Performance of creatinine-based equations to estimate glomerular filtration rate with a methodology adapted to the context of drug dosage adjustment

Pierre Delanaye*[1,2] Jonas Björk*[3,4], Marie Courbebaisse[5], Lionel Couzi[6], Natalie Ebert[7], Björn O. Eriksen[8], R. Neil Dalton[9], Laurence Dubourg[10], Francois Gaillard[11], Cyril Garrouste[12], Anders Grubb[13], Lola Jacquemont[14], Magnus Hansson[15], Nassim Kamar[16], Edmund J. Lamb[17], Christophe Legendre[18], Karin Littmann[19], Christophe Mariat[20], Toralf Melsom[8], Lionel Rostaing[21], Andrew D. Rule[22], Elke Schaeffner[7], Per-Ola Sundin[23], Ulla Berg[24], Kajsa Åsling-Monemi[24], Luciano Selistre[25], Anna Åkesson[26,27], Anders Larsson[28], Arend Bökenkamp[29], Hans Pottel**[30], Ulf Nyman**[31]

[1]Department of Nephrology-Dialysis-Transplantation, University of Liège (ULg CHU), CHU Sart Tilman, Liège, Belgium.
[2]Department of Nephrology-Dialysis-Apheresis, Hopital Universitaire Caremeau, Nimes, France
[3]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden
[4]Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden
[5]Physiology Department, Georges Pompidou European Hospital, Assistance Publique Hôpitaux de Paris, Paris Descartes University, INSERM U1151-CNRS UMR8253, Paris, France
[6]CHU de Bordeaux, Nephrologie - Transplantation - Dialyse, Université de Bordeaux, CNRS-UMR 5164 Immuno ConcEpT, France.
[7]Charité Universitätsmedizin Berlin, Institute of Public Health, Berlin, Germany.
[8]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsö, Norway.
[9]The Wellchild Laboratory, Evelina London Children's Hospital, London, United Kingdom.
[10]Néphrologie, Dialyse, Hypertension et Exploration Fonctionnelle Rénale, Hôpital Edouard Herriot, Hospices Civils de Lyon, France.
[11]Renal Transplantation Department, Assistance Publique–Hôpitaux de Paris (AP-HP), France.
[12]Department of Nephrology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France.
[13]Department of Clinical Chemistry, Skåne University Hospital, Lund, Lund University, Sweden.
[14]Renal Transplantation Department, CHU Nantes, Nantes University, Nantes, France.
[15]Function area Clinical Chemistry, Karolinska University Laboratory, Karolinska University Hospital Huddinge and Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden.
[16]Department of Nephrology, Dialysis and Organ Transplantation, CHU Rangueil, INSERM U1043, IFR –BMT, University Paul Sabatier, Toulouse, France.

[17]Clinical Biochemistry, East Kent Hospitals University NHS Foundation Trust, Canterbury, United Kingdom.
[18]Hôpital Necker, AP-HP & Université Paris Descartes, Paris, France.
[19]Department of Medicine Huddinge (MedH), Karolinska Institute, Huddinge, Sweden.
[20]Service de Néphrologie, Dialyse et Transplantation Rénale, Hôpital Nord, CHU de Saint-Etienne, France.
[21]Service de Néphrologie, Hémodialyse, Aphérèses et Transplantation Rénale, Hôpital Michallon, CHU Grenoble-Alpes, France.
[22]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA.
[23] Department of Geriatrics, School of Medical Sciences, Örebro University, Örebro, Sweden.
[24]Department of Clinical Science, Intervention and Technology, Division of Pediatrics, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden
[25]Mestrado em Ciências da Saúde -Universidade Caxias do Sul Foundation CAPES, Brazil
[26]Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden
[27]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden
[28]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden
[29]Department of Paediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[30]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium
[31]Department of Translational Medicine, Division of Medical Radiology, Lund University, Malmö, Sweden

*Pierre Delanaye and J. Björk shared first authorship.

**U. Nyman and Hans Pottel Delanaye shared last/senior authorship.

Corresponding author: Prof. dr. Pierre Delanaye, Department of Dialysis, CHU Sart Tilman, 4000 Liège, Belgium, tel +32 4 3668023, fax + 32 4 3667405, Email: pierre_delanaye@yahoo.fr

ORCID: https://orcid.org/0000-0002-1480-5761

Pierre Delanaye, Jonas Björk, Marie Courbebaisse, Natalie Ebert, Björn O. Eriksen, Laurence Dubourg, Francois Gaillard, Anders Grubb, Edmund J. Lamb, Christophe Mariat, Toralf Melsom, Andrew D. Rule, Elke Schaeffner, Arend Bökenkamp, Luciano Selistre, Hans Pottel, Ulf Nyman are members of the European Kidney Function Consortium.

