EFLM Syllabus Course
Kidney and Urine

EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Assessment of kidney function and diagnosis of chronic kidney disease

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September, 2021

Speaker affiliations

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Conflict of interest disclosure

I disclose the following (but nothing with the current lecture)

Consultancy Agreements	Immunodiagnostic Systems limited; ARK Biosciences
Ownership Interest	Nothing to disclose.
Research Funding	Nothing to disclose.
Honoraria	Sanofi, Bayer, AstraZeneca, Amgen, Menarini, Siemens, Fresenius
Patents and Inventions	Nothing to disclose.
Scientific Advisor or Membership	Nothing to disclose.
Speakers Bureau	Nothing to disclose.
Other Interests/Relationships	Nothing to disclose.

Learning outcomes

If you attend this lecture, at the end you will know/understand/learn:

1. How to measure glomerular filtration rate
2. How to estimate glomerular filtration rate
3. How to diagnose chronic kidney disease

The Glomerular Filtration Rate is usually the best parameter to assess the global kidney function.

So, how to measure (or estimate GFR)?

Measuring GFR
How? Why?

Renal function: concept of clearance

Clearance of a solute (ml/min):

volume of plasma cleared (« purified ») of this substance per time

$$Cl = [U] \times [V] / [P]$$

Ideal marker for GFR:

- Constant production
- No effect on GFR, non toxic
- Not bound to protein, freely filtrated through glomerulus
- No secretion, no absorption by the tubules
- No extra renal clearance
- Easy to measure

Available on the market…

Markers	Strenghts	Limitations
Inulin	Gold standard (or historic) Safe	Costly, Dosage neither easy nor standardized Doubt with plasma clearance and bolus
Iothalamate	The most popular in USA Isotopic or “cold” method	Tubular secretion Cannot be used if allergy to iodine
Iohexol	External quality control Relatively easy to measure	Cannot be used if allergy to iodine
^{51}Cr-EDTA	Easy to measure	Only isotopic Not available in USA
^{99m}Tc-DTPA	Easy to measure	Only isotopic Binding to proteins Short half-time

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305

We have biomarkers
Now, how to proceed?

Urinary clearance

Plasma clearance

Urinary clearance

Constant infusion, marker at equilibrium

Plasma measurement of the marker

Collect Urine (every half or every hour) and measurement of urine flow, urine measurement of the marker

Repeated 3 or 4 times

Cl = [U] x [V]/ [P] (mean of three collections)

Plasmatic Clearance = Dose / AUC

Theoritically, α and β must be calculated

↓

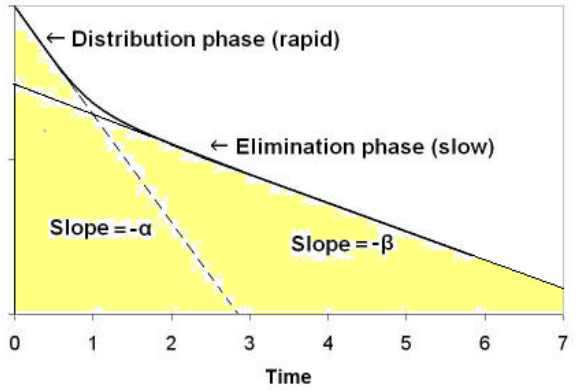
Not easy in practice (many samples)

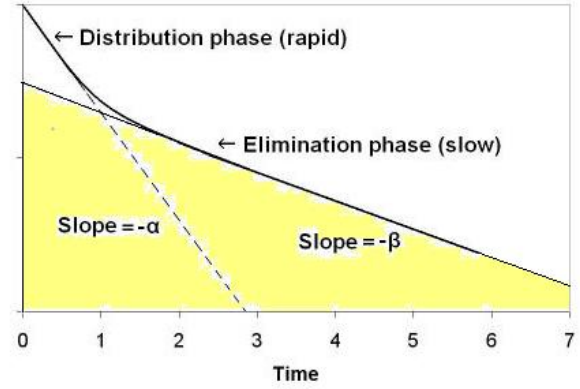
↓

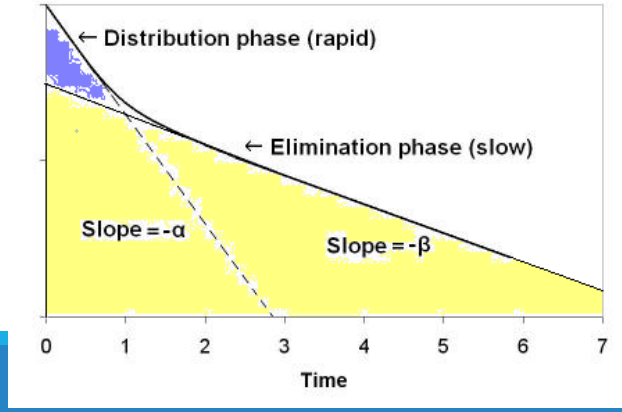
Only slope ß after equilibrium is calculated

↓

Brochner-Mortensen mathematical correction for estimation of distribution phase



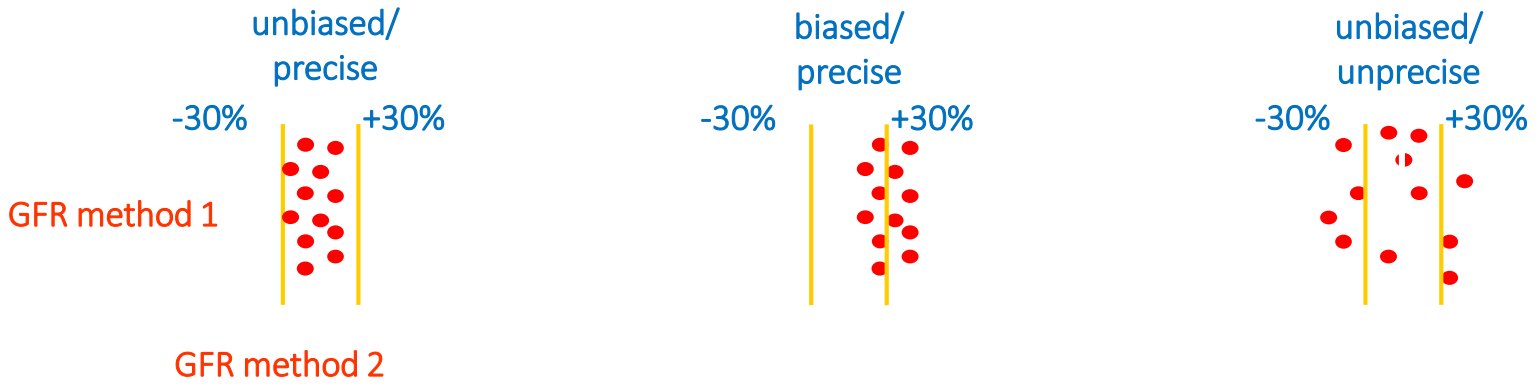




Are they equivalent?

Statistics

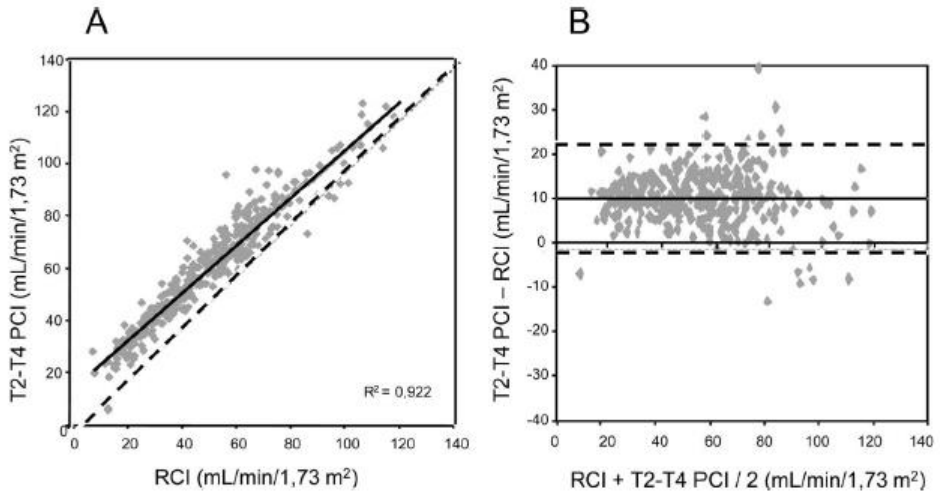
- Good correlation: a *"sine qua non"* condition but insufficient
- Bias: mean difference between two values = the systematic error
- Precision: SD around the bias = the random error
- Accuracy 30% = % of eGFR between ± 30% of measured GFR



Plasma versus Urinary clearances

Evaluation of Sample Bias for Measuring Plasma Iohexol Clearance in Kidney Transplantation

Arnaud Stolz,[1] Guillaume Hoizey,[2] Olivier Toupance,[1] Sylvie Lavaud,[1] Fabien Vitry,[3] Jacques Chanard,[1] and Philippe Rieu[1,4,5]



	n	Bias ml/min/1.73m² (%)	Precision (SD) (ml/min/1.73m²)
T2-T4	342	+10 (+27%)	±6
T2-T6	342	+8 (+21%)	±6
T2-T24	215	+3 (+8.8%)	±5

Stolz A, Transplantation, 2010, 89, 440

Urinary and plasma methods: pro-con

More physiological

More costly

More cumbersome

Less precision (urine recolt!)

Plasma clearance: single- or multiple samples

Nephrol Dial Transplant. 2018 Oct 1;33(10):1778-1785.

ndt
Nephrology Dialysis Transplantation

Single- versus multiple-sample method to measure glomerular filtration rate

Pierre Delanaye[1,*], Martin Flamant[2,*], Laurence Dubourg[3,4], Emmanuelle Vidal-Petiot[2], Sandrine Lemoine[3], Etienne Cavalier[5], Elke Schaeffner[6], Natalie Ebert[6,**] and Hans Pottel[7,**]

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Available on the market…

Markers	Strength	Limitations
Inulin	"Gold standard" (or historical)	Costly No standardized dosage, not available in US Impossible for plasma clearance Anaphylactic shock

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

Available on the market…

Markers	Strength	Limitations
Inulin	"Gold standard" (or historical)	Costly No standardized dosage, not available in US Impossible for plasma clearance Anaphylactic shock
Iothalamate	Mostly used in USA Isotopique ou "froide"	Tubular secretion Iodine Allergy

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

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Iothalamate	Mostly used in USA Isotopic or not	Tubular secretion Iodine Allergy
Iohexol	Most used in Europe Non isotopic	Iodine Allergy

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
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Available on the market…

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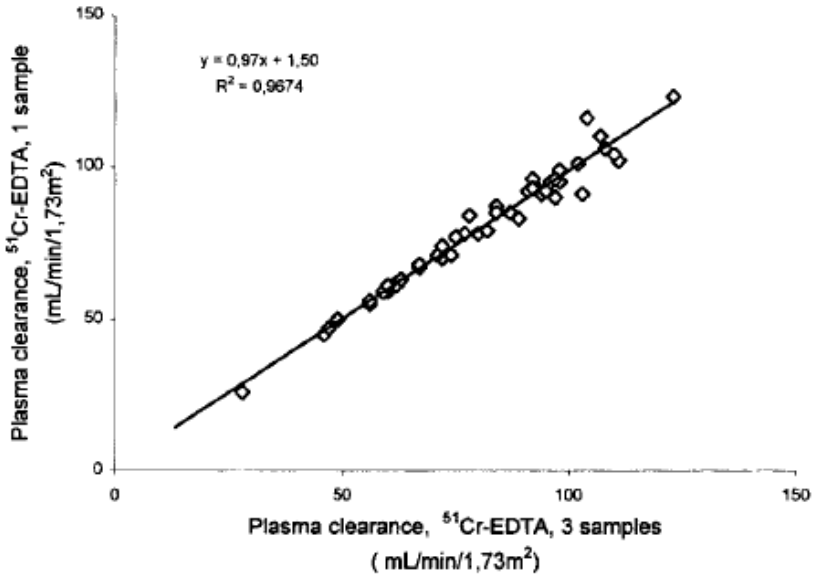
Iothalamate	Mostly used in USA Isotopic or not	Tubular secretion Iodine Allergy
Iohexol	Most used in Europe Non isotopic	Iodine Allergy
EDTA	Easy to measure	Isotopic Not available anymore
DTPA	Easy to measure	Isotopic Binding to proteins?

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

Are they equivalent?

EDTA versus iohexol

N=49



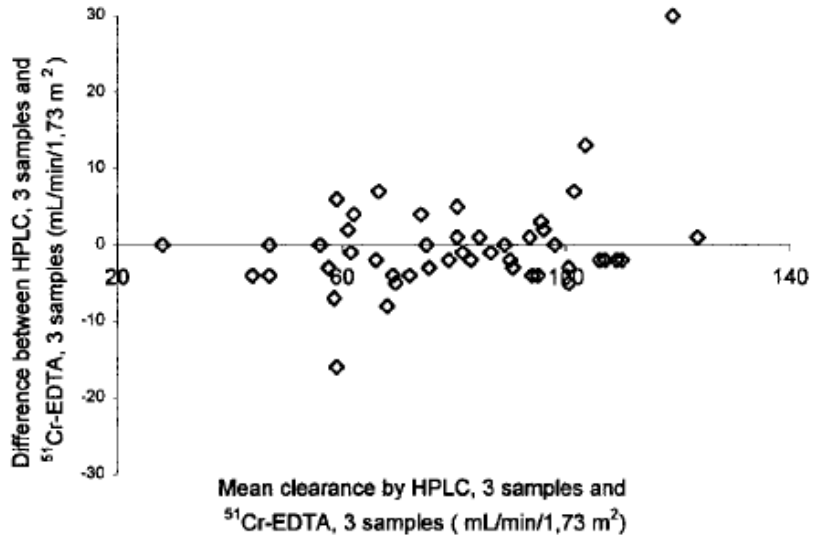


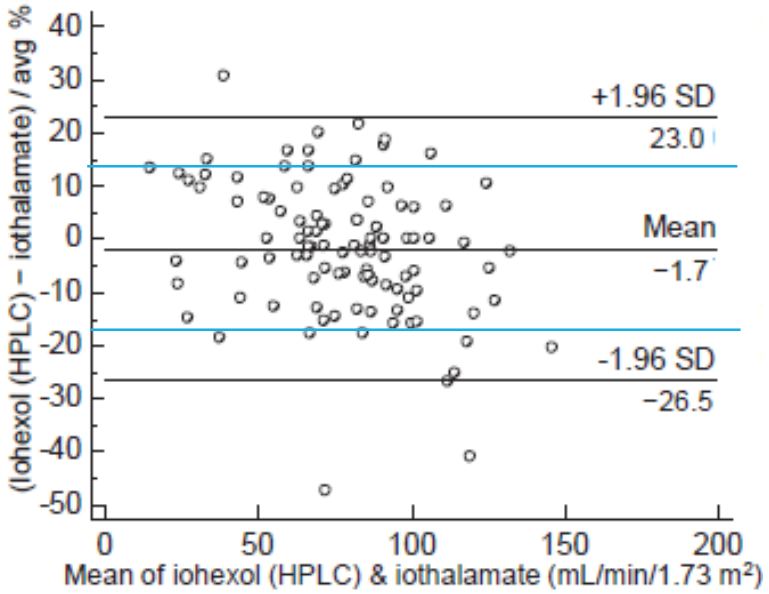
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	Clearance range (ml/min)	Difference (ml/min)	
		Mean	SD
Multiple-point clearance: 3 samples ^{51}Cr-EDTA *vs* 3 samples iohexol			
^{51}Cr-EDTA *vs* HPLC	28–134	−0.16	6.17
^{51}Cr-EDTA *vs* X-ray fluorescence	29–134	0.58	4.95
Single-point clearance: 3 samples ^{51}Cr-EDTA *vs* 1 sample			
^{51}Cr-EDTA *vs* ^{51}Cr-EDTA	26–123	−0.7	3.59
^{51}Cr-EDTA *vs* HPLC	27–125	−1.7	5.94
^{51}Cr-EDTA *vs* X-ray fluorescence	32–116	−1.32	5.78

Brandstrom, NDT, 1998, 13, 1176

Iothalamate versus iohexol

N=102



Accuracy (concordance):
Within 30%: 98%
Within 15%: 80%

Delanaye P, AJKD, 2016, 68, 329

AJKD
Original Investigation

Measuring GFR: A Systematic Review

*Inga Soveri, MD, PhD,[1] Ulla B. Berg, MD, PhD,[2] Jonas Björk, PhD,[3] Carl-Gustaf Elinder, MD, PhD,[4] Anders Grubb, MD, PhD,[5] Ingegerd Mejare, PhD,[6] Gunnar Sterner, MD, PhD,[7] and Sten-Erik Bäck, MSc, PhD,[5] on behalf of the SBU GFR Review Group**

Table 1. Bias and Accuracy of Index Methods Compared to Reference Method When Measuring Glomerular Filtration Rate

	No. of Pts/ Studies	Median Bias[a] (95% CI)	Mean Bias (95 % CI)	P_{30} (95% CI)	P_{10} (95% CI)	Sufficient Accuracy	Scientific Evidence	Comments[b]
Criteria for sufficient precision		≤±5%	≤±10%	≥80%	≥50%			
Index method								
DTPA								
Renal clearance	126/5	−2 (−4 to 2)	−1 (−6 to 5)	87 (81 to 93)	53 (45 to 62)	Yes	⊕⊕◯◯	Inconsistency, −1; imprecision, −1
Plasma clearance	89/2	20 (18 to 35)	13 (5 to 22)	56 (47 to 68)	19 (13 to 29)	No	⊕⊕◯◯	Study limitations −1; imprecision −1
^{51}Cr-EDTA								
Renal clearance	198/9	−5 (−7 to −3)	−2 (−8 to 4)	95 (92 to 98)	56 (50 to 64)	Yes	⊕⊕⊕◯	Imprecision, −1
Plasma clearance	126/5	3 (−1 to 8)	8 (1 to 15)	86 (80 to 92)	50 (42 to 59)	Yes	⊕⊕⊕◯	Imprecision, −1
Iohexol								
Renal clearance	47/2	−7 (−10 to 0)	−7 (−16 to 2)	100[c]	53 (41 to 70)	Yes	⊕⊕◯◯	Imprecision, −2
Plasma clearance	172/5	3 (0 to 6)	2 (−4 to 9)	86 (81 to 91)	50 (43 to 58)	Yes	⊕⊕⊕◯	Imprecision, −1
Iothalamate								
Renal clearance	548/13	−1 (−2 to 0)	6 (1 to 11)	97 (95 to 98)	66 (62 to 70)	Yes	⊕⊕⊕⊕	
Plasma clearance	61/1	9 (0 to 15)	11 (−6 to 29)	82 (73 to 92)	33 (23 to 47)	—	⊕◯◯◯	Study limitations, −1; imprecision, −2
Inulin								
Plasma clearance	39/2	2 (−3 to 6)	1 (−9 to 11)	100[c]	72 (59 to 87)	Yes	⊕⊕◯◯	Imprecision, −1; indirectness, −1

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage. Renal inulin clearance served as reference method. Mean bias, P_{10}, and P_{30} were estimated using generalized linear mixed models based on normal distribution (mean bias) or Poisson distribution (P_{10}, P_{30}; log-transformed outcome and robust variance estimation), with a random intercept for each study and a fixed effect for each index method ("unadjusted model results"; see Statistical Methods section). All analyses were weighed with respect to number of participants in each study. Estimates were obtained as marginal means.

