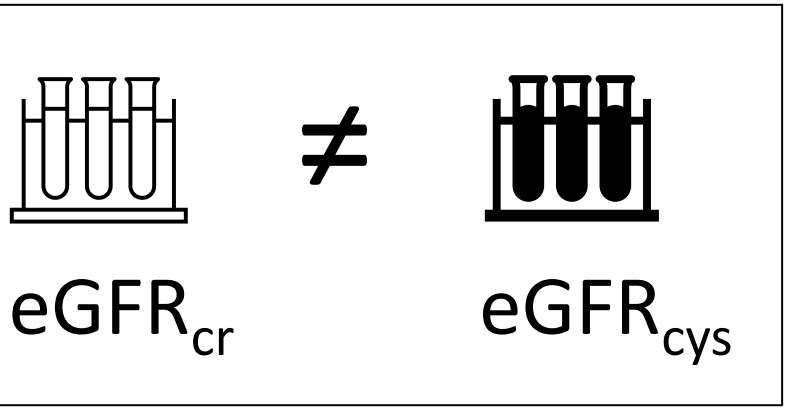
	Replacing $eGFR_{cr}$ by $eGFR_{cr\text{-}cys}$		Replacing $eGFR_{cys}$ by $eGFR_{cr\text{-}cys}$	
	$eGFR_{cys} < eGFR_{cr}$	$eGFR_{cys} > eGFR_{cr}$	$eGFR_{cys} < eGFR_{cr}$	$eGFR_{cys} > eGFR_{cr}$
Participants, n	4465	713	4465	713
Total reclassified, n (%)	2838 (63.6)	284 (39.8)	2407 (53.9)	161 (22.6)
Correctly reclassified, n (%)	1700 (38.1)	174 (24.4)	1396 (31.3)	108 (15.1)
Incorrectly reclassified, n (%)	1138 (25.5)	110 (15.4)	1011 (22.6)	53 (7.4)
Net difference, %	12.6	9.0	8.6	7.7

Subgroups


eGFRcys<eGFRcr
Overall
Age
Sex
BMI
mGFR
Cancer
CVD
DM
HF
Liver disease
Median bias, mL/min/1.73m2
20
15
10
5
0
-5
-10
-15
-20
Overall
<65 ≥65
F M
<25 ≥25
<60 ≥60
No Yes
eGFRcr
eGFRcys
eGFRcr−cys


eGFRcys>eGFRcr
Overall
Age
Sex
BMI
mGFR
Cancer
CVD
DM
HF
Liver disease
Median bias, mL/min/1.73m2
20
15
10
5
0
-5
-10
-15
-20
Overall
<65 ≥65
F M
<25 ≥25
<60 ≥60
No Yes
eGFRcr
eGFRcys
eGFRcr−cys

Conclusion



If creatinine and/or cystatin C are influenced by non-GFR determinants

eGFR$_{cr}$

eGFR$_{cys}$

Combining both markers improves precision by reducing errors that are due to variation in the non-GFR determinants of each marker

eGFR$_{cr-cys}$

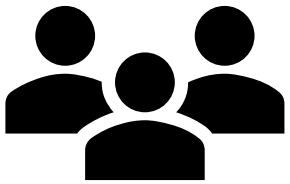
AJKD

Original Investigation

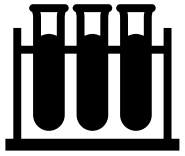
Discordances Between Creatinine- and Cystatin C–Based Estimated GFR and Adverse Clinical Outcomes in Routine Clinical Practice

Juan-Jesús Carrero, Edouard L. Fu, Yingying Sang, Shoshana Ballew, Marie Evans, Carl-Gustaf Elinder, Peter Barany, Lesley A. Inker, Andrew S. Levey, Josef Coresh, and Morgan E. Grams

How common are large differences between $eGFR_{cr}$ and $eGFR_{cys}$, and does it influence prognosis?