Principal investigator statement

The authors confirm that the Principal Investigator for this paper is Pierre DELANAYE and that he had direct clinical responsibility for patients

Running head

Estimating GFR for drug dosage adjustment

Keywords

glomerular filtration rate, drug adjustment, chronic kidney disease

Word count: 2776

Table count: 3

Figure count: 2

What is already known

Estimating glomerular filtration rate is used to adjust drug dosage.

Cockcroft-Gault equation is still frequently used.

What this study adds

Measured GFR was compared with eGFR equations in 14,804 participants

Results showed that the Cockcroft-Gault equation had the poorest performance of all estimating equations.

For drug dosage, the Cockcroft-Gault equation should not be used, as its performance is poor.

Abstract

Aim The Cockcroft-Gault (CG) creatinine-based equation is still used to estimate glomerular filtration rate (eGFR) for drug dosage adjustment. Incorrect eGFR may lead to hazardous over- or underdosing

Methods In a cross-sectional analysis, CG was validated against measured GFR (mGFR) in 14,804 participants and compared with the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), Lund-Malmö-Revised (LMR), and European-Kidney-Function-Consortium (EKFC) equations. Validation focused on bias, imprecision, and accuracy (percentage of estimates within ±30% of mGFR, P30), overall and stratified for mGFR, age, and body mass index at mGFR <60 mL/min, as well as classification in mGFR stages.

Results The CG equation performed worse than the other equations, overall and in mGFR, age and BMI subgroups in terms of bias (systematic overestimation), imprecision and accuracy except for patients ≥65 years where bias and P30 were similar to MDRD and CKD-EPI, but worse than LMR and EKFC. In subjects with mGFR<60 mL/min and at BMI [18.5-25[kg/m², all equations performed similarly and for BMI<18.5kg/m² CG and LMR had the best results though all equations had poor P30-accuracy. At BMI≥25kg/m² the bias of the CG increased with increasing BMI (+17.2mL/min at BMI≥40kg/m²). The four more recent equations also classified mGFR stages better than CG.

Conclusions The CG equation showed poor ability to estimate GFR overall and in analyses stratified for GFR, age, and BMI. CG was inferior to correctly classify the patients in the mGFR staging compared to more recent creatinine-based equations.

Introduction

Creatinine-based glomerular filtration rate (GFR) equations are commonly used in daily clinical practice to estimate GFR (eGFR)[1–3]. eGFR is needed for dose adjustment of many drugs whose pharmacokinetics can be influenced by the level of kidney function [4,5]. Even with the emergence of new biomarkers [6,7], the most commonly used equations in clinical practice are still those based on the measurement of serum creatinine (SCr) [1–3,8]. We have recently proposed and validated a new creatinine-based equation which has the potential to estimate GFR accurately throughout the whole GFR and age range [1]. However, in the context of drug dosage adjustment, the comparison of the performance of equations requires specific methodological adaptations. First, although the Cockcroft and Gault (CG) equation is not recommended by any guidelines in nephrology, this equation is still used and considered particularly in the context of drug dosage adjustment. Of note, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) do not rule in favour of particular equation [9,10]. Second, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, the EMA and FDA recommend to use GFR without indexation to body surface area (BSA) in the context of drug dosage adjustment [9–11]. Thus, measured GFR and CG must be used without BSA indexing and equations that use BSA indexation may need to be "de-indexed"[12]. This requirement makes it possible to analyse the performance of eGFR equations according to body mass index (BMI), because weight is an important part of both BSA and CG equations, whereas weight is not present in other eGFR equations. Third, dosage adjustment should be applied for the vast majority of drugs, whenever GFR declines below 45 mL/min. Moreover, drug dosage is dependent on the classification of patients into the different categories of GFR, as suggested by KDIGO (category 3a: 45-60 ml/min, 3b: 30-45 ml/min, 4: 15-30 mL/min and 5: <15 mL/min)[13]. Very few studies have taken these specificities into account to compare the performance of the CG with other equations, and most studies have only compared CG with the Modification of Diet in Renal Disease (MDRD) Study equation [14–16]. In the current article, we used a large cohort of adults with measured GFR to study and compare CG's performance with other equations such as the MDRD study equation[17] but also

the Chronic Kidney Disease Epidemiology (CKD-EPI) equation[2], Lund-Malmö Revised (LMR) equation[8], and the new European Kidney Function Consortium (EKFC) equation (EKFC being an evolution of the previous Full Age Spectrum equation)[1].