Abbreviations and definitions: ⊕⊕⊕⊕, strong evidence; ⊕⊕⊕◯, moderately strong evidence; ⊕⊕◯◯, limited evidence; ⊕◯◯◯, insufficient evidence; ^{51}Cr-EDTA, chromium 51–labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; CI, confidence interval; Imprecision, N < 100 in meta-analysis (−1), P_{30} lower 95% CI ≤ 80%, P_{10} lower 95% CI ≤ 50%, or median bias 95% CI ≥ ±5% (−1); Inconsistency, inconsistency in study outcomes that cannot be explained by differences in study design (−1); Indirectness, limited generalizability (−1); P_{10}, percentage of measurements by index method that differed no more than 10% from reference method; P_{30}, percentage of measurements by index method that differed no more than 30% from reference method; pts, patients; Study limitations, risk of bias due to shortcomings in individual studies (−1).

[a]Median bias was calculated directly (using the weights) for each index method together with nonparametric CIs.

[b]Strength of scientific evidence.

[c]The generalized linear mixed model does not yield valid estimates of confidence limits when estimated proportion (eg, P_{30}) is 100%.

Soveri I, Am J Kidney Dis, 2014, 64, 411

We still need for a better standardization

Standardization for procedure

Urinary versus plasma

Number of samples and timing of samples

(Whatever the marker…)

Table 4. Available procedures to perform iohexol clearance

Methodology	Indication in clinical practice	Indication in clinical research	Bibliographic examples where the procedure is described into details
Urinary clearance	Increased extracellular volume (oedema, ascites, intensive care units, etc.)	Basic (physiologic) studies Specific populations (cirrhotic, intensive care, nephrotic syndrome, oedema, etc.)	[36, 77, 125, 170]
Plasma clearance			
Multiple samples (first or fast, second or slow exponential curves and calculation of area under the curve)	High GFR values ('hyperfiltrating') subjects	Development of equations to estimate GFR Studies in hyperfiltrating patients	[52, 93, 171]
Multiple samples only for second and slow component (2 h after injection, 4 samples over 5 or 6 h, 1 sample/h) + BM correction	High precision determination (see text)	Development of equations to estimate GFR Clinical research with GFR as main endpoint	[126, 172]
Idem + late sample (8 h or 24 h)	Pre-dialysis subjects	Research in pre-dialysis subjects	[52, 77]
Simplified two or three sample method (2 samples: first at 2 or 3 h and second at 4 or 5 h) + BM correction	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint	[69, 116]
Simplified single-sample method + Jacobsson correction [110]	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint Epidemiological research	[14, 173]

Suggestions (expert opinion-based) according to the clinical or experimental context.
GFR, glomerular filtration rate; CKD, chronic kidney disease; BM, Brochner-Mortensen correction [116].

Delanaye P, Clin Kidney J, 2016, 9, 700

EKFC

Nephrol Dial Transplant (2018) 33: 1778–1785
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Advance Access publication 8 January 2018

Single- versus multiple-sample method to measure glomerular filtration rate

Pierre Delanaye[1,*], Martin Flamant[2,*], Laurence Dubourg[3,4], Emmanuelle Vidal-Petiot[2], Sandrine Lemoine[3], Etienne Cavalier[5], Elke Schaeffner[6], Natalie Ebert[6,**] and Hans Pottel[7,**]

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**These authors equally contributed as last senior author.

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Comparison of Plasma Clearance With Early-Compartment Correction Equations and Urinary Clearance in High GFR Ranges

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AJKD

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RESEARCH LETTER

Concordance Between Iothalamate and Iohexol Plasma Clearance

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Original Investigation — AJKD

Comparability of Plasma Iohexol Clearance Across Population-Based Cohorts

Bjørn O. Eriksen, Elke Schaeffner, Toralf Melsom, Natalie Ebert, Markus van der Giet, Vilmundur Gudnason, Olafur S. Indridasson, Amy B. Karger, Andrew S. Levey, Mirjam Schuchardt, Liv K. Sørensen, and Runolfur Palsson

Rationale & Objective: Glomerular filtration rate (GFR) estimation based on creatinine or cystatin C level is currently the standard method for assessing GFR in epidemiologic research and clinical trials despite several important and well-known limitations. Plasma iohexol clearance has been proposed as an inexpensive method for measuring GFR that could replace estimated GFR in many research projects. However, lack of standardization for iohexol assays and the use of different protocols such as single- and multiple-sample methods could potentially hamper comparisons across studies. We compared iohexol assays and GFR measurement protocols in 3 population-based European cohorts.

Study Design: Cross-sectional investigation.

Setting & Participants: Participants in the Age, Gene/Environment Susceptibility-Kidney Study (AGES-Kidney; n = 805), the Berlin Initiative Study

Results: Frozen samples from the 3 studies were obtained and iohexol concentrations were remeasured in the laboratory at the University Hospital of North Norway. Lin's concordance correlation coefficient ρ was >0.96 and C_b (accuracy) was >0.99 for remeasured versus original serum iohexol concentrations in all 3 cohorts, and Passing-Bablok regression did not find differences between measurements, except for a slope of 1.025 (95% CI, 1.006-1.046) for the log-transformed AGES-Kidney measurements. The multiple-sample iohexol clearance measurements in AGES-Kidney and BIS were compared with single-sample GFRs derived from the same iohexol measurements. Mean bias for multiple-sample relative to single-sample GFRs in AGES-Kidney and BIS were −0.25 and −0.15 mL/min, and 99% and 97% of absolute differences were within 10% of the multiple-sample result, respectively.

Complete author and article information provided before references.

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Am J Kidney Dis. XX(XX):1-9. Published online Month X, XXXX.

doi: 10.1053/j.ajkd.2019.10.008

Comparison of Early-Compartment Correction Equations for GFR Measurements

Check for updates

Pierre Delanaye[1,210], Laurence Dubourg[3,10], Martin Flamant[4,10], Eric Yayo[5], Justine B. Bukabau[6], Emmanuelle Vidal-Petiot[4], Sandrine Lemoine[3], Etienne Cavalier[7,10], Elke Schaeffner[8,10], Dagui Monnet[5], Ernest K. Sumaili[6], Natalie Ebert[8,10] and Hans Pottel[9,10]

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[10]PD, LD, MF, EC, ES, NE, and HP are members of the European Kidney Function Consortium.

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Choice of the marker (personal opinion)

Only « cold », non-isotopic methods are easy to implement worldwide

Iohexol is available worldwide, easy to measure

Perfect stability (central laboratory)

EQUAS (Equalis, Sweden) is available

Cr-EDTA, inulin, iothalamate not (or no more or not easily) available in Europe…

DE GRUYTER

Clin Chem Lab Med 2019;57(7):1006-1011

Gunnar Nordin, Sara Ekvall, Carolina Kristoffersson, Ann-Sofie Jonsson, Sten-Erik Bäck, Niclas Rollborn and Anders Larsson*

Accuracy of determination of the glomerular filtration marker iohexol by European laboratories as monitored by external quality assessment

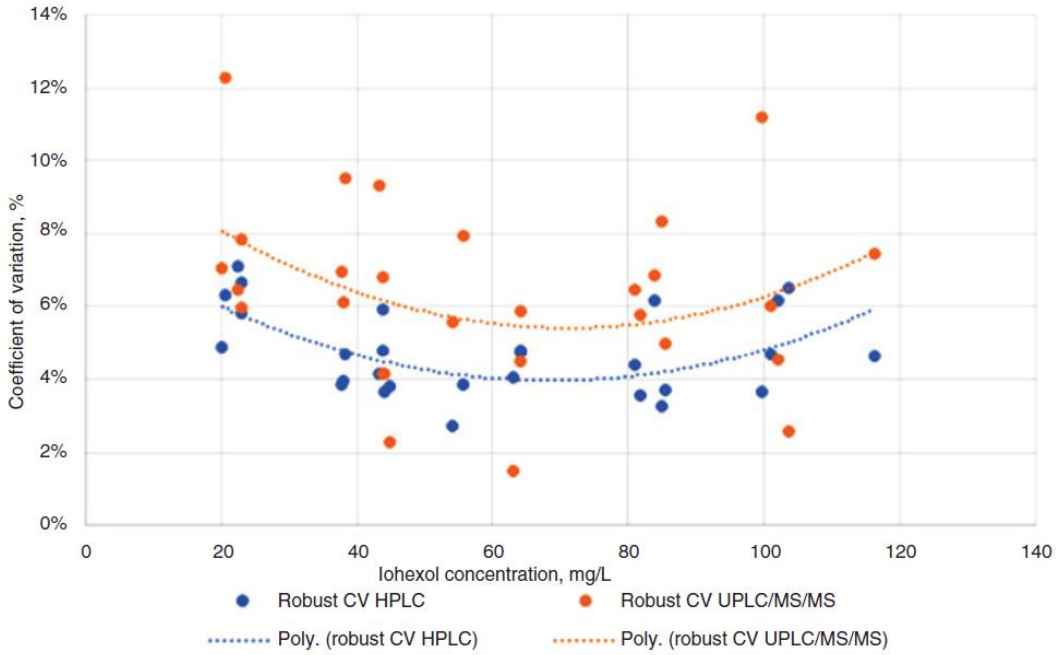

Figure 1: Mean interlaboratory CV (y-axis) vs. measured concentration of iohexol (x-axis) for laboratories using either HPLC or UPLC/MS/MS.

14 EQA rounds
N=27 to 34

HPLC: 4,1%
MS/MS: 6,4%

nephron Clinical Practice

Clinical Practice: Original Paper

Nephron
DOI: 10.1159/000489898

Nephron. 2018;140(1):1-8.

Safety of Iohexol Administration to Measure Glomerular Filtration Rate in Different Patient Populations: A 25-Year Experience

Flavio Gaspari[a] Surabhi Thakar[b] Fabiola Carrara[a] Annalisa Perna[a]
Matias Trillini[a] Maria Carolina Aparicio[a] Olimpia Diadei[a] Silvia Ferrari[a]
Antonio Cannata[a] Nadia Stucchi[a] Piero Ruggenenti[a, c] Giuseppe Remuzzi[a, c, d]
Norberto Perico[a]

[a]IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [b]Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN, USA; [c]Nephrology and Dialysis Unit, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [d]Department of Biomedical and Clinical Sciences 'L. Sacco', University of Milan, Milan, Italy

15,147 GFR measurements in 2891 patients
only one treatment-related event of moderate intensity was identified
flushing, urticaria, and itching, without sequelae after IV methylprednisolone

Iohexol in CHU Liège

Iohexol (plasma clearance), 5 mL bolus

5 hours

Samples at 2, 3, 4 et 5 hours (longer if very low eGFR)

Brochner-Mortensen

50 to 100 euros

Conclusions

Measuring GFR is not so cumbersome

Standardization (marker, procedure and measurement) might still be improved

Iohexol is the best balance between physiology and feasibility

Iohexol is safe

Iohexol is the only chance for a worldwide standardized mGFR

Role of laboratory is central

Measuring GFR: Why?
A question of precision!

Starting dialysis

Sarcopenia

Extreme body size

Cirrhosis, USI

Fibrates, cimetidine, trimethoprim (and other therapies)

Hyperfiltration

Dosing potential nephrotoxic drug (especially if abnormal BMI)

Living Kidney Donor selection

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, 14, p1861

Measuring GFR: Why?
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Impact of estimation versus direct measurement of predonation glomerular filtration rate on the eligibility of potential living kidney donors

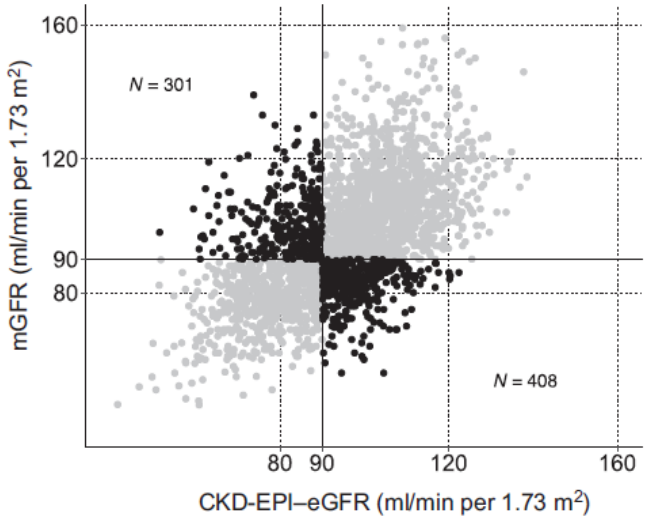
see commentary on page 738

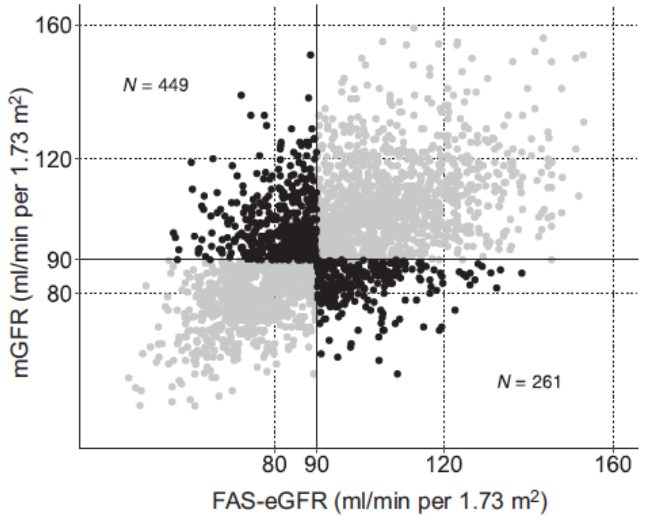
François Gaillard[1,2], Marie Courbebaisse[2,3], Nassim Kamar[4,5,18], Lionel Rostaing[6,18], Lola Jacquemont[7,8], Maryvonne Hourmant[7,8], Arnaud Del Bello[4], Lionel Couzi[9,10], Pierre Merville[9,10], Paolo Malvezzi[6], Benedicte Janbon[6], Bruno Moulin[11], Nicolas Maillard[12], Laurence Dubourg[13,14], Sandrine Lemoine[13], Cyril Garrouste[15], Hans Pottel[16], Christophe Legendre[1,2], Pierre Delanaye[17,19] and Christophe Mariat[12,19]

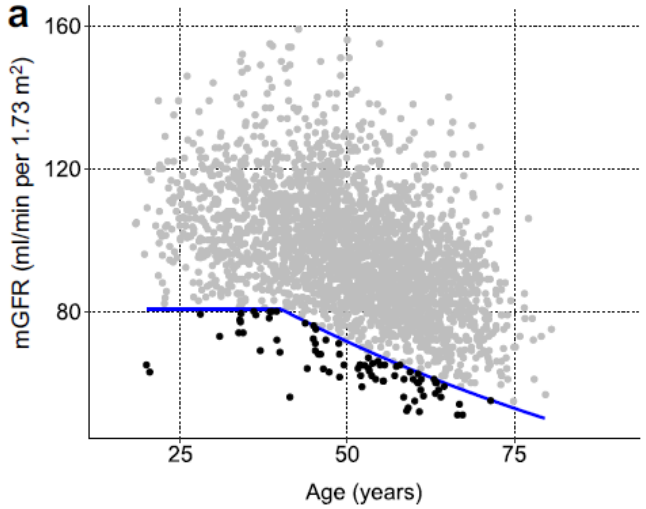
Kidney International (2019) **95,** 896–904;