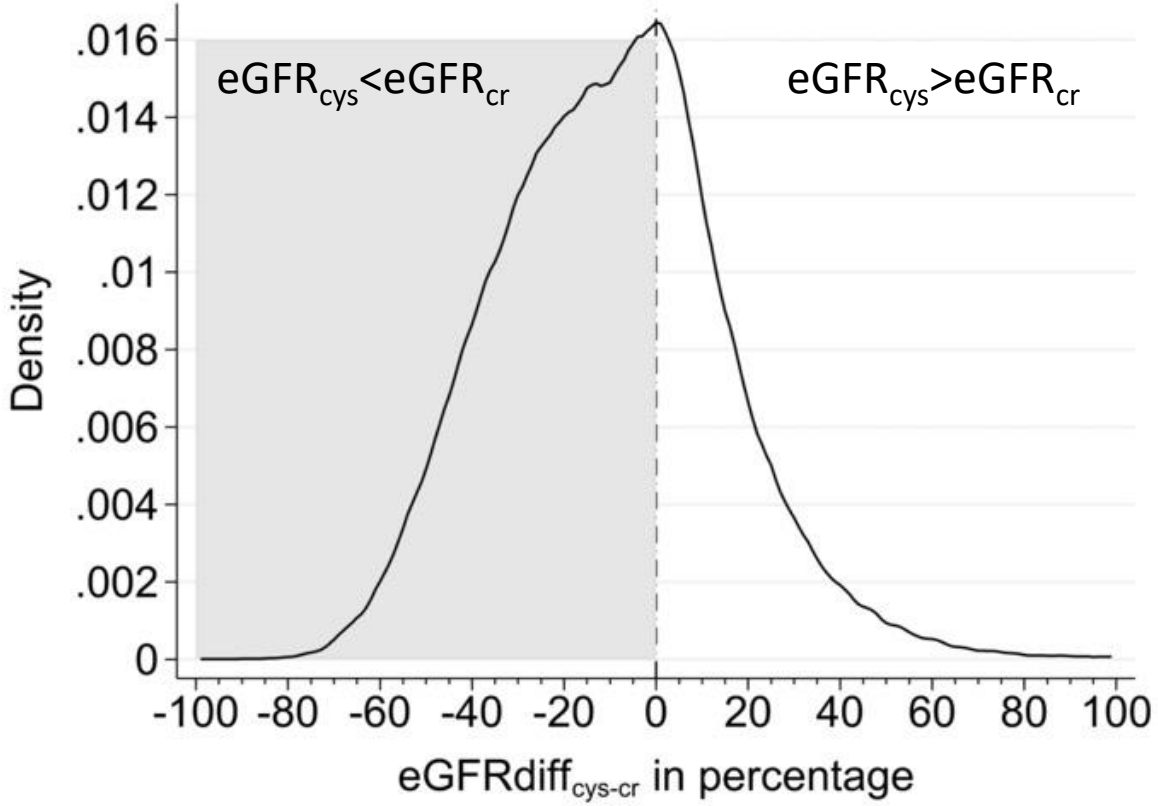


N = 158,663
same-day outpatient creatinine
& cystatin C testing



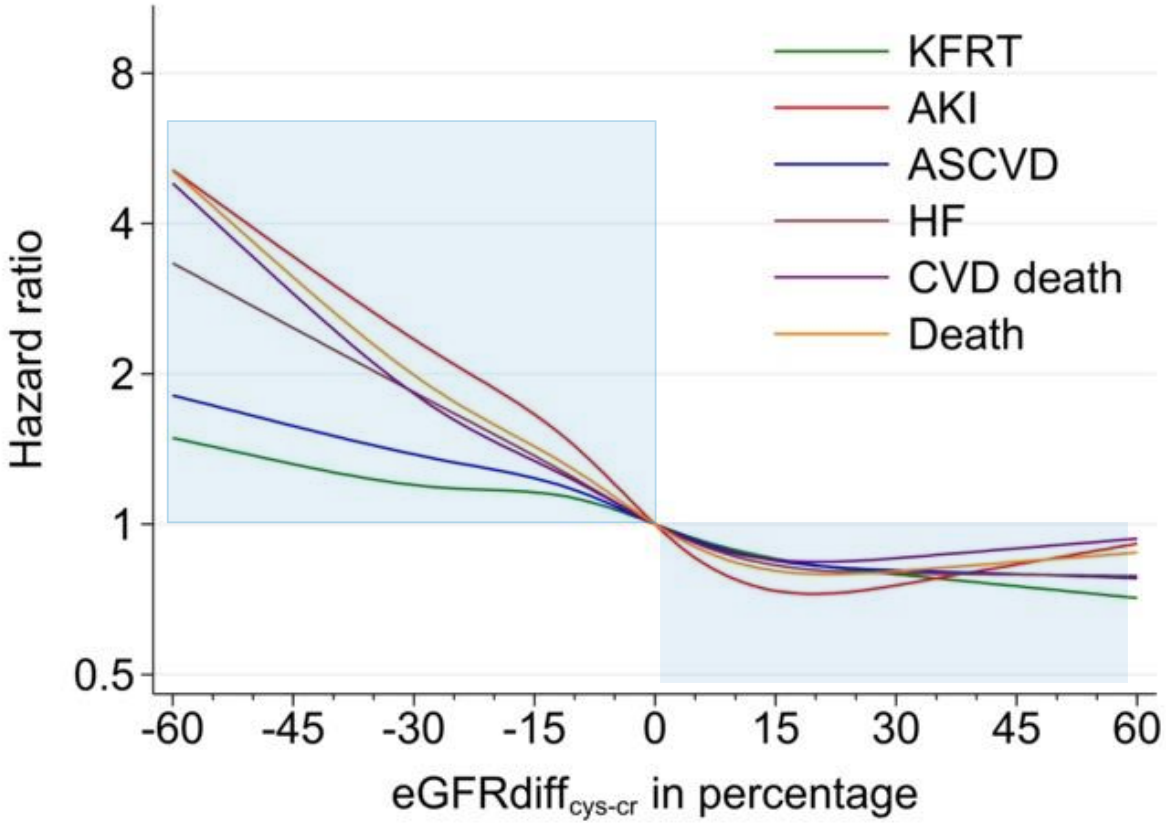
$eGFR_{diff}$ (%) = ($eGFR_{cys}$-$eGFR_{cr}$)/$eGFR_{cr}$

Prevalence and magnitude of discordances



- Majority of determinations (65%) had negative eGFRdiff$_{cys-cr}$
- On average, eGFR$_{cys}$ was 10% lower or 7 ml/min/1.73 m^2 lower than eGFR$_{cr}$
- In 32% of determinations eGFR$_{cys}$ was >15 ml/min/1.73m^2 lower compared to eGFR$_{cr}$

Prognostic implications



Hazard ratios were adjusted for age, sex, hypertension, diabetes, history of CVD, baseline eGFR$_{cr}$, log(UACR)

Annals of Internal Medicine

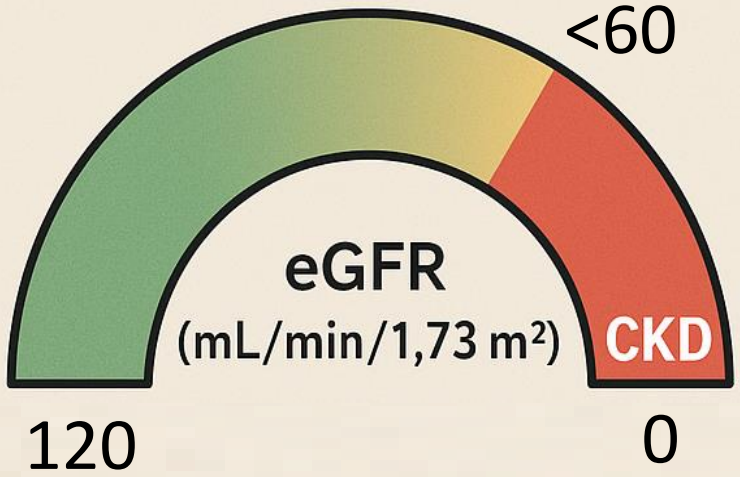
ORIGINAL RESEARCH

Association of Low Glomerular Filtration Rate With Adverse Outcomes at Older Age in a Large Population With Routinely Measured Cystatin C

Edouard L. Fu, PhD; Juan-Jesus Carrero, PharmD, PhD; Yingying Sang, MS; Marie Evans, MD, PhD; Junichi Ishigami, MD, PhD; Lesley A. Inker, MD, MS; Morgan E. Grams, MD, MHS, PhD; Andrew S. Levey, MD; Josef Coresh, MD, PhD*; and Shoshana H. Ballew, PhD*

Uncertainty about CKD threshold in older patients

Threshold for defining CKD in part based on association between $eGFR_{cr}$ and risks



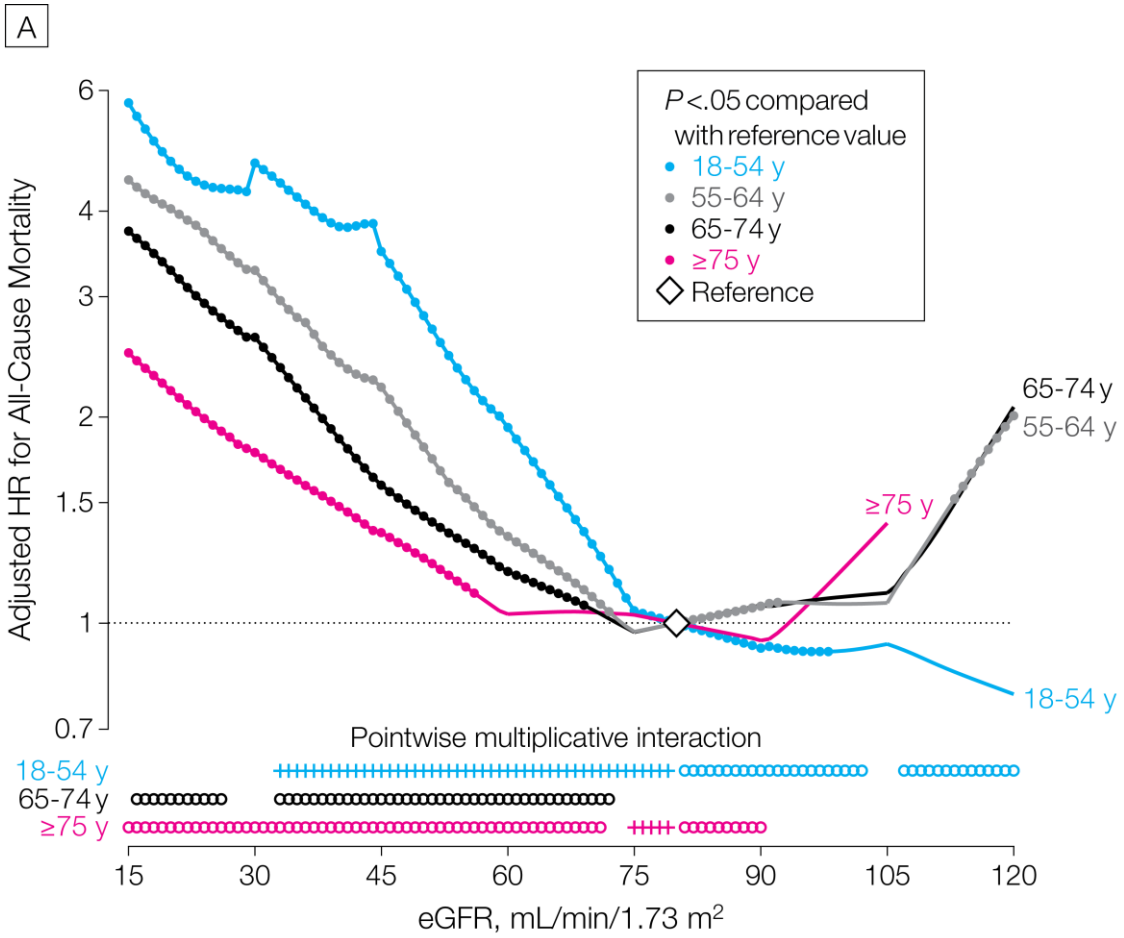
Weaker because of older age or because of less accurate eGFR?

Younger adults

Common threshold:
< 60 mL/min/1,73 m²

Weaker association, less accurate $eGFR_{cr}$

Risk not elevated for eGFR 60 mL/min/1.73m² at older age



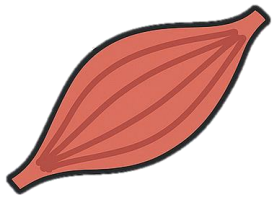
REVIEW www.jasn.org

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]

Hallan SI, Matsushita K, Sang Y, et al. Age and Association of Kidney Measures With Mortality and End-stage Renal Disease. *JAMA.* 2012;308(22):2349–2360. doi:10.1001/jama.2012.16817

But couldn't it just be due to inaccurate $eGFR_{cr}$?