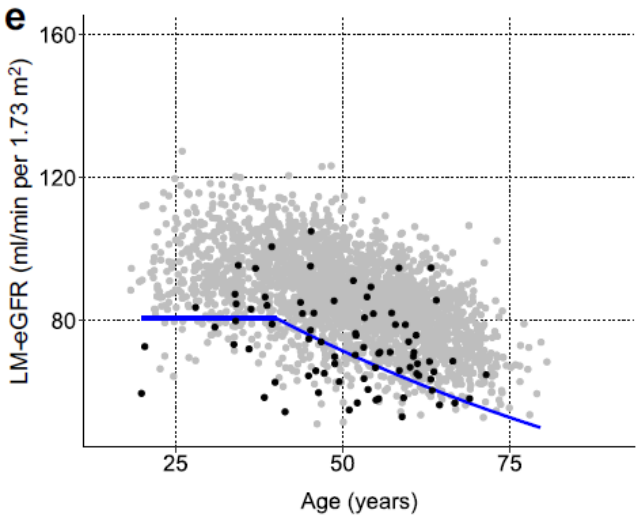
N=2,733 candidates for living kidney donation

Measured GFR and standardized creatinine


N = 301
N = 408
mGFR (ml/min per 1.73 m²)
CKD-EPI–eGFR (ml/min per 1.73 m²)
160
120
90
80
80 90 120 160


N = 449
N = 261
mGFR (ml/min per 1.73 m²)
FAS-eGFR (ml/min per 1.73 m²)
160
120
90
80
80 90 120 160


a
mGFR (ml/min per 1.73 m²)
Age (years)
160
120
80
25 50 75


e
LM-eGFR (ml/min per 1.73 m²)
Age (years)
160
120
80
25 50 75

Estimating GFR

Serum creatinine

One of the most prescribed analyte in clinical chemistry

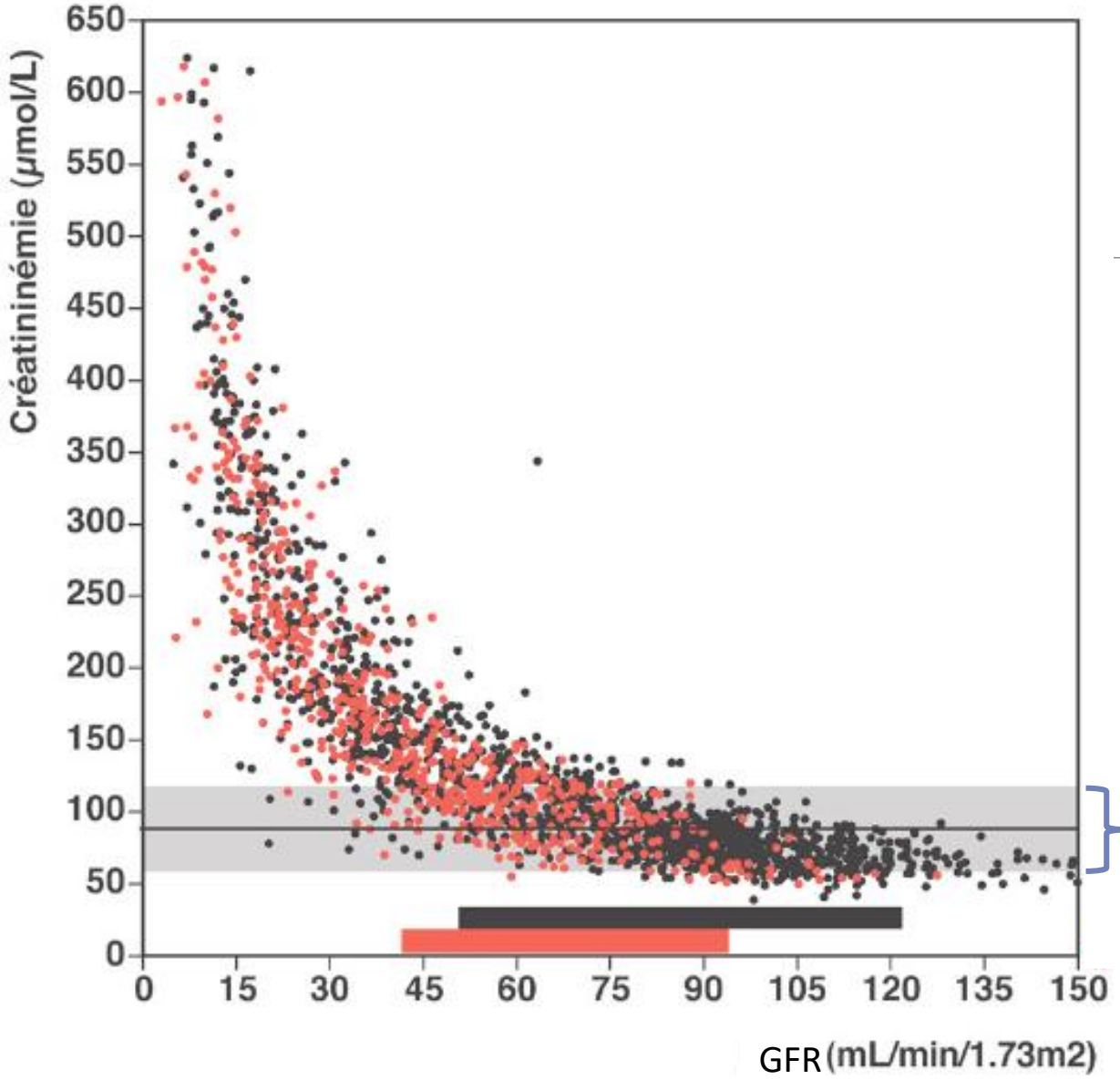
…but the most important is to know its limitations

Physiological limitations

Analytical limitations

“Mathematical” limitations

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



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

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

S. Creatinine lab normality range

With the kind permission of Marc Froissart

Serum Creatinine

Exponential relationship between serum creatinine and GFR!!!

In a given patient,

if serum creatinine increased from 0.6 to 1.2 mg/dl

=> decrease in GFR of 50%

if serum creatinine increased from 2.0 to 3.0 mg/dl

=> decrease in GFR of 25%

Analytical limitations

Jaffe

Pseudochromogen: glucose, fructose, ascorbate, proteins, urate, acetoacetate, acetone, pyruvate => false positive

Bilirubins: false negative

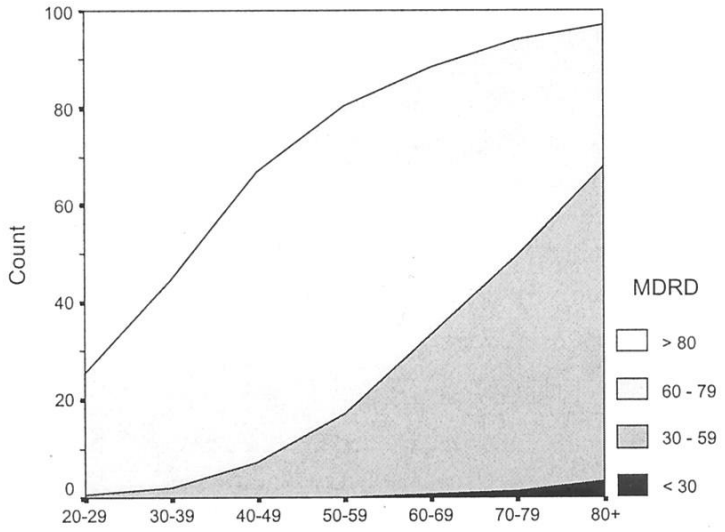
Analytical limitations

Different Jaffe-Enzymatic methods, different calibration by different manufacturers

Few (fewer) interferences with enzymatic methods

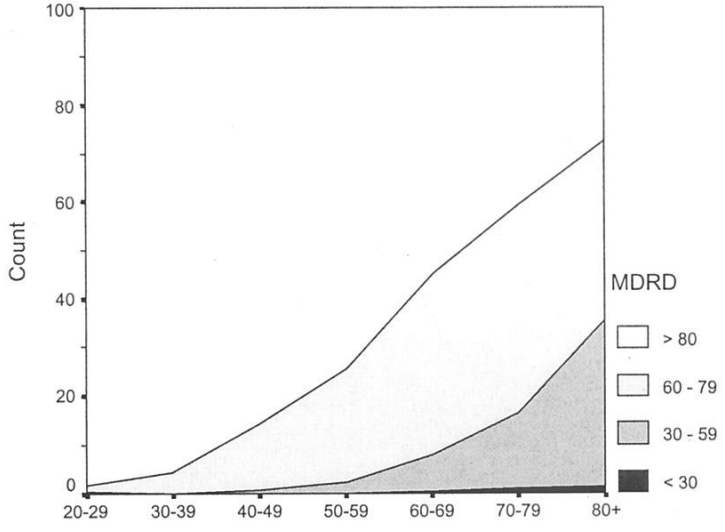
Analytical limitations: impact

UNCALIBRATED



N	3037	2827	2138	1422	1670	1241	916	Total 13251
≥ 80	74.6%	55.2%	33.0%	19.5%	11.7%	6.1%	2.8%	41.8%
60-79	24.8%	42.7%	59.7%	63.3%	54.9%	44.2%	29.4%	45.4%
30-59	0.6%	2.0%	7.2%	17.2%	32.7%	48.5%	64.6%	12.5%
< 30	<0.1%	<0.1%	<0.1%	<0.1%	0.7%	1.2%	3.2%	0.3%

CALIBRATED



3037	2827	2138	1422	1670	1241	916	Total 13251
98.3%	95.7%	85.7%	74.4%	55.1%	40.7%	27.5%	82.1%
1.5%	4.2%	13.5%	23.3%	36.9%	42.7%	37.0%	14.5%
0.2%	<0.1%	0.8%	2.4%	7.6%	15.7%	34.3%	3.2%
<0.1%	<0.1%	<0.1%	<0.1%	0.5%	0.9%	1.2%	0.2%

Coresh, J. et al. J Am Soc Nephrol 2002;13:2811-2816

Improvements in the last years…

Clinica Chimica Acta 412 (2011) 2070–2075

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

A multicentric evaluation of IDMS-traceable creatinine enzymatic assays

Laurence Piéroni [a], Pierre Delanaye [b,*], Anne Boutten [c], Anne-Sophie Bargnoux [d], Eric Rozet [e], Vincent Delatour [f], Marie-Christine Carlier [g], Anne-Marie Hanser [h], Etienne Cavalier [i], Marc Froissart [j], and Jean-Paul Cristol [d]
On behalf of the Société Française de Biologie Clinique [1]

[a] Biochimie Métabolique, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France
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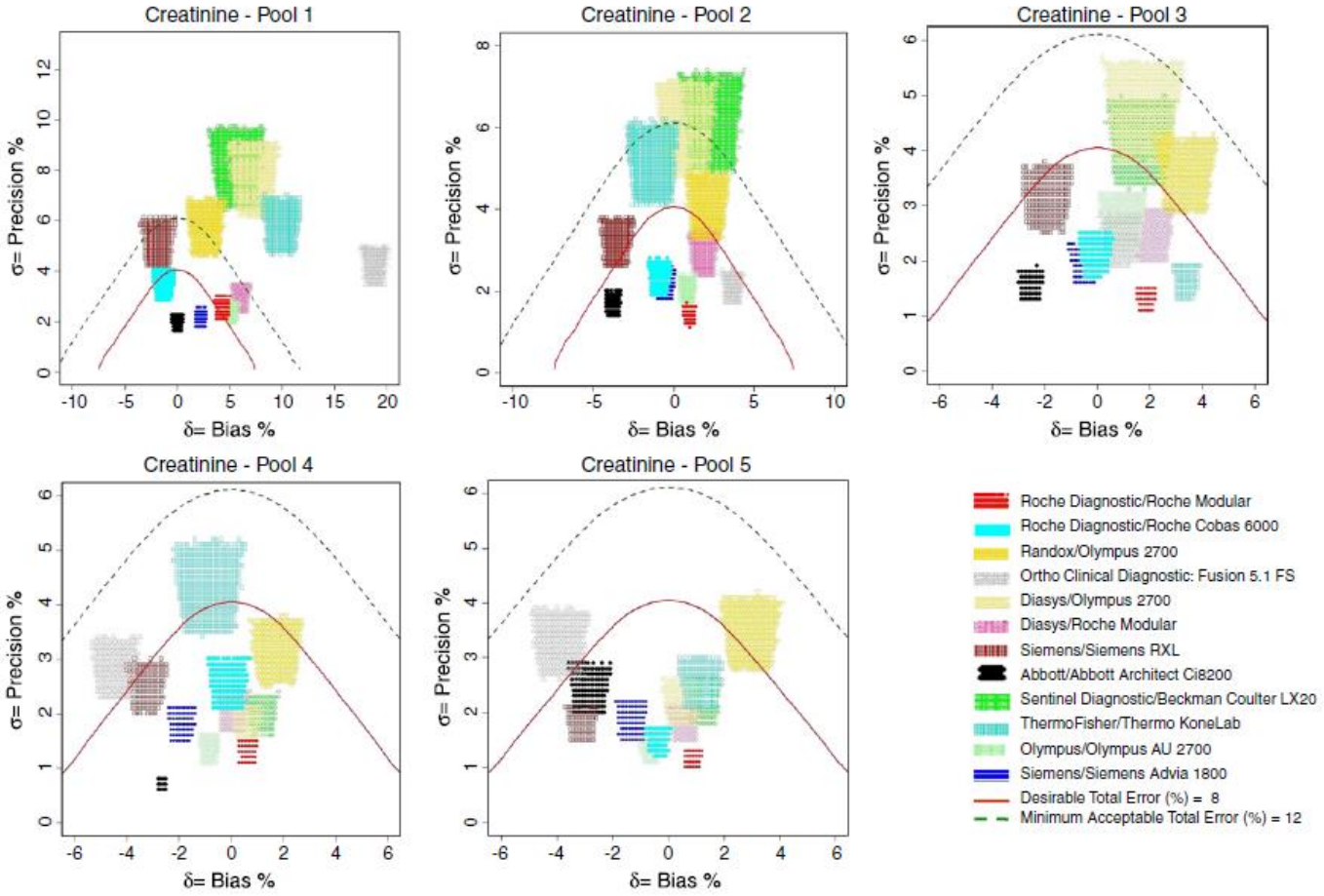
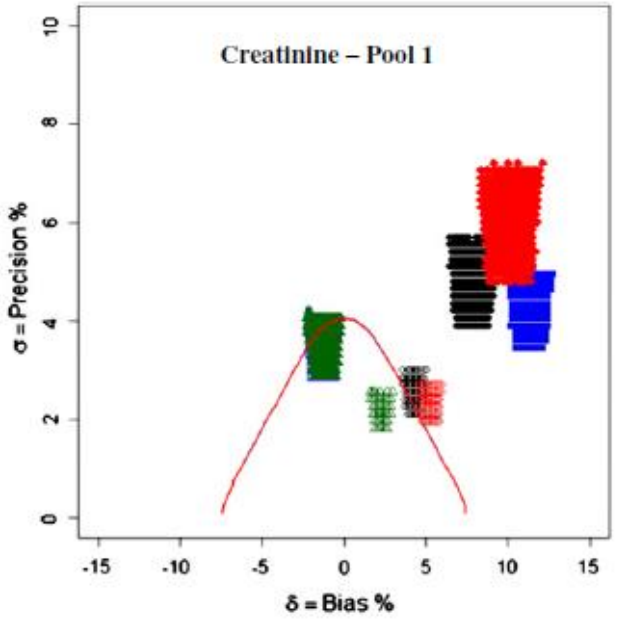
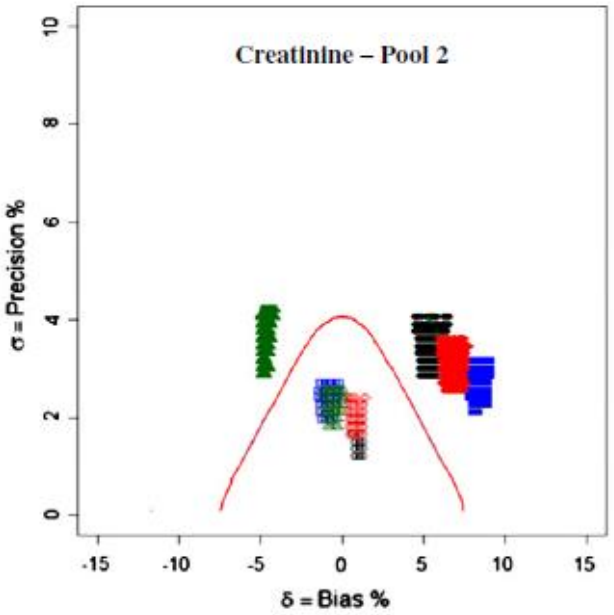
[h] Biochimie, Hospices civils, Colmar, France
[i] Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium
[j] Physiologie Rénale, Hôpital Européen Georges Pompidou, APHP, Paris, France

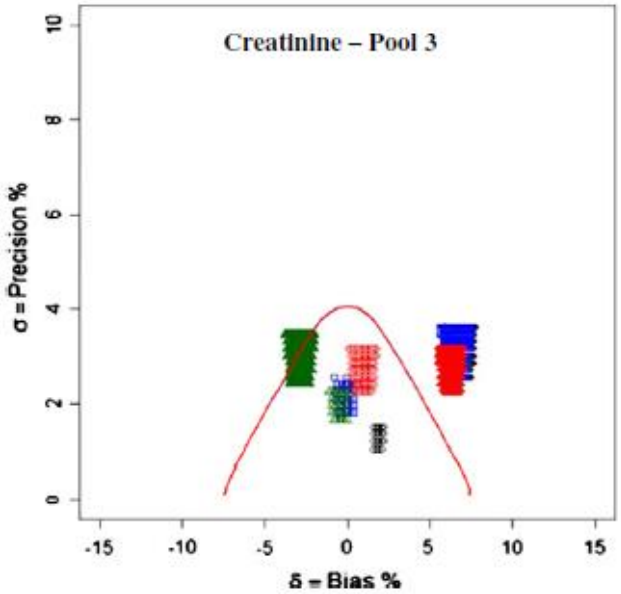
Results of GC-IDMS from LNE

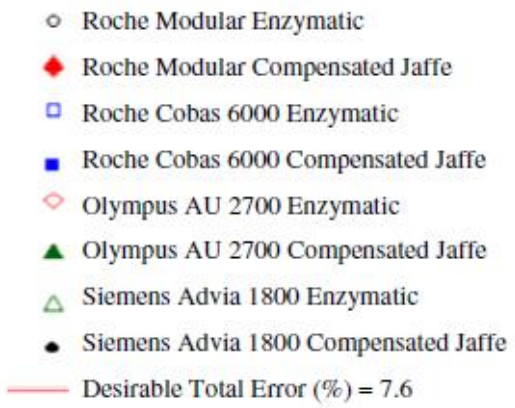
Pool 5: 174.5 +/-3.1 µmol/L
Pool 4: 149.7 +/-2.9 µmol/L
Pool 3: 97.9 +/-1.7 µmol/L
Pool 2: 74.4 +/-1.4 µmol/L
Pool 1 : 35.9 +/-0.9 µmol/L











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

Physiological limitations

Production (relatively) constant but muscular production => serum creatinine is dependent of muscualr mass, not only GFR

- gender
- age
- ethnicity
- Muscular mass(creatine)

Extra-renal production (bacterial)

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

Physiological limitations

Tubular secretion of creatinine

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

Drugs interaction with creatinine

- Tubular secretion inhibition

  cimetidine, trimethoprim, dolutegravir
- fibrates
- « high concentrations » interactions

  acetylcystein, dobutamin, lidocain, ascorbate

Creatinine: to the trash?

Very cheap (0.04€ /Jaffe)

Good specificty

Good analytical CV

Important to favor for enzymatic methods

Creatinine clearance

Not recommended by any guidelines

Creatinine tubular secretion

Lack of precision:

errors in urine collection

22 to 27% for « trained » patients
50 to 70 % for others

large intra-individual variability for creatinine excretion

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

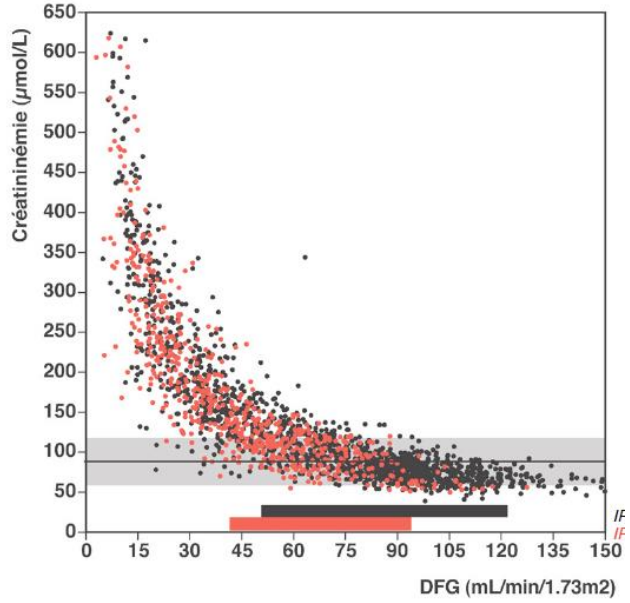
Creatinine-based equations

Why such equations?

Conceptualize the hyperbolic association between creatinine and GFR?

Interpreting the result of creatinine by gender, age, ethnicity?

Decrease the IC (?)



Bjornsson	men : (27-0.173×age)×weight×0.7/Cr women : (25-0.175×age)×weight×0.7/Cr
Davis	(140-age)/ Cr×(0.85 if woman)
Edwards	men : 94.3/Cr-1.8 women : 69.9/Cr+2.2
Gates	men : $89.4\times Cr^{-1.2}+(55-age)\times 0.447\times Cr^{-1.1}$ women : $60\times Cr^{-1.1}+(56-age)\times 0.3\times Cr^{-1.1}$
Hull	(145-age-3)/ Cr×(0.85 if woman)
Jelliffe	98-(0.8×(age-20))/Cr×(0.9 if woman)
Mawer	men :weight×(29.3-(0.203×age))×(1-0.03×Cr)/(14.4×Cr)×(70/weight) women :weight×(25.3-(0.175×age))×(1-0.03×Cr)/(14.4×Cr)×(70/weight)
Nankivell	$6700/(Cr\times 88.4)+weight/4-urea/2-(100/height^2)+35$ $6700/(Cr\times 88.4)+weight/4-urea/2-(100/height^2)+25$
Walser	men :$7.57/(Cr\times 0.0884)^{-1}-0.103\times age+0.096\times weight-6.66$ women :$6.05/(Cr\times 0.0884)^{-1}-0.08\times age+0.08\times weight-4.81$
Mayo	$\exp(1.911+5.249/Cr-2.114/Cr^2-0.00686\times age-0.205$ if woman)
Salazar	men : $((137-age)\times 0.285\times weight+(12.1\times height^2))/(51\times Cr)$ women : $((140-age)\times 0.285\times weight+(12.1\times height^2))/(60\times Cr)$

Which one?

Cockcroft

MDRD

CKD-EPI

Others

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

Cockcroft and Gault

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

4-Variable MDRD study equation (IDMS traceable)

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

Cockcroft Vs MDRD Vs CKD-EPI

	Cockcroft	MDRD	CKD-EPI
Population	Canada 1976	USA 1999	« International » 2009
N	249	1628	5504+2750+3896
Mean GFR	73	40	68
GFR	Creatinine clearance	Iothalamate	Diverse
Assay	« Jaffe »	Jaffe calibrated	Jaffe calibrated
% women	4	40	43-45%
% black	0 (?)	12	10-32%
Mean age	18-92	51	47-50
Mean weight	72	79.6	79-82
BSA indexation	No	Yes	Yes
Internal Validation	No	Yes	Yes

Cockcroft DW, Nephron, 1976, 16, p31
Levey AS, Ann Intern Med, 1999, 130, p461
Levey AS, Ann Intern Med, 2009, p604

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.

CLINICAL EPIDEMIOLOGY www.jasn.org

Evaluation of the Modification of Diet in Renal Disease Study Equation in a Large Diverse Population

Lesley A. Stevens,* Josef Coresh,† Harold I. Feldman,‡ Tom Greene,§ James P. Lash,‖ Robert G. Nelson,¶ Mahboob Rahman,** Amy E. Deysher,* Yaping (Lucy) Zhang,* Christopher H. Schmid,* and Andrew S. Levey*

*Tufts-New England Medical Center, Boston, Massachusetts; †Johns Hopkins University, Baltimore, Maryland; ‡University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; §University of Utah, Salt Lake City, Utah; ‖University of Illinois at Chicago, Chicago, Illinois; ¶National Institutes of Health, Phoenix, Arizona; and **Case Western Reserve University, Cleveland, Ohio

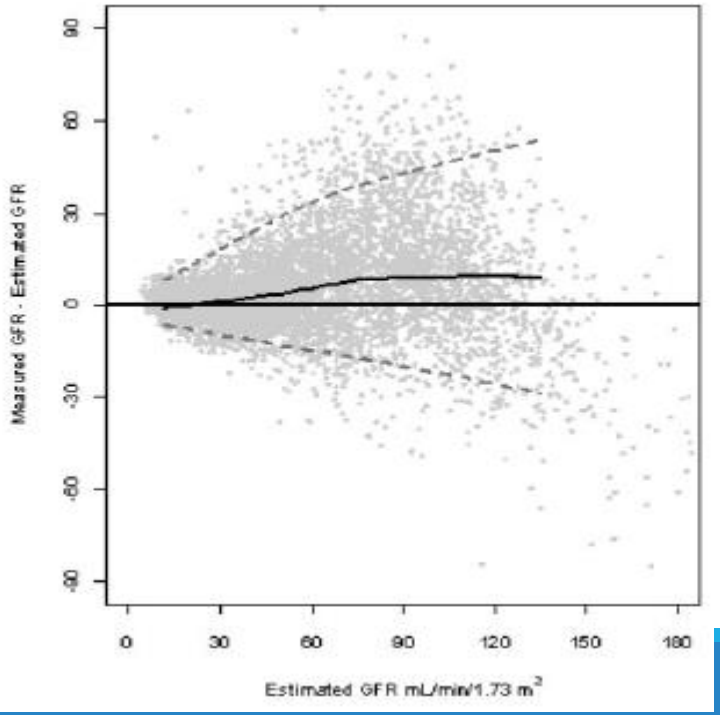
J Am Soc Nephrol 18: 2749–2757, 2007.

- CKD-EPI
- Urinary clearance of iothalamate in at least 250 subjects
- 5504 subjects (2874 with GFR<60)
- Creatinine calibrated (different ways)

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

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

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



MDRD: the strengths

Excellent accuracy, bias, precision in stage 3-4 CKD

Best accuracy observed: 80-85%

Better than Cockcroft especially in precision

MDRD: the limitations

- MDRD more bias (absolute) and less precision in high GFR
- Non negligible proportion of subjects with stage 2 classified as stage 3 CKD

MDRD: limitations = creatinine analytical limitations

CRITICAL DIFFERENCE = f(CVa, CVi)

= 19% (Jaffe)

Male, Caucasian, 60 y:

Creat = 1.00 mg/dL

≈ GFR_{MDRD}=76 ml/min/1.73m²

Creatinine= 0.81 mg/dL

GFR_{MDRD}= 97 ml/min/1,73m²

Creatinine= 1.19 mg/dL

GFR_{MDRD}= 62 ml/min/1,73m²

Kuster N, Clinica Chimica Acta, 2014, 428C, 89

Delanaye P, J Nephrol, 2014, 27, 467

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 (less impact)
- Median GFR in the development = 68 mL/min/1.73 m^2

Figure. Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.

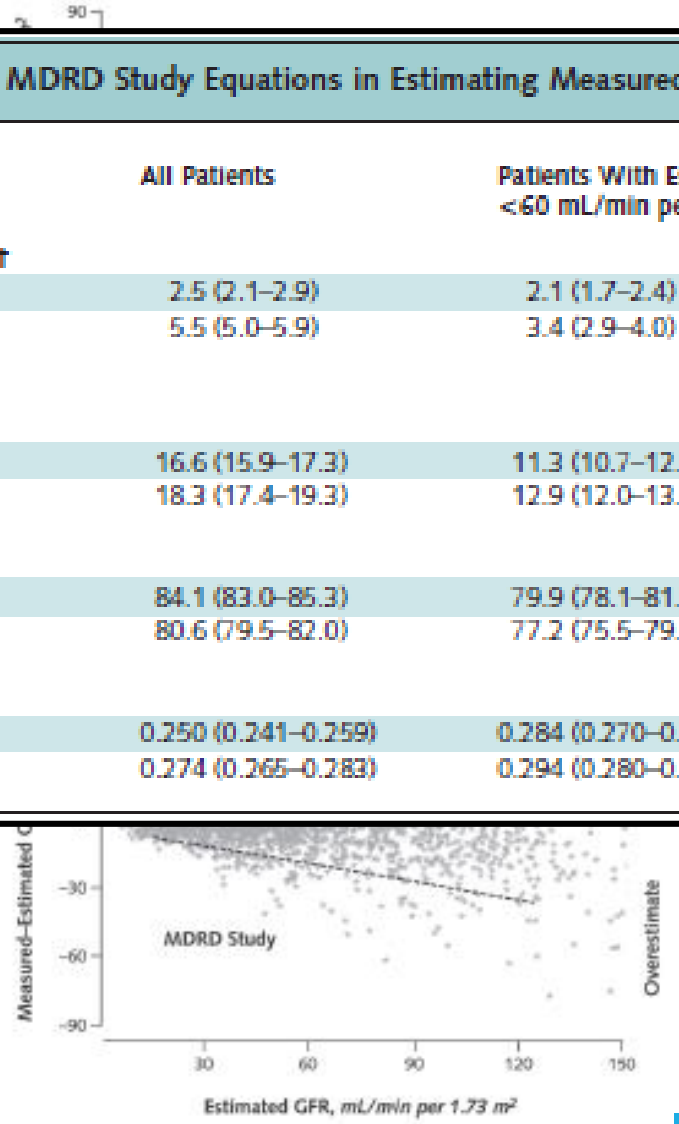


Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

Variable and Equation	All Patients	Patients With Estimated GFR <60 mL/min per 1.73 m²	Patients With Estimated GFR ≥60 mL/min per 1.73 m²
Median difference (95% CI), *mL/min per 1.73 m²*†			
CKD-EPI	2.5 (2.1–2.9)	2.1 (1.7–2.4)	3.5 (2.6–4.5)
MDRD Study	5.5 (5.0–5.9)	3.4 (2.9–4.0)	10.6 (9.8–11.3)
Interquartile range for differences (95% CI), *mL/min per 1.73 m²*‡			
CKD-EPI	16.6 (15.9–17.3)	11.3 (10.7–12.1)	24.2 (22.8–25.3)
MDRD Study	18.3 (17.4–19.3)	12.9 (12.0–13.6)	25.7 (24.4–27.1)
P_{30} (95% CI), %§			
CKD-EPI	84.1 (83.0–85.3)	79.9 (78.1–81.7)	88.3 (86.9–89.7)
MDRD Study	80.6 (79.5–82.0)	77.2 (75.5–79.0)	84.7 (83.0–86.3)
Root mean square error (95% CI)			
CKD-EPI	0.250 (0.241–0.259)	0.284 (0.270–0.298)	0.213 (0.203–0.223)
MDRD Study	0.274 (0.265–0.283)	0.294 (0.280–0.308)	0.248 (0.238–0.258)

Discussion:
MDRD or CKD-EPI ?

Lower CKD prevalence in epidemiological studies

Better prediction of CVD => better at the population level

Better bias in GFR >60 (90?) ml/min/1.73m² but not better precision

=> not better at the individual level

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

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)

Nephrol Dial Transplant (2019) 34: 287–294
doi: 10.1093/ndt/gfy086
Advance Access publication 11 May 2018

Chronic kidney disease staging with cystatin C or creatinine-based formulas: flipping the coin