Low creatinine production, so **artificially high** $eGFR_{cr}$

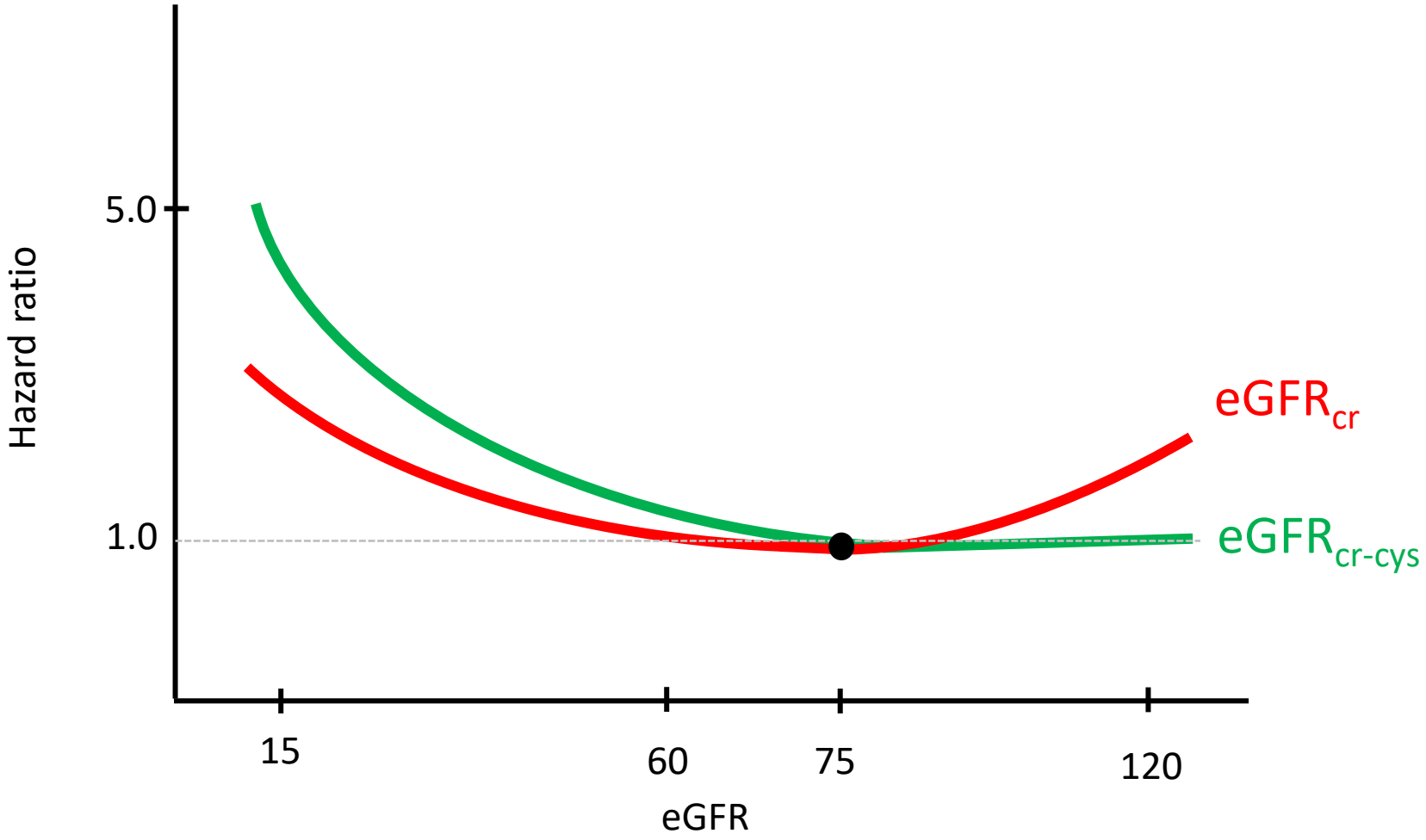
Low muscle mass

Frailty

At **high risk** of adverse events

Diluted $eGFR_{cr}$ and risk relation!

Hypothesis



Baseline characteristics

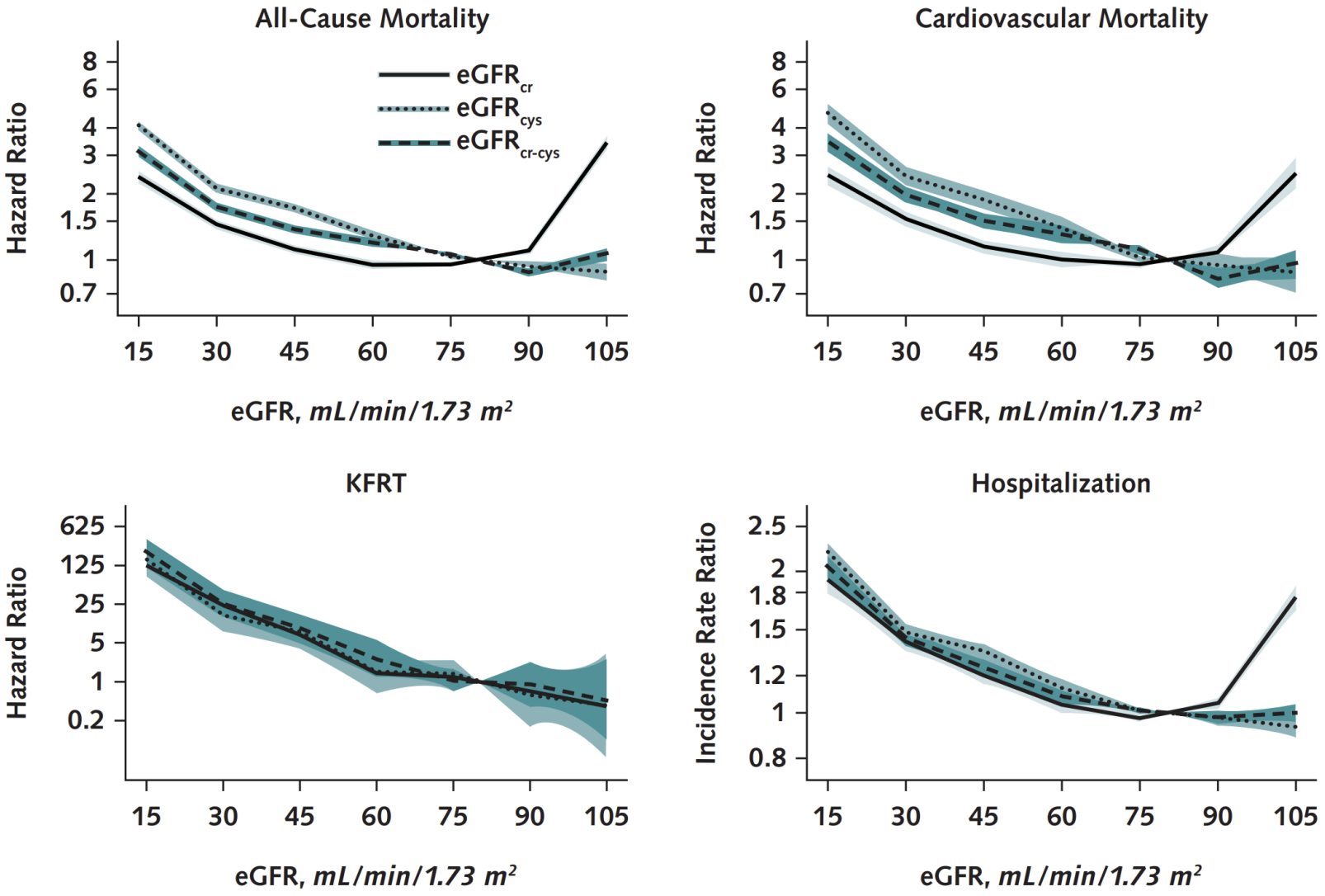
Table 1. Baseline Characteristics of Persons Aged 65 Years or Older With Creatinine Testing and the Subset With Same-Day Creatinine and Cystatin C Testing in Stockholm During 2010–2019