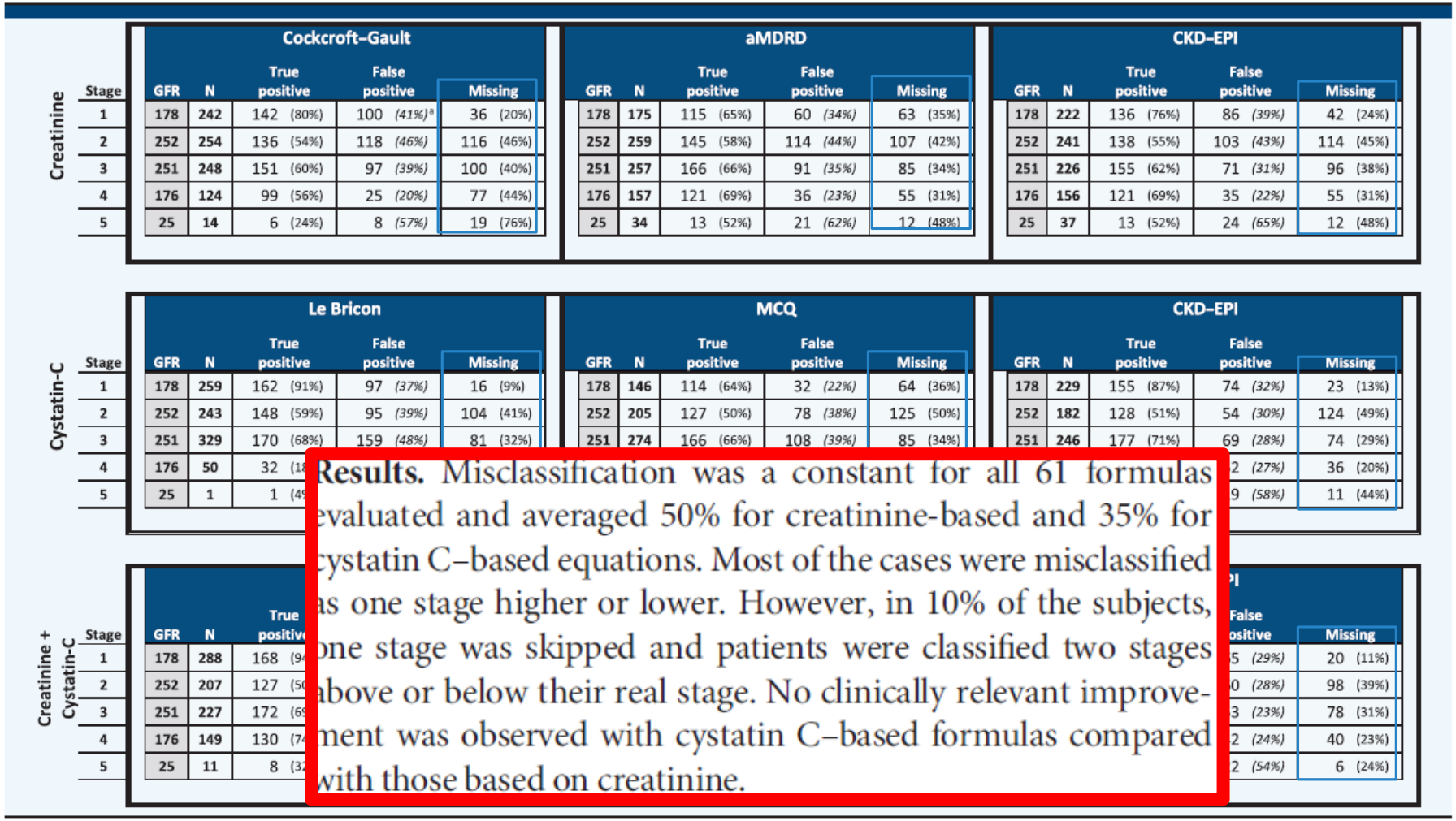
Sergio Luis-Lima[1], Beatriz Escamilla-Cabrera[2], Natalia Negrín-Mena[1], Sara Estupiñán[2], Patricia Delgado-Mallén[2], Domingo Marrero-Miranda[2], Ana González-Rinne[2], Rosa Miquel-Rodríguez[2], María Ángeles Cobo-Caso[2], Manuel Hernández-Guerra[3], Juana Oramas[4], Norberto Batista[4], Ana Aldea-Perona[1], Pablo Jorge-Pérez[5], Carlos González-Alayón[3], Miguel Moreno-Sanfiel[3], Juan Antonio González-Rodríguez[6], Laura Henríquez[7], Raquel Alonso-Pescoso[7], Laura Díaz-Martín[1], Federico González-Rinne[1], Bernardo Alio Lavín-Gómez[8], Judith Galindo-Hernández[7], Macarena Sánchez-Gallego[7], Alejandra González-Delgado[9], Alejandro Jiménez-Sosa[1], Armando Torres[2,10] and Esteban Porrini[10]

N=882

Clairance plasmatique d'iohexol

4-174 mL/min/1.73m²

Table 2. Classification of patients in CKD stages by a representative group of nine creatinine and/or cystatin C–based formulas



Creatinine

Stage	GFR	N	Cockcroft–Gault True positive	Cockcroft–Gault False positive	Cockcroft–Gault Missing	aMDRD GFR	aMDRD N	aMDRD True positive	aMDRD False positive	aMDRD Missing	CKD–EPI GFR	CKD–EPI N	CKD–EPI True positive	CKD–EPI False positive	CKD–EPI Missing
1	178	242	142 (80%)	100 (41%)[a]	36 (20%)	178	175	115 (65%)	60 (34%)	63 (35%)	178	222	136 (76%)	86 (39%)	42 (24%)
2	252	254	136 (54%)	118 (46%)	116 (46%)	252	259	145 (58%)	114 (44%)	107 (42%)	252	241	138 (55%)	103 (43%)	114 (45%)
3	251	248	151 (60%)	97 (39%)	100 (40%)	251	257	166 (66%)	91 (35%)	85 (34%)	251	226	155 (62%)	71 (31%)	96 (38%)
4	176	124	99 (56%)	25 (20%)	77 (44%)	176	157	121 (69%)	36 (23%)	55 (31%)	176	156	121 (69%)	35 (22%)	55 (31%)
5	25	14	6 (24%)	8 (57%)	19 (76%)	25	34	13 (52%)	21 (62%)	12 (48%)	25	37	13 (52%)	24 (65%)	12 (48%)

Cystatin-C

Stage	GFR	N	Le Bricon True positive	Le Bricon False positive	Le Bricon Missing	MCQ GFR	MCQ N	MCQ True positive	MCQ False positive	MCQ Missing	CKD–EPI GFR	CKD–EPI N	CKD–EPI True positive	CKD–EPI False positive	CKD–EPI Missing
1	178	259	162 (91%)	97 (37%)	16 (9%)	178	146	114 (64%)	32 (22%)	64 (36%)	178	229	155 (87%)	74 (32%)	23 (13%)
2	252	243	148 (59%)	95 (39%)	104 (41%)	252	205	127 (50%)	78 (38%)	125 (50%)	252	182	128 (51%)	54 (30%)	124 (49%)
3	251	329	170 (68%)	159 (48%)	81 (32%)	251	274	166 (66%)	108 (39%)	85 (34%)	251	246	177 (71%)	69 (28%)	74 (29%)
4	176	50	32 (18											2 (27%)	36 (20%)
5	25	1	1 (4											9 (58%)	11 (44%)

Creatinine + Cystatin-C

Stage	GFR	N	True positiv											False ositive	Missing
1	178	288	168 (9											5 (29%)	20 (11%)
2	252	207	127 (5											0 (28%)	98 (39%)
3	251	227	172 (6											3 (23%)	78 (31%)
4	176	149	130 (7											2 (24%)	40 (23%)
5	25	11	8 (3											2 (54%)	6 (24%)

Results. Misclassification was a constant for all 61 formulas evaluated and averaged 50% for creatinine-based and 35% for cystatin C–based equations. Most of the cases were misclassified as one stage higher or lower. However, in 10% of the subjects, one stage was skipped and patients were classified two stages above or below their real stage. No clinically relevant improvement was observed with cystatin C–based formulas compared with those based on creatinine.

'True positives cases' represent the subjects that were corretly classified in each CKD stage by eGFR. 'False positives cases' represent the patients who were classified in one CKD stage based on eGFR when actually belonging to a different stage. 'Missing cases' represent the cases that were not classified in the corresponding CKD stage.

[a]The percentage of false positive cases refers to the number of cases defined in each CKD stage by mGFR (grey column). The percentage of true positive and missing cases refers to the number of cases defined in each CKD stage by eGFR.

REVIEWS

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

Performance of equations in specific populations

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

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

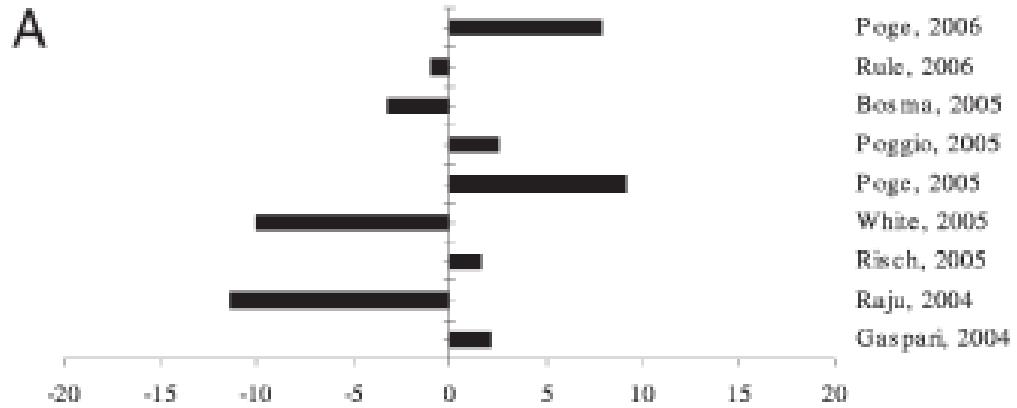


Table 3. Accuracy of Prediction Equations

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

MDRD – CKD-EPI: nothing else?

The Bis Equation

The Lund-Malmö equation

The FAS equation

Other biomarkers: cystatin C

Schaeffner, Ann intern Med, 2012, 157, 471
Bjork, Scand J Urol Nephrol, 2012, 46, 212
Pottel H, submitted
Seronie-Vivien, CCLM, 2008,

Ulf Nyman*, Anders Grubb, Anders Larsson, Lars-Olof Hansson, Mats Flodin, Gunnar Nordin, Veronica Lindström and Jonas Björk

The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population

Clin Chem Lab Med 2014, 52(6), 815-824

Revised Lund-Malmö Study equation (LM Revised) [34]

$$_{e}X-0.0158\times Age+0.438\times \ln(Age)$$

Female	pCr<150 µmol/L:	$X=2.50+0.0121\times(150-pCr)$
Female	pCr≥150 µmol/L:	$X=2.50-0.926\times\ln(pCr/150)$
Male	pCr<180 µmol/L:	$X=2.56+0.00968\times(180-pCr)$
Male	pCr≥180 µmol/L:	$X=2.56-0.926\times\ln(pCr/180)$

Lund-Malmo

n=3495 (by 2847 subkects), iohexol, IDMS serum creatinine

Mean GFR = 60 mL/min/1,73 m²

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 calibrated creatinine

n=11,251 development and internal validation

n=8,378 external validation

n=1,254 children (2 et 18 years)

7 + 6 cohorts

« Caucasians »

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:

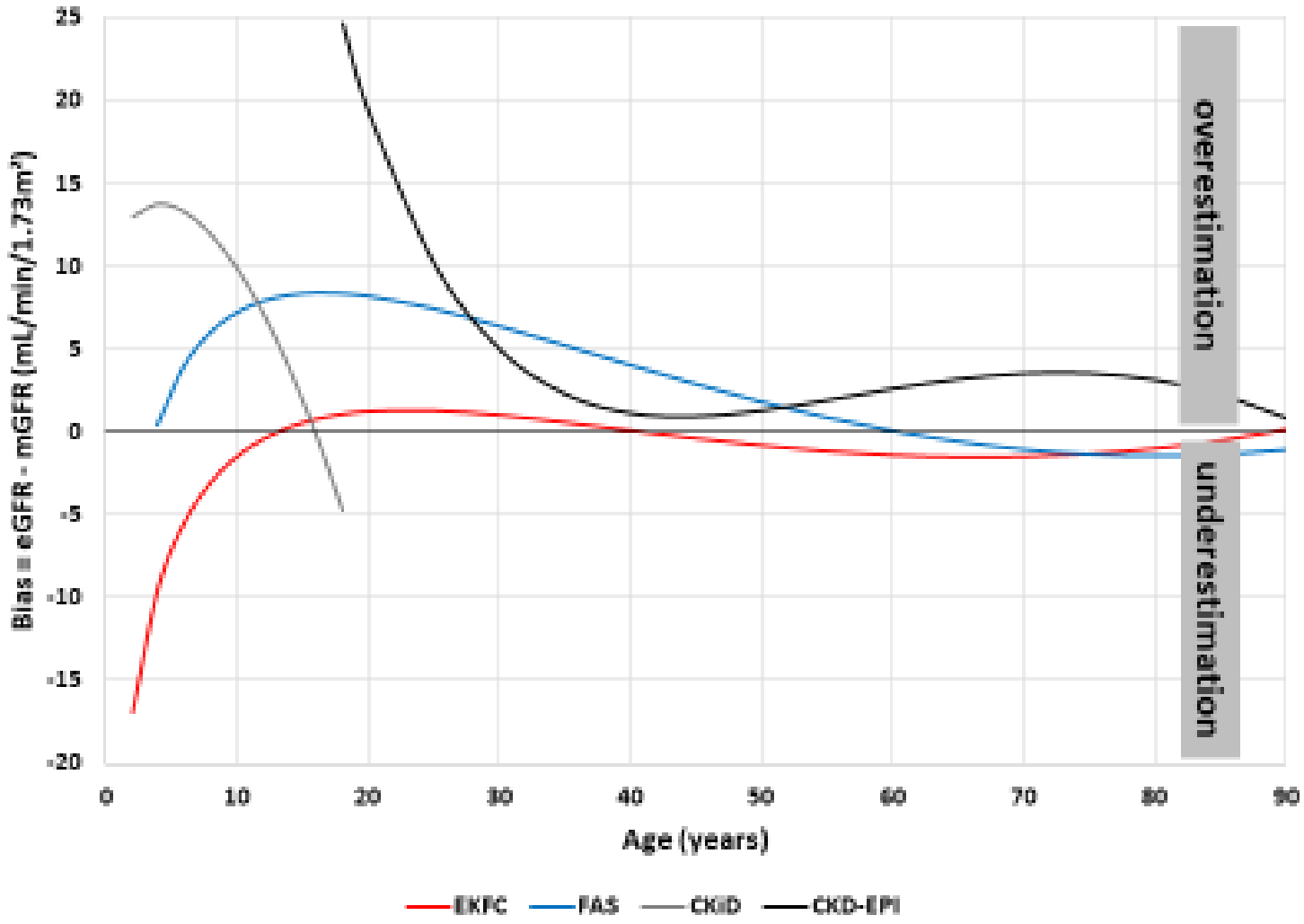
$$\ln(Q) = 3.080 + 0.177 \times Age - 0.223 \times \ln(Age) - 0.00596 \times Age^2 + 0.0000686 \times Age^3$$

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.

Age Group	Equation		
	EKFC	FAS	CKiD
Children (2 to <18 y)			
Median bias (95% CI), *mL/min/1.73 m²*			
All (*n* = 1254)	-1.2 (-2.7 to 0.0)	6.7 (4.8 to 8.1)	6.2 (4.6 to 7.7)
eGFR <75 mL/min/1.73 m² (*n* = 324)	-5.7 (-7.0 to -3.9)	-0.8 (-2.6 to 0.8)	-1.8 (-2.9 to -0.1)
eGFR ≥75 mL/min/1.73 m² (*n* = 930)	1.1 (-0.4 to 3.0)	10.8 (9.0 to 13.1)	11.2 (9.2 to 13.4)
Imprecision, SD (P25–P75)			
All (*n* = 1254)	27.8 (-14.9 to 11.0)	70.6 (-7.4 to 22.8)	56.6 (-7.7 to 23.6)
eGFR <75 mL/min/1.73 m² (*n* = 324)	20.3 (-18.1 to 2.3)	20.0 (-12.2 to 7.6)	18.2 (-10.2 to 7.2)
eGFR ≥75 mL/min/1.73 m² (*n* = 930)	29.6 (-14.4 to 14.3)	80.1 (-5.3 to 29.1)	63.7 (-6.5 to 30.9)
Accuracy P30 (95% CI), %			
All (*n* = 1254)	79.7 (77.4 to 81.9)	74.2 (71.7 to 76.6)	73.2 (70.8 to 75.7)
eGFR <75 mL/min/1.73 m² (*n* = 324)	73.8 (68.9 to 78.6)	77.8 (73.2 to 82.3)	80.2 (75.9 to 84.6)
eGFR ≥75 mL/min/1.73 m² (*n* = 930)	81.7 (79.2 to 84.2)	72.9 (70.0 to 75.8)	70.8 (67.8 to 73.7)


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

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www.kidney-international.org clinical investigation

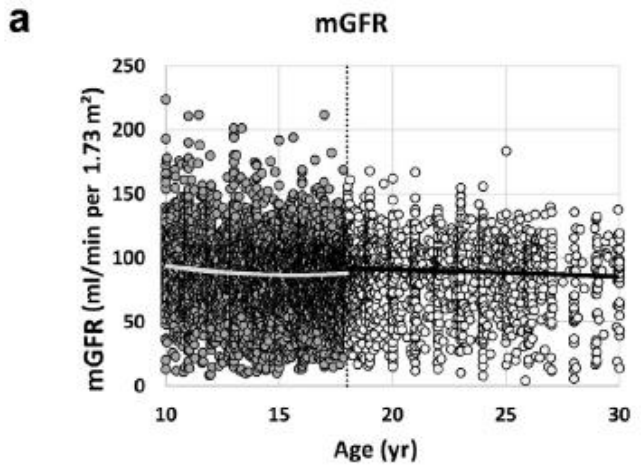
Estimating glomerular filtration rate at the transition from pediatric to adult care

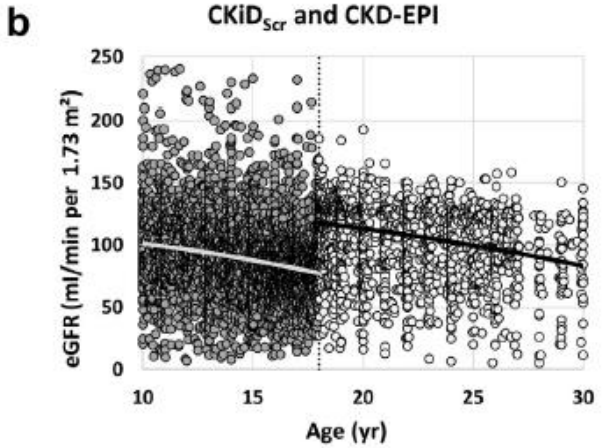
Hans Pottel[1,13], Jonas Björk[2,3,13], Arend Bökenkamp[4,13], Ulla Berg[5], Kajsa Åsling-Monemi[5], Luciano Selistre[6], Laurence Dubourg[7,13], Magnus Hansson[8], Karin Littmann[8], Ian Jones[9], Per Sjöström[9], Ulf Nyman[10,12,13] and Pierre Delanaye[11,12,13]