Characteristic	Population With Creatinine Testing	Subset With Creatinine and Cystatin C Testing				
		Overall	Aged 65–74 y	Aged ≥75 y	UACR <30 mg/g*	UACR ≥30 mg/g*
Persons, *n*	432 198	82 154	39 562	42 592	29 998	11 214
Mean age (SD), *y*	73 (8)	77 (8)	70 (3)	83 (6)	76 (8)	76 (8)
Mean $eGFR_{cr}$ (SD), *mL/min/1.73 m²*	78 (18)	67 (22)	74 (21)	61 (21)	69 (21)	54 (25)
Mean $eGFR_{cr\text{-}cys}$ (SD), *mL/min/1.73 m²*	–	61 (24)	70 (23)	53 (21)	63 (23)	47 (24)
Mean $eGFR_{cys}$ (SD), *mL/min/1.73 m²*	–	54 (24)	64 (24)	45 (20)	56 (23)	40 (22)
Female, %	55.0	49.9	43.6	55.9	51.3	36.0
Hypertension, %	35.4	80.3	74.9	85.5	81.9	92.4
Antihypertensive medication use, %	19.9	75.9	71.1	80.6	77.8	88.3
Diabetes, %	10.4	24.6	26.3	23.2	31.2	52.1
History of cardiovascular disease, %	23.5	40.5	30.0	50.5	38.2	50.8
Mean total cholesterol level (SD)†						
mmol/L	5.1 (1.2)	5.1 (1.2)	5.1 (1.2)	5.0 (1.2)	5.0 (1.2)	4.7 (1.2)
mg/dL	196 (46)	195 (46)	197 (47)	192 (46)	193 (46)	183 (48)
Mean HDL cholesterol level (SD)†						
mmol/L	1.4 (0.5)	1.4 (0.5)	1.4 (0.5)	1.5 (0.5)	1.5 (0.5)	1.3 (0.4)
mg/dL	55 (18)	55 (18)	55 (18)	56 (18)	56 (18)	49 (17)
Median UACR (IQR), *mg/g*†	16 (6–58)	17 (6–68)	13 (5–58)	22 (8–79)	8.0 (4.4–14.2)	113 (52–362)

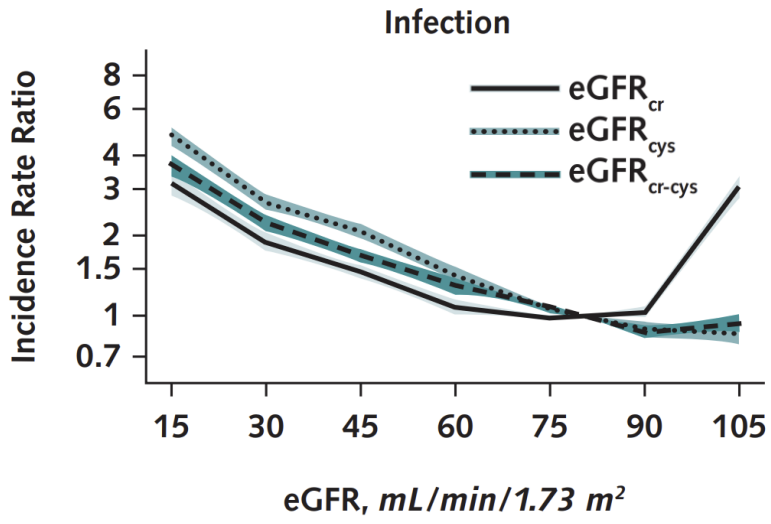
$eGFR_{cr}$ = estimated glomerular filtration rate using creatinine level; $eGFR_{cr\text{-}cys}$ = estimated glomerular filtration rate using creatinine and cystatin C levels; $eGFR_{cys}$ = estimated glomerular filtration rate using cystatin C level; HDL = high-density lipoprotein; UACR = urinary albumin–creatinine ratio.

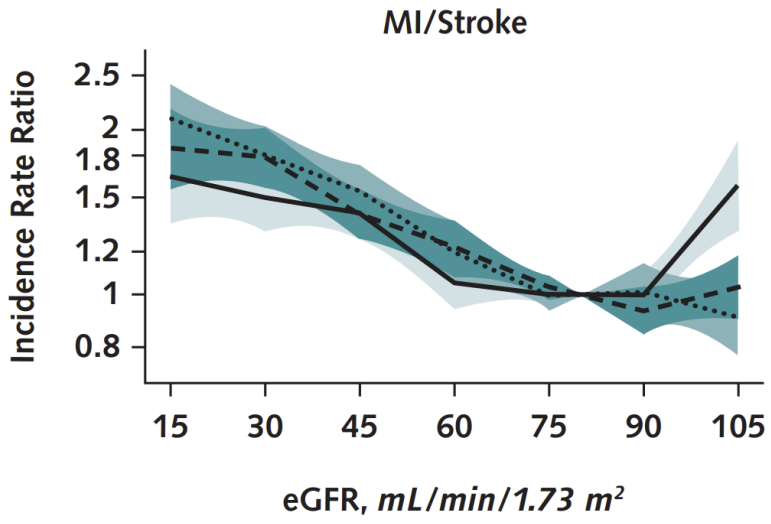
* Converted using dipstick values when UACR was missing.

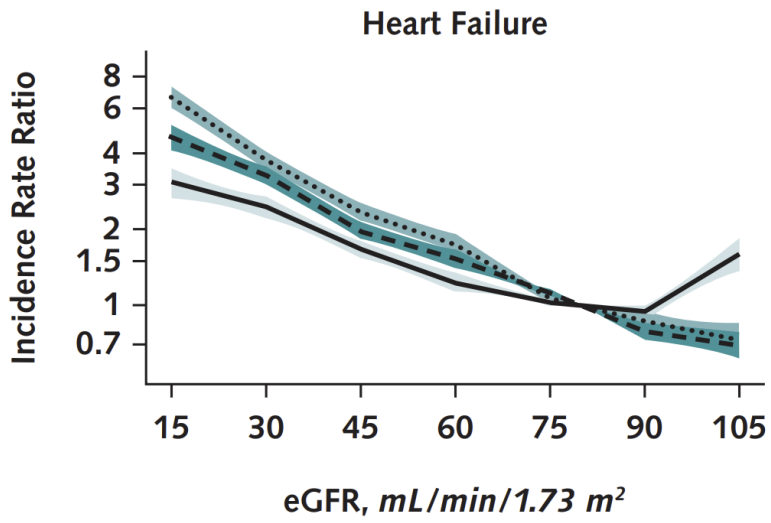
† In the population tested for creatinine, data on total cholesterol level, HDL cholesterol level, and UACR were missing in 29.4%, 44.3%, and 64.8% of persons, respectively. In the subset of persons tested for creatinine and cystatin C, the respective proportions of missing data were 24.5%, 32.7%, and 49.8% overall; 16.5%, 23.0%, and 46.3% among persons aged 65 to 74 years; 32.0%, 41.7%, and 53.1% among those aged ≥75 years; 15.2%, 21.4%, and 0% among those with UACR <30 mg/g; and 13.4%, 19.8%, and 0% among those with UACR ≥30 mg/g. To convert UACR from mg/g to mg/mmol, multiply by 0.113. The numbers shown are before multiple imputation.

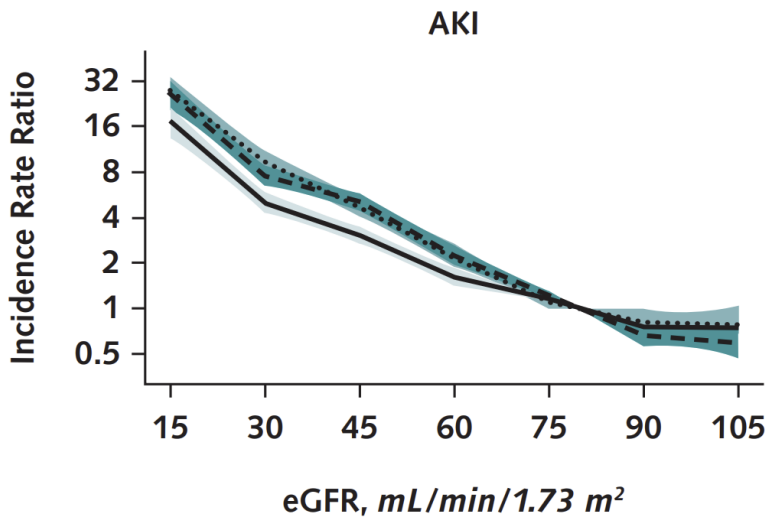


Adjusted for age, sex, hypertension, diabetes, CVD, log(UACR). For CV death, hospitalization, MI/stroke, and heart failure also adjustment for total cholesterol, HDL cholesterol and antihypertensive medication use









Adjusted for age, sex, hypertension, diabetes, CVD, log(UACR). For CV death, hospitalization, MI/stroke, and heart failure also adjustment for total cholesterol, HDL cholesterol and antihypertensive medication use

Conclusion

- Magnitude of hazard ratios for wide range of outcomes: $eGFR_{cys} > eGFR_{cr\text{-}cys} > eGFR_{cr}$
- Strong U-shaped relationship for $eGFR_{cr}$
- Differences in risks for $eGFR_{cr}$, $eGFR_{cys}$, $eGFR_{cr\text{-}cys}$ due to non-GFR determinants

Conclusions

Conclusion

- Findings support increased use of cystatin C for clinical management
- eGFRcr-cys performs best with P30 close to 90% regardless of equation used, also in case of discordances, and for epidemiological purposes
- Wide variation in eGFRcr performance, with poorest performance for CKD-EPI 2021
  - What should we use in Europe? Keep using CKD-EPI 2009 or switch to EKFC?