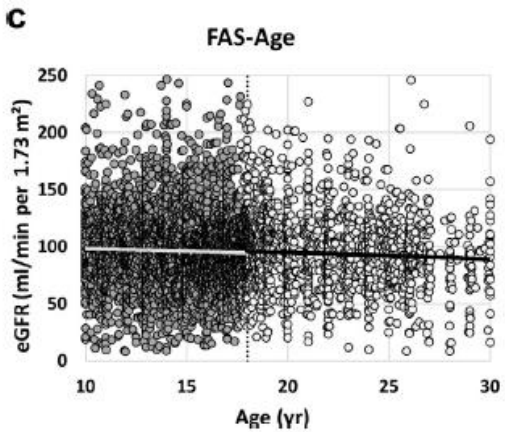
[1]Department of Public Health and Primary Care, Katholieke Universiteit Leuven Campus Kulak Kortrijk, Kortrijk, Belgium; [2]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden; [3]Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden; [4]Emma Children's Hospital, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [5]Department of Clinical Science, Intervention, and Technology, Division of Pediatrics, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden; [6]Mestrado em Ciências da Saúde—Universidade Caxias do Sul Foundation, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil; [7]Exploration Fonctionnelle Rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France; [8]Department of Laboratory Medicine, Division of Clinical Chemistry, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden; [9]Department of Laboratory Medicine, Örebro University Hospital, Örebro, Sweden; [10]Department of Translational Medicine, Division of Medical Radiology, Lund University, Malmö, Sweden; and [11]Nephrology-Dialysis-Transplantation, University of Liège, Centre Hospitalier Universitaire du Sart Tilman, Liège, Belgium

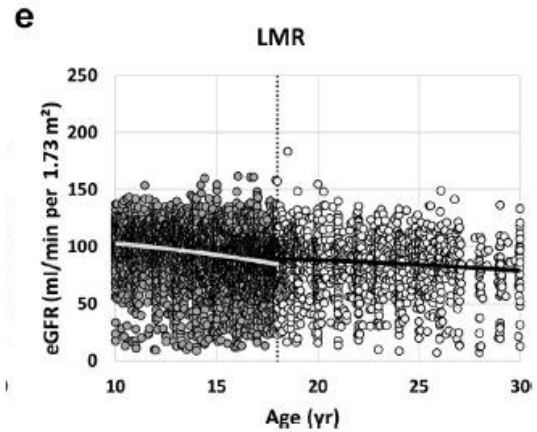
5764 children, adolescents and young adults

Median results


a
mGFR
mGFR (ml/min per 1.73 m²)
250
200
150
100
50
0
10
15
20
25
30
Age (yr)


b
CKiD$_{Scr}$ and CKD-EPI
eGFR (ml/min per 1.73 m²)
250
200
150
100
50
0
10
15
20
25
30
Age (yr)


c
FAS-Age
eGFR (ml/min per 1.73 m²)
250
200
150
100
50
0
10
15
20
25
30
Age (yr)


e
LMR
eGFR (ml/min per 1.73 m²)
250
200
150
100
50
0
10
15
20
25
30
Age (yr)

Ethnic, race factors in Africa and Europe

NO

RESEARCH LETTER

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

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

Néphrologie & Thérapeutique 12 (2016) 454–459

Article original

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

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

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

PLOS ONE

RESEARCH ARTICLE

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

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

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* justinebuk@yahoo.fr

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

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]

[1]Renal Unit, Department of Internal Medicine, Kinshasa University Hospital, University of Kinshasa, Kinshasa, Democratic Republic of Congo; [2]Département de Biochimie, UFR Sciences Pharmaceutiques et Biologiques, Université Felix Houphouet Boigny, Abidjan, Ivory Coast; [3]Département de Néphrologie, UFR Sciences Médicales, Université Felix Houphouet Boigny, Abidjan, Ivory Coast; [4]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium; [5]Division of Clinical Chemistry, CHU Sart Tilman (ULg CHU), University of Liège, Liège, Belgium; and [6]Division of Nephrology-Dialysis-Transplantation, CHU Sart Tilman (ULg CHU), University of Liège, Liège, Belgium

N=494

Iohexol

Standardized creatinine

Table 3 | Performance of equations in the whole cohort (N = 494)

Equation	Absolute bias (95% CI)	Absolute SD	Accuracy within 30% (95% CI)	Lin's CCC (95% CI)
MDRD	−7.8 (−9.5 to −6.1)	19.4	76.1 (72.3 to 79.9)	0.73 (0.67 to 0.78)
MDRD ef	8.2 (6.1 to 10.2)	23.3	73.3 (69.4 to 77.2)	0.70 (0.61 to 0.77)
CKD-EPI	0.0 (−1.6 to 1.6)	18.1	77.7 (74.1 to 81.4)	0.81 (0.76 to 0.84)
CKD-EPI ef	13.3 (11.4 to 15.2)	21.3	64.6 (60.3 to 68.8)	0.71 (0.66 to 0.76)

The « racial » factor in creatinine-based equations

Is « race » the good word?

Is it clinical science or sociology?

It is highy debated in US…

EDITORIAL

Removal of Race From Estimates of Kidney Function
First, Do No Harm

Keith C. Norris, MD; Nwamaka D. Eneanya, MD, MPH; L. Ebony Boulware, MD, MPH

Clinical Chemistry 00:0
1-2 (2021)

PERSPECTIVE www.jasn.org

Separate and Unequal: Race-Based Algorithms and Implications for Nephrology

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JAMA Network Open

Invited Commentary | Nephrology

Systemic Kidney Transplant Inequities for Black Individuals: Examining the Contribution of Racialized Kidney Function Estimating Equations

L. Ebony Boulware, MD, MPH; Tanjala S. Purnell, PhD, MPH; Dinushika Mohottige, MD, MPH

Uncertainty in Estimated Glomerular Filtration Rate Is Much Larger than the Race Adjustment Term

To the Editor:

W. Greg Miller*[a]

[a]Department of Pathology, Virginia Commonwealth University, Richmond, VA, USA

JAMA Network Open™

Original Investigation | Nephrology

Association of the Estimated Glomerular Filtration Rate With vs Without a Coefficient for Race With Time to Eligibility for Kidney Transplant

Leila R. Zelnick, PhD; Nicolae Leca, MD; Bessie Young, MD, MPH; Nisha Bansal, MD, MAS

Letters

RESEARCH LETTER

Clinical Implications of Removing Race From Estimates of Kidney Function

Over the past year, medical centers across the US have removed race adjustment from estimated glomerular filtration rate from serum creatinine (eGFRcr), with many now reporting the "White/Other" value for all patients. These changes follow calls to reconsider the use of race in estimating kidney function[1] and in medicine broadly.[2] We analyzed potential changes in recommended care using eGFRcr with and without race among Black individuals in the US (individuals who are not Black would not be affected).

Supplemental content

VIEWPOINT

Reconsidering the Consequences of Using Race to Estimate Kidney Function

Nwamaka Denise Eneanya, MD, MPH
Renal-Electrolyte and Hypertension Division, Perelman School of Medicine, University of Pennsylvania, Philadelphia; and Palliative and Advanced Illness Research Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Estimated GFR equations are distinct because they assert that existing organ function is different between individuals who are identical except for race.

Fri

REVIEW

The « race » correction in estimating glomerular filtration rate: an European point of view

Pierre Delanaye[a,b], *Christophe Mariat*[c], *Etienne Cavalier*[d], *Richard J. Glassock*[e], *François Gemenne*[f,g], *and Hans Pottel*[h]

Curr Opin Nephrol Hypertens 2021, 29:000–000
DOI:10.1097/MNH.0000000000000739

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*

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

Table 3. Use of the CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012), and CKD-EPI Creatinine–Cystatin C Equations (2012) in the External-Validation Data Set Comprising 1119 Participants.*

Variable	Estimated GFR			
	Overall	<60	60–89	≥90
	ml/min/1.73 m² of body-surface area			
Bias — median difference (95% CI)				
Creatinine equation	3.7 (2.8 to 4.6)	1.8 (1.1 to 2.5)	6.6 (3.5 to 9.2)	11.1 (8.0 to 12.5)
Cystatin C equation	3.4 (2.3 to 4.4)	0.4 (−0.5 to 1.4)	6.0 (4.6 to 8.5)	8.5 (6.5 to 11.2)
Creatinine–cystatin C equation	3.9 (3.2 to 4.5)	1.3 (0.5 to 1.8)	6.9 (5.0 to 8.9)	10.6 (9.5 to 12.7)
Average of creatinine and cystatin C†	3.5 (2.8 to 4.1)	0.4 (−0.3 to 0.8)	6.5 (4.6 to 8.4)	11.9 (9.9 to 13.9)
Precision — IQR of the difference (95% CI)				
Creatinine equation	15.4 (14.3 to 16.5)	10.0 (8.9 to 11.0)	19.6 (17.3 to 23.2)	25.0 (21.6 to 28.1)
Cystatin C equation	16.4 (14.8 to 17.8)	11.0 (10.0 to 12.4)	19.6 (16.1 to 23.1)	22.6 (18.8 to 26.3)
Creatinine–cystatin C equation	13.4 (12.3 to 14.5)	8.1 (7.3 to 9.1)	15.9 (13.9 to 18.1)	18.8 (16.8 to 22.5)
Average of creatinine and cystatin C equations†	13.9 (12.9 to 14.7)	7.9 (7.1 to 9.0)	15.8 (13.9 to 17.7)	18.6 (16.1 to 22.2)
Accuracy — % (95% CI)‡				
$1-P_{30}$				
Creatinine equation	12.8 (10.9 to 14.7)	16.6 (13.6 to 19.7)	10.2 (6.4 to 14.2)	7.8 (5.1 to 11.0)
Cystatin C equation	14.1 (12.2 to 16.2)	21.4 (18.2 to 24.9)	12.7 (8.5 to 17.4)	2.2 (0.6 to 3.9)
Creatinine–cystatin C equation	8.5 (7.0 to 10.2)	13.3 (10.7 to 16.1)	5.3 (2.7 to 8.2)	2.3 (0.9 to 4.2)
Average of creatinine and cystatin C equations†	8.2 (6.7 to 9.9)	12.1 (9.5 to 14.8)	6.4 (3.6 to 9.7)	2.9 (1.3 to 4.9)
$1-P_{20}$				
Creatinine equation	32.9 (30.1 to 35.7)	37.2 (33.1 to 41.2)	31.1 (25.1 to 37.4)	26.5 (21.7 to 31.4)
Cystatin C equation	33.0 (30.3 to 35.7)	42.1 (38.2 to 46.1)	29.3 (23.6 to 35.4)	19.4 (15.4 to 23.7)
Creatinine–cystatin C equation	22.8 (20.4 to 25.2)	28.6 (25.1 to 32.4)	17.8 (13.3 to 22.9)	16.2 (12.4 to 20.5)
Average of creatinine and cystatin C equations†	23.7 (21.3 to 26.1)	29.1 (25.7 to 32.8)	17.6 (13.2 to 22.4)	18.8 (14.6 to 23.2)

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

CKD-EPI:

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

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

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

Cystatin C

+ for Combined, children

No race coefficient

“Cost-effectiveness?”

Some imprecision still persists at the individual level

Standardization is possible but still not fully achieved

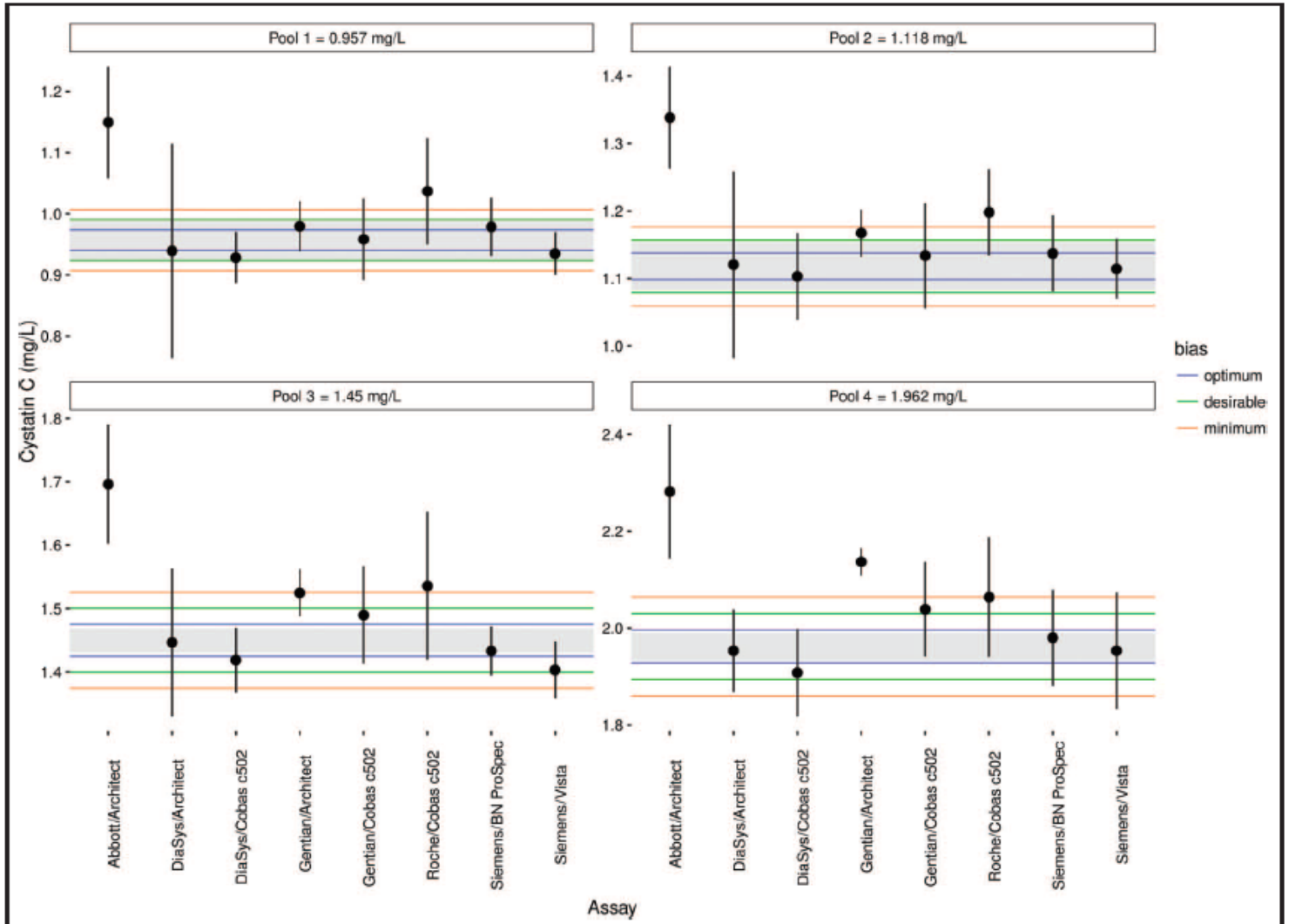


Fig. 1. Biases between the commercial assays and the IDMS target value for CysC.

The figure shows the reference material values and the areas of their uncertainty (grey zone), the mean (SD) of the results from the evaluated systems, and lines depicting the bias specifications (red, green, and blue lines correspond to the optimal, desirable, and minimum quality levels, respectively).

Bargnoux AS, Clin Chem, 2017, 63, p833

ACKD

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

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

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

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

ELSEVIER

American Journal of Kidney Diseases

Available online 7 December 2020

In Press, Corrected Proof

Original Investigations

A New Panel-Estimated GFR, Including β_2-Microglobulin and β-Trace Protein and Not Including Race, Developed in a Diverse Population

Lesley A. Inker [1], Sara J. Couture [1], Hocine Tighiouart [2, 3], Alison G. Abraham [4], Gerald J. Beck [5], Harold I. Feldman [7], Tom Greene [8], Vilmundur Gudnason [9, 10], Amy B. Karger [11], John H. Eckfeldt [11], Bertram L. Kasiske [13], Michael Mauer [12], Gerjan Navis [14], Emilio D. Poggio [6], Peter Rossing [15], Michael G. Shlipak [16], Andrew S. Levey [1], CKD-EPI GFR Collaborators

Show more

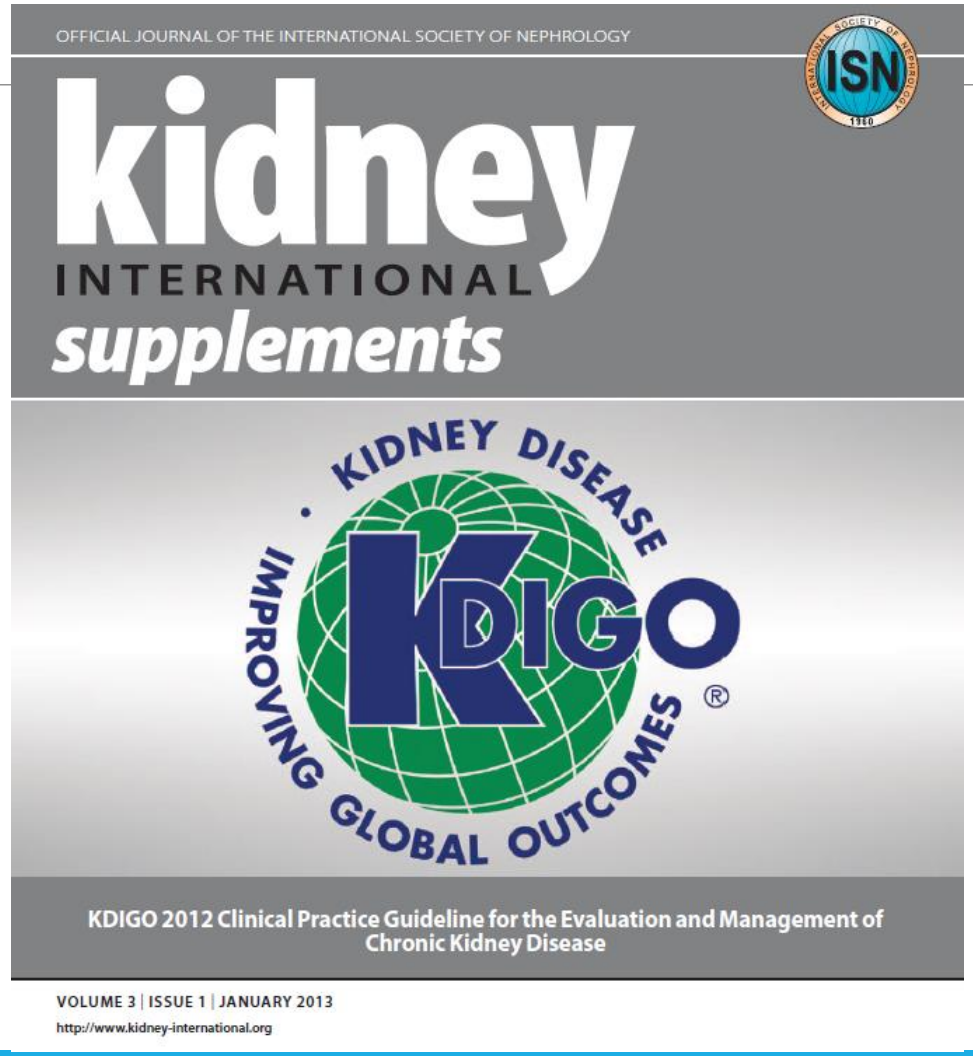
Biomarkers Panel: β-trace protein, β2-microglubuline, Cystatin C

Métabolomic?