Impact on clinical guidelines/consensus statements

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

PRIMER

Moving forward from Cockcroft-Gault creatinine clearance to race-free estimated glomerular filtration rate to improve medication-related decision-making in adults across healthcare settings: A consensus of the National Kidney Foundation Workgroup for Implementation of Race-Free eGFR-Based Medication-Related Decisions

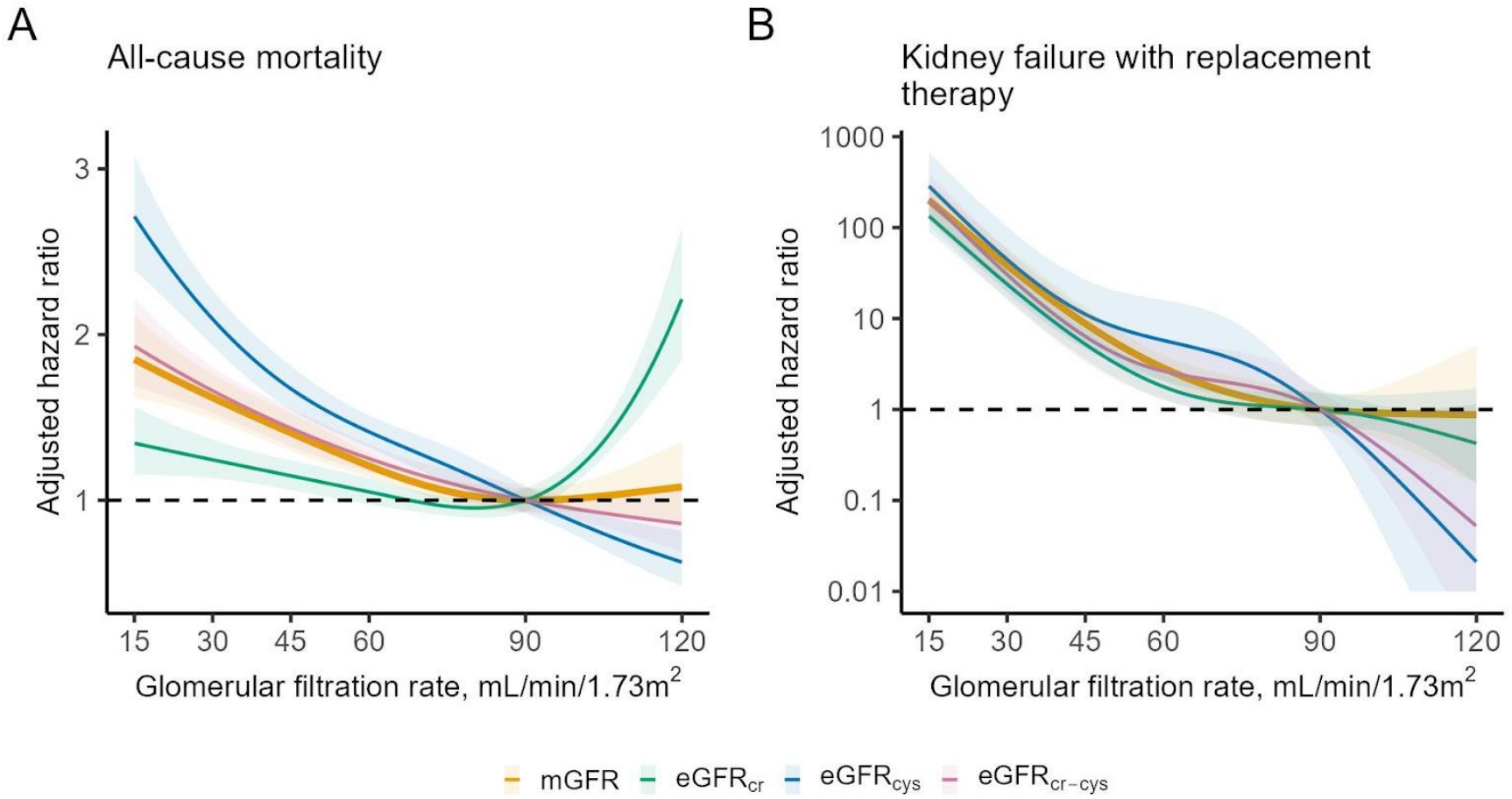
DE GRUYTER Clin Chem Lab Med 2025; 63(3): 525–534

Guidelines and Recommendations

Etienne Cavalier*, Tomáš Zima, Pradip Datta, Konstantinos Makris, Elke Schaeffner, Michel Langlois, Mario Plebani and Pierre Delanaye, on behalf of the EFLM Task Group on Chronic Kidney Disease