Simple? Cost-effectiveness?

CKD diagnosis

International guidelines in Nephrology



Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73m²) 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			

Figure 9 | Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

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.

Must be confirmed at 3 months…

60 mL/min/1.73 m^2

Justification of this cut-off

Simplicity

Half of normal measured GFR but arbitrary (and maybe not correct)

Because GFR < 60 mL/min/1.73 m^2 is associated with a higher mortality risk

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Caroline S Fox, Kunihiro Matsushita, Mark Woodward, Henk J G Bilo, John Chalmers, Hiddo J Lambers Heerspink, Brian J Lee, Robert M Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A Vassalotti, Kazumasa Yamagishi, Josef Coresh, Paul E de Jong, Chi-Pang Wen, Robert G Nelson, for the Chronic Kidney Disease Prognosis Consortium

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis

Bakhtawar K Mahmoodi, Kunihiro Matsushita, Mark Woodward, Peter J Blankestijn, Massimo Cirillo, Takayoshi Ohkubo, Peter Rossing, Mark J Sarnak, Bénédicte Stengel, Kazumasa Yamagishi, Kentaro Yamashita, Luxia Zhang, Josef Coresh, Paul E de Jong, Brad C Astor, for the Chronic Kidney Disease Prognosis Consortium

ONLINE FIRST

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

BMJ 2013;346:f324 doi: 10.1136/bmj.f324 (Published 29 January 2013)

RESEARCH

Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis

Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data

*Kunihiro Matsushita, Shoshana H Ballew, Josef Coresh, Hisatomi Arima, Johan Ärnlöv, Massimo Cirillo, Natalie Ebert, Jade S Hiramoto, Heejin Kimm, Michael G Shlipak, Frank L J Visseren, Ron T Gansevoort, Csaba P Kovesdy, Varda Shalev, Mark Woodward, Florian Kronenberg, for the Chronic Kidney Disease Prognosis Consortium**

Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data

Kunihiro Matsushita, Josef Coresh, Yingying Sang, John Chalmers, Caroline Fox, Eliseo Guallar, Tazeen Jafar, Simerjot K Jassal, Gijs W D Landman, Paul Muntner, Paul Roderick, Toshimi Sairenchi, Ben Schöttker, Anoop Shankar, Michael Shlipak, Marcello Tonelli, Jonathan Townend, Arjan van Zuilen, Kazumasa Yamagishi, Kentaro Yamashita, Ron Gansevoort, Mark Sarnak, David G Warnock, Mark Woodward, Johan Ärnlöv,

http://www.kidney-international.org clinical investigation

Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar

Chi Pang Wen[1,2], Kunihiro Matsushita[3], Josef Coresh[3], Kunitoshi Iseki[4], Muhammad Islam[5], Ronit Katz[6], William McClellan[7], Carmen A. Peralta[8], HaiYan Wang[9], Dick de Zeeuw[10], Brad C. Astor[11,12], Ron T. Gansevoort[13], Andrew S. Levey[14], Adeera Levin[15] and for the Chronic Kidney Disease Prognosis Consortium

Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts

Marije van der Velde[1], Kunihiro Matsushita[2], Josef Coresh[2], Brad C. Astor[2], Mark Woodward[3], Andrew S. Levey[4], Paul E. de Jong[1], Ron T. Gansevoort[1] and the Chronic Kidney Disease Prognosis Consortium

Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts

Ron T. Gansevoort[1], Kunihiro Matsushita[2], Marije van der Velde[1], Brad C. Astor[2], Mark Woodward[3], Andrew S. Levey[4], Paul E. de Jong[1], Josef Coresh[2] and the Chronic Kidney Disease Prognosis Consortium

Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts

Brad C. Astor[1], Kunihiro Matsushita[1], Ron T. Gansevoort[2], Marije van der Velde[2], Mark Woodward[3], Andrew S. Levey[4], Paul E. de Jong[2], Josef Coresh[1] and the Chronic Kidney Disease Prognosis Consortium

GFR in Healthy Aging: an Individual Participant Data Meta-Analysis of Iohexol Clearance in European Population-Based Cohorts

Bjørn O. Eriksen,[1,2] Runolfur Palsson,[3,4] Natalie Ebert,[5] Toralf Melsom,[1,2] Markus van der Giet,[6] Vilmundur Gudnason,[4,7] Olafur S. Indridasson,[3] Lesley A. Inker,[8] Trond G. Jenssen,[1,9] Andrew S. Levey,[8] Marit D. Solbu,[1,2] Hocine Tighiouart,[10,11] and Elke Schaeffner[5]

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

J Am Soc Nephrol. 2020 Jul;31(7):1602-1615.

- RENIS, BIS, AGES
- 50-97 years
- Iohexol clearance
- N=3274 and 987 healthy

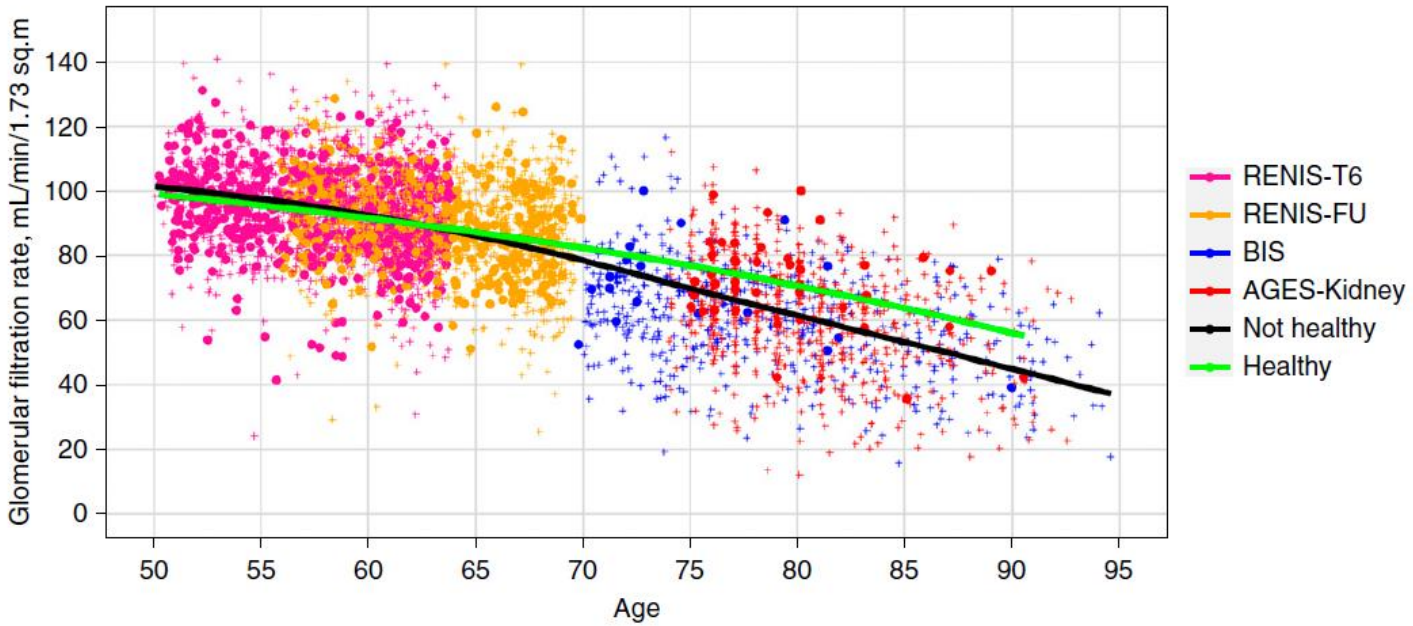


Figure 2. Unadjusted GFR according to cohort and health status. Body surface area–indexed GFR measured as plasma iohexol clearance and plotted against age in the RENIS, BIS, and AGES-Kidney cohorts (n=4209). The marker colors indicate cohort membership. Filled circles indicate measurements in persons who were healthy and crosses in persons who were unhealthy. Measurements for both the baseline (RENIS-T6) and the follow-up examinations (RENIS-FU) of the same persons in the RENIS cohort are shown. The red and green curves represent unadjusted locally estimated scatterplot smoothing fits to measurements in people who were unhealthy and healthy, respectively.

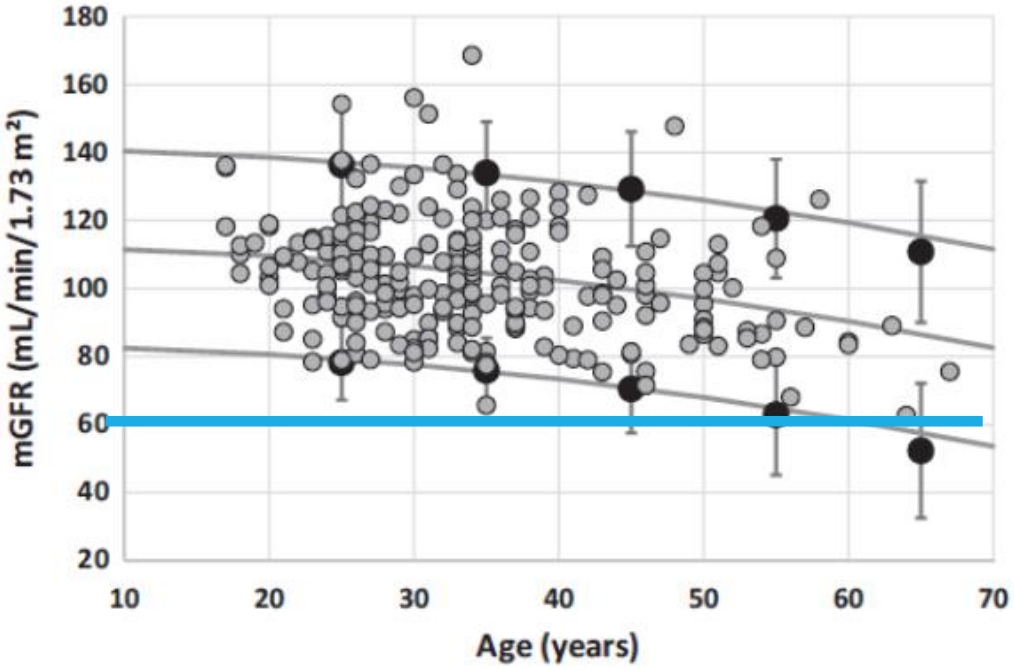


FIGURE 2: mGFR percentiles according to age. The solid grey circles are mGFR results and solid grey lines are 2.5th, 50th and 97.5th percentiles for mGFR in the current African population. The solid black circles with error bars are upper and lower reference limits obtained from the meta-analysis study including 633 Caucasian potential living kidney donors.

GFR by iohexol plasma clearance in healthy population (Côte d'Ivoire)

Yayo E, Nephrol Dial Transplant, 2018, 33, 1176

What about « prognostic » argument

ORIGINAL CONTRIBUTION

ONLINE FIRST

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

Stein I. Hallan, MD, PhD
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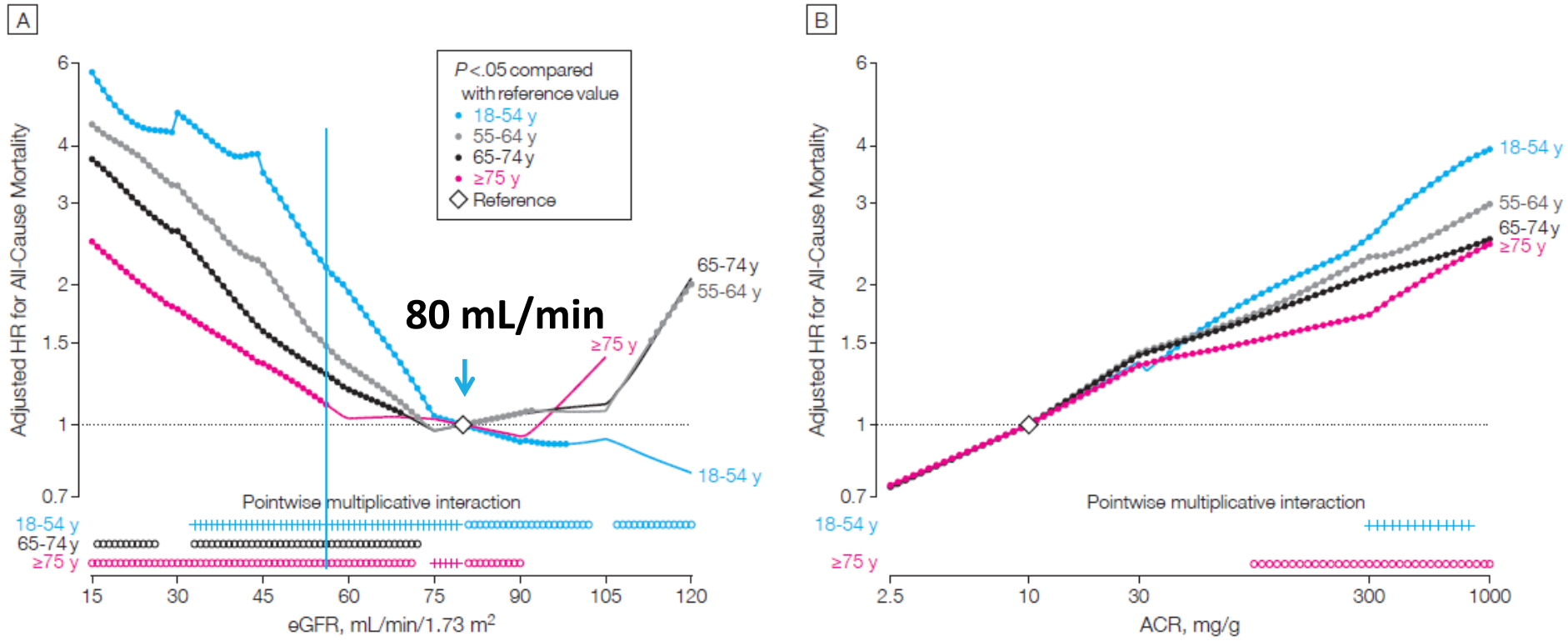
Brad C. Astor, PhD, MPH
Ron T. Gansevoort, MD, PhD
Adeera Levin, MD
Chi-Pang Wen, MD, MPH, DrPH
Josef Coresh, MD, PhD
for the Chronic Kidney Disease Prognosis Consortium

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

N=2,051,044
33 general or high risk cohorts
13 CKD cohorts
Mean follow-up: 5.3 years

Figure 1. Adjusted Hazard Ratios (HRs) for All-Cause Mortality and Mean Mortality Rates According to eGFR and ACR Within Each Age Category



The same GFR reference group is considered for all age

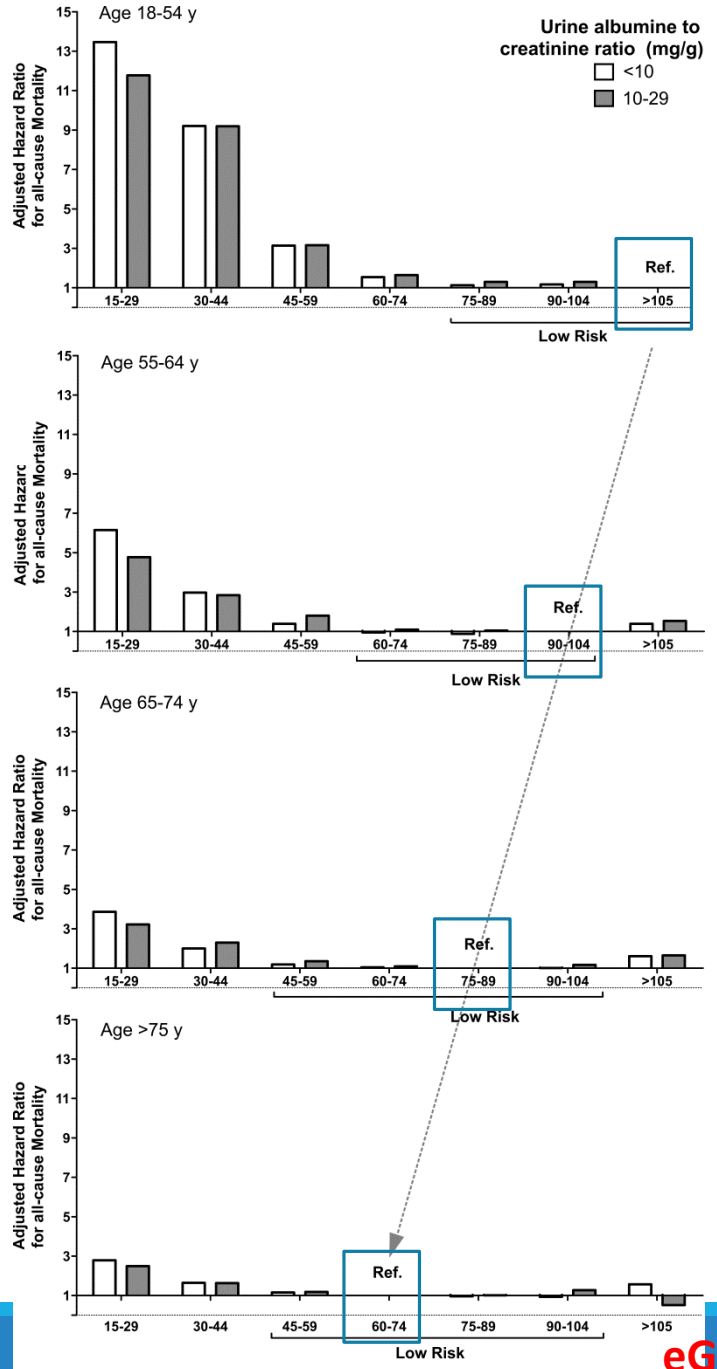
Reference can however change

Age 18-54 y =>

Age 55-64 y =>

Age 65-74 y =>

Age >75 y =>

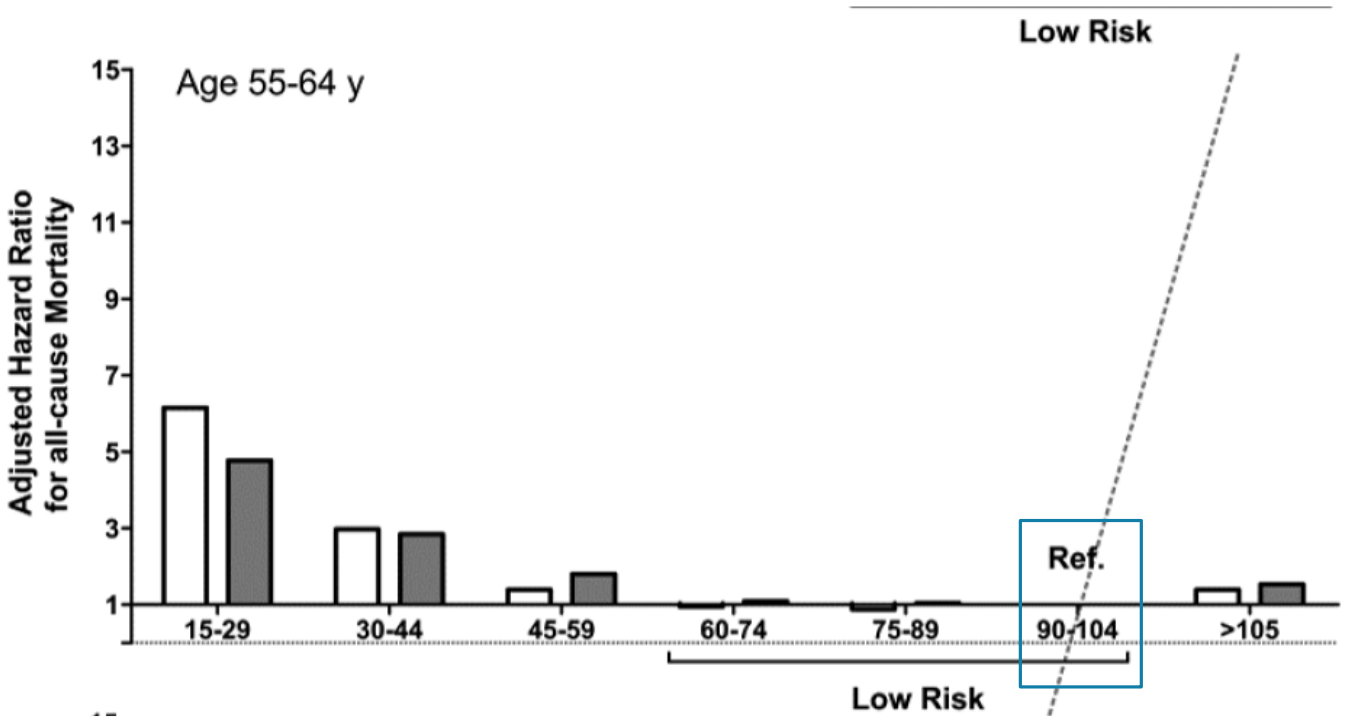


Data from:

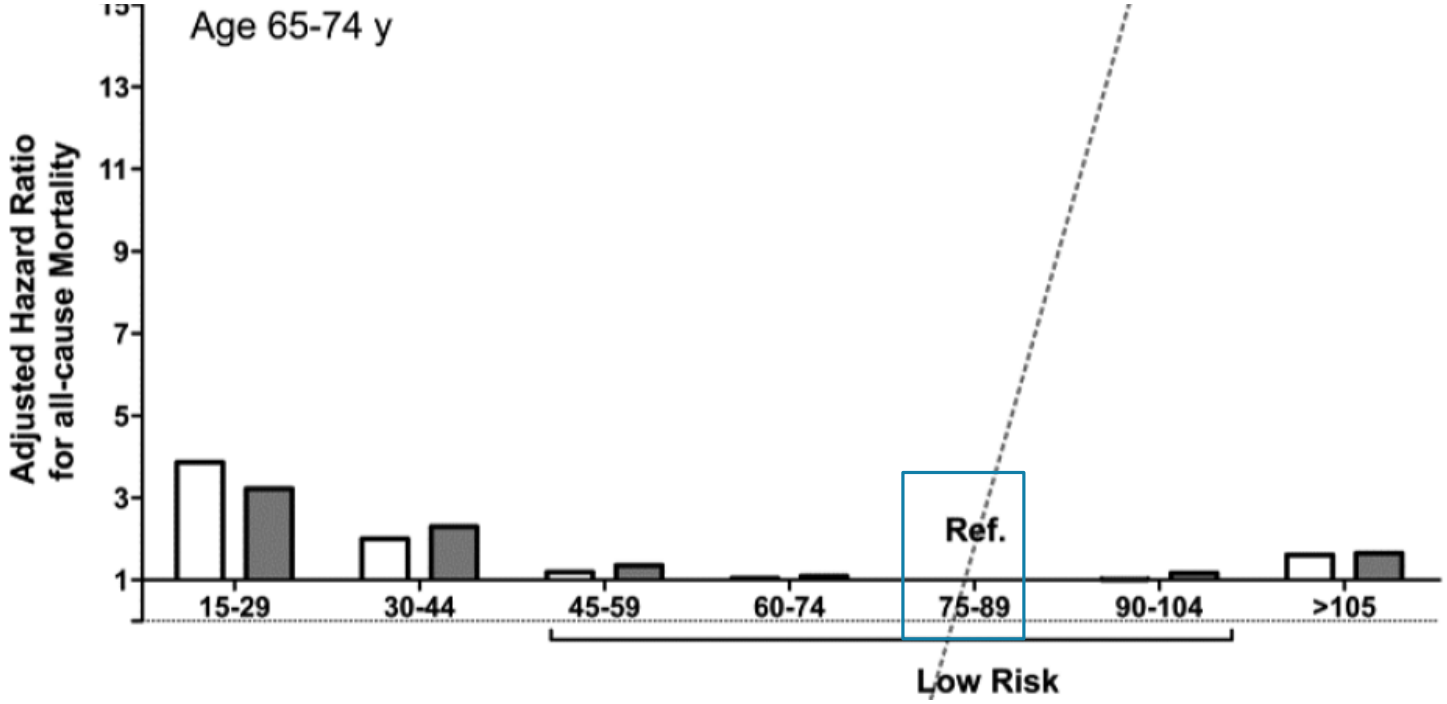
JAMA. 2012;308(22):2349-2360

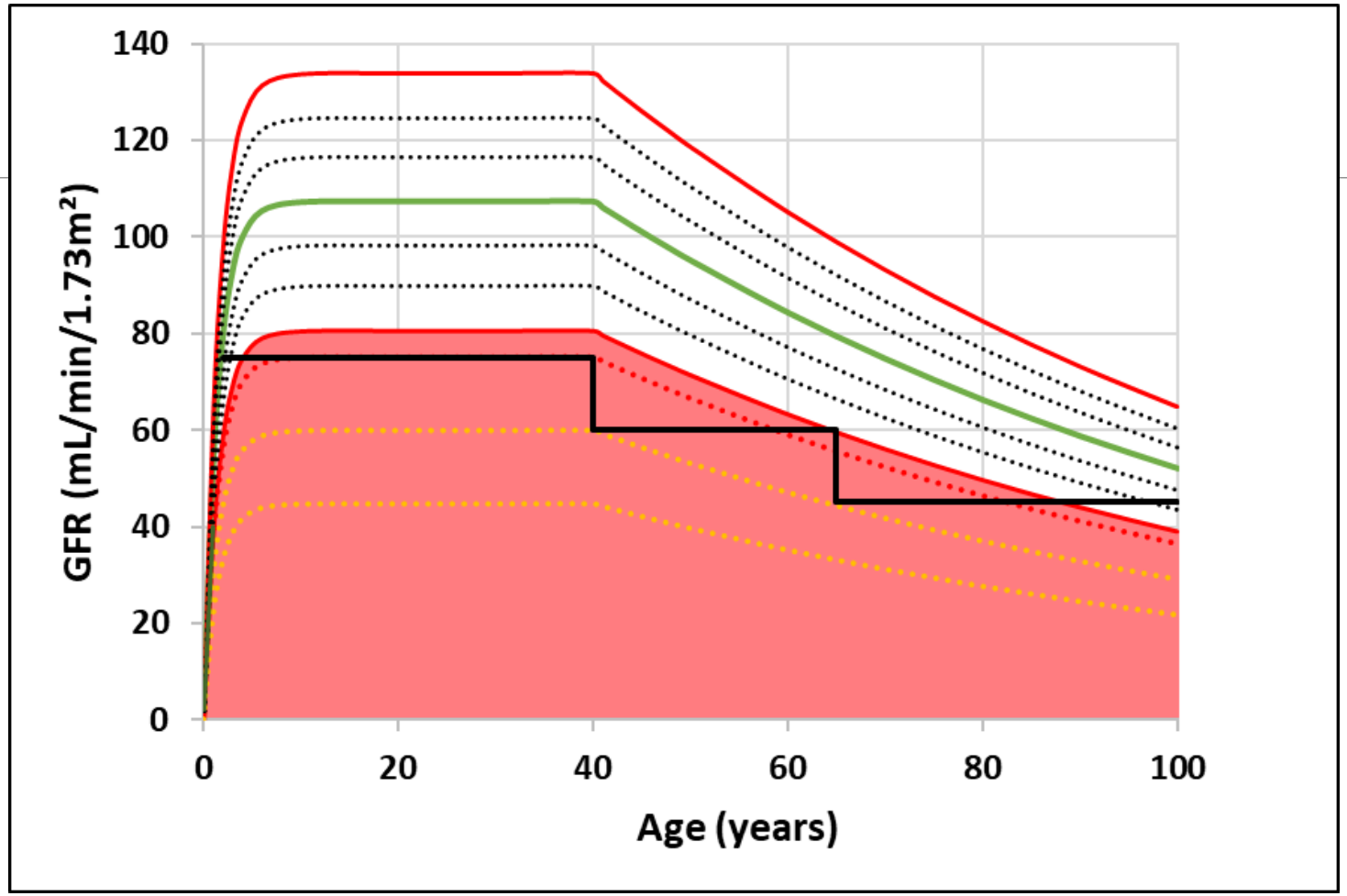
Delanaye P, Clin Biochem Rev, 2016, p17
Glassock RJ, J Bras Nefrol, 2017, p59

Age 55-64 y


Low Risk
Age 55-64 y
Adjusted Hazard Ratio for all-cause Mortality
15
13
11
9
7
5
3
1
Ref.
15-29
30-44
45-59
60-74
75-89
90-104
>105
Low Risk

Age 64-75 y


Age 65-74 y
Adjusted Hazard Ratio for all-cause Mortality
13
11
9
7
5
3
1
Ref.
15-29
30-44
45-59
60-74
75-89
90-104
>105
Low Risk


140
120
100
80
60
40
20
0
GFR (mL/min/1.73m²)
0
20
40
60
80
100
Age (years)

clinical investigation www.kidney-international.org

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

see commentary on page 1090

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

2,120,147 creatinine values for 218,437 individuals, 306,531 proteinuria measurements for 86,364 individuals and 6973 individuals carrying a kidney disease diagnosis. Median age was 63 years (range, 18–106) and 47% were male.

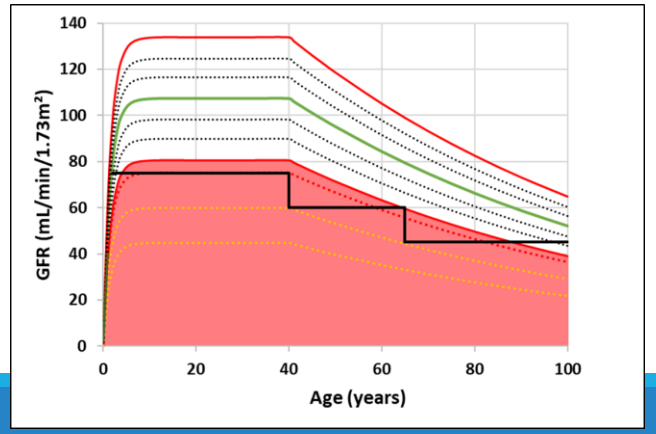

Table 4 | Mean annual prevalence of chronic kidney disease defined by the KDIGO criteria or age-adapted eGFR thresholds

	KDIGO criteria			Age-adapted eGFR thresholds		
Criteria for CKD	eGFR	eGFR and proteinuria	eGFR, proteinuria, and kidney disease diagnosis	eGFR	eGFR and proteinuria	eGFR, proteinuria, and kidney disease diagnosis
All						
Single-value criterion[a]	6.41 (6.36–6.49)	11.60 (11.54–11.65)	12.14 (12.08–12.20)	3.98 (3.94–4.01)	9.66 (9.61–9.71)	10.34 (10.29–10.40)
KDIGO criteria	4.72 (4.68–4.76)	5.35 (5.31–5.38)	5.94 (5.90–5.98)	2.20 (2.18–2.22)	2.93 (2.90–2.96)	3.64 (3.61–3.67)
Men						
Single-value criterion[a]	5.32 (5.26–5.37)	10.63 (10.55–10.71)	11.10 (11.02–11.18)	3.26 (3.21–3.30)	9.16 (9.09–9.23)	9.80 (9.72–9.87)
KDIGO criteria	3.92 (3.89–3.97)	4.66 (4.61–4.71)	5.13 (5.08–5.19)	1.93 (1.90–1.96)	2.67 (2.63–2.71)	3.27 (3.23–3.32)
Women						
Single-value criterion[a]	7.50 (7.44–7.57)	12.57 (12.49–12.65)	13.19 (13.10–13.27)	4.70 (4.65–4.75)	10.16 (10.08–10.23)	10.90 (10.82–10.98)
KDIGO criteria	5.52 (5.47–5.58)	6.04 (5.98–6.09)	6.75 (6.69–6.81)	2.76 (2.72–2.80)	3.19 (3.15–3.24)	4.01 (3.96–4.06)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.
[a]Single-value criterion: single eGFR and proteinuria measurements were randomly chosen from available measurements each year.
Data are presented as percentage (95% confidence interval).

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.

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

Clinical case #1:

Candidate to living kidney donation

Women, 45 years old

Serum Creatinine at 0,90 mf/dL

Would you recommend to measure GFR?

Clinical case #2:

Seminoma in young obese patient (BMI at 41 kg/m^2)

Chemotherapy with carboplatin

Creatinine at 1,2 mg/dL

How do you estimate GFR for drug dosage adaptation?

Test your knowledge

If you have carefully followed this lecture, you will know the answers to these questions:

Question 1: Which method of measuring GFR is the best balance between physiology and feasibility ?

Question 2: What are the main limitations of serum creatinine?

Question 3: What are the main limitations of estimating GFR?

Question 4: Which are the advantages of cystatin C?

Question 5: Which are the current definitions of CKD? Which is its main limitation?