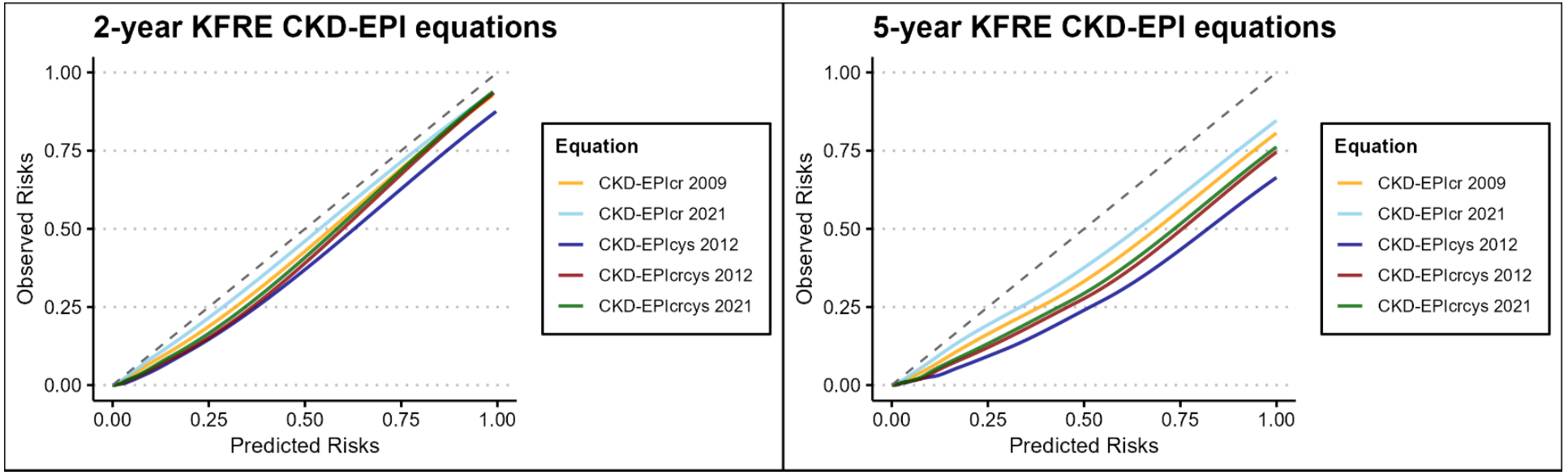
Recommendations for European laboratories based on the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

In progress: measured GFR and adverse outcomes



In progress: Influence of filtration marker on KFRE

Equation	C-statistic 2-year KFRE	C-statistic 5-year KFRE
CKD-EPIcr 2009	0.959 (0.952 - 0.964)	0.943 (0.938 - 0.948)
CKD-EPIcr 2021	0.959 (0.953 - 0.965)	0.943 (0.939 - 0.949)
CKD-EPIcys 2012	0.952 (0.946 - 0.959)	0.929 (0.924 - 0.935)
CKD-EPIcr-cys 2012	0.959 (0.953 - 0.965)	0.942 (0.937 - 0.947)
CKD-EPIcr-cys 2021	0.960 (0.953 - 0.965)	0.942 (0.937 - 0.947)



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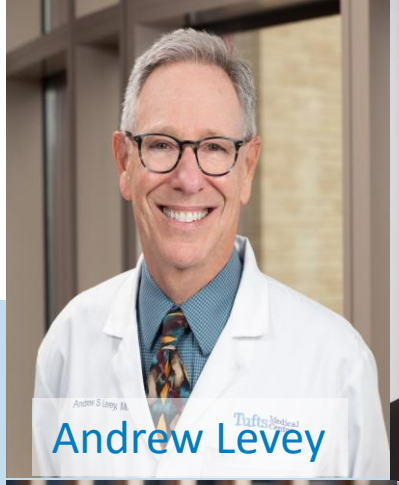

Andrew Levey

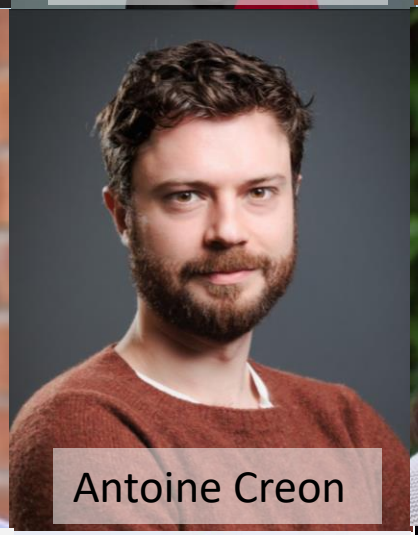

Josef Coresh

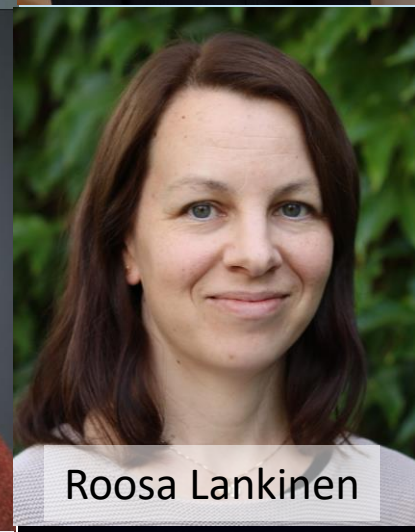

Morgan Grams


Lesley Inker

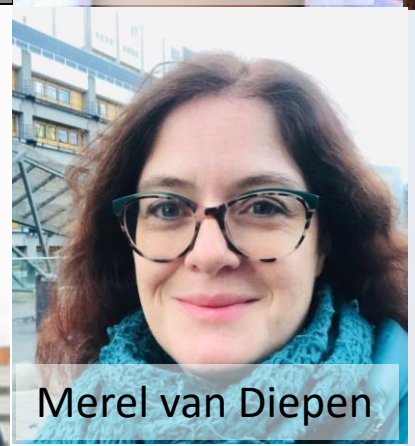

Juan-Jesus Carrero

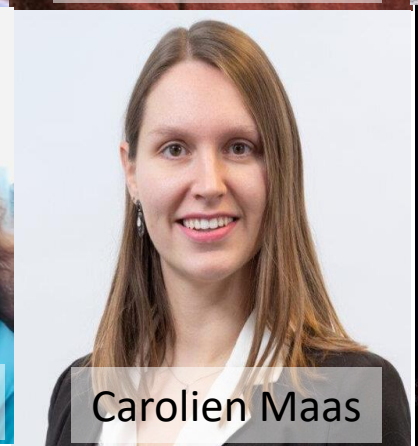

William Russell


Antoine Creon


Roosa Lankinen


Friedo Dekker


Merel van Diepen


Carolien Maas


Malou Magnani