Methods

Design overview

Data on 18,805 patients representing 12 cohorts from Europe and the US were available as previously described [1]. Because we focused on adults, values in subjects younger than 18 years were excluded, and 149 values were not considered because weight or height were unavailable, leaving a final cohort of 14,804 subjects. Analysis was limited to the first GFR measurement obtained per patient (if more than one was available). Data collection was planned after GFR measurement (retrospective design). Data were anonymised from the source cohorts for the analysis performed at Lund University, Sweden. All procedures involving subjects and data were in agreement with the ethical principles for medical research involving human subjects established in the World Medical Association Declaration of Helsinki. The study has been reviewed and approved by the Regional Ethical Board in Lund, Sweden (Registration No 2018/220).

Participants

Data on GFR were collected and centralized by the European Kidney Function Consortium (EKFC), which was endorsed by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). Data were from participants (all non-black) in previously published research studies as well as patients undergoing measured GFR as part of their clinical care at nephrology centres. An overview of the participating centres, the measurement methods used in these centres, and the patient characteristics in the centres have been published before [1,18,19].

Covariates

Age, gender, height, weight and SCr were obtained from medical records. SCr was measured with assays traceable to the gold standard isotope dilution mass spectrometry (IDMS) method or was corrected to IDMS method levels (in case of the Chronic Renal Insufficiency Cohort (CRIC) Study) [20].

Outcomes

Measured GFR was obtained using either plasma clearance (based on the decay of the plasma concentrations over time) or urinary clearance (based on urine excretion rate divided by plasma concentration) of exogenous filtration markers (iohexol, inulin, ^{51}Cr-EDTA, or iothalamate), all methods with sufficient accuracy [21,22]. All results of measured GFR were non-indexed for BSA. GFR equations used for analysis are described in Table S1. GFR results based on MDRD, CKD-EPI, LMR and EFKC equations were de-indexed for BSA using the Du Bois equation [12,23].

Data and Statistical Analysis

Performances of equations

Performance of the equations were compared with usual metrics: median bias (i.e. eGFR – mGFR) with 95% confidence intervals (CI), imprecision (interquartile range (IQR)), and P30-accuracy (percentage of eGFR-values within ±30% of mGFR) with 95% CI. Evaluation in different subgroups were also done according to GFR (<15, [15-30[, [30-45[, [45-60[mL/min)[24]. Focusing on GFR <60 mL/min, we also performed analyses stratified by age (18-40[, [40-65[and ≥ 65 years) and BMI (<18.5, [18.5-25[, [25-30[, [30-35[, [35-40[and ≥40 kg/m²). The target for bias is zero. Imprecision should be as low as possible. The goal for P30 was 100%, yet P30 > 75% has been considered as "sufficient for good clinical decision making" by Kidney Disease Outcomes Quality Initiative (K/DOQI), although their goal was to reach a P30 > 90% [25,26]. The EKFC equation has been partly derived from subjects included in the current analysis. Because an equation tends to perform better in the cohort used for its development, we performed a sensitivity analysis in the external validation cohort described in the seminal article, excluding subjects younger than 18 years (n=7,124) and omitting subjects who lacked information on height or weight (n=149), leading to a final sample of 6,975.

Median quantiles for bias across the age spectrum were graphically presented using fractional polynomials (linear, square and cubic). Likewise, accuracy P30 (%) was graphically presented across the age spectrum using cubic splines with two free knots and using 3rd degree polynomials.

Classification of patients

In patients with mGFR lower than 60 mL/min (n=4,328), we calculated (percentage) and compared the ability of each equation to correctly classify subjects in the same stage as measured GFR using McNemar's test[27]. Also, we calculated the total percentage of patients who have been classified into a different CKD stage by the equation compared to mGFR, using the relevant thresholds (<15, [15-30[, [30-45[, [45-60[mL/min) [24,28]. A p-value < 0.05 was considered as significant.

All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Medcalc (Medcalc Software Ltd, Ostend, Belgium).

Role of the Funding Source

Swedish Research Council (Vetenskapsrådet; grant no. 2019 – 00198). Professor J. Björk has funding from the Swedish Research Council (VR) in order to conduct large scale epidemiological studies linked with registered data from health care. This funding source was at no time involved in design, analysis, presentation or interpretation of the results from the present study.

Results

The characteristics of study participants are summarized in Table S2. Further details on each cohort can be found in Appendix Tables S3. The mean ± SD age was 55.1±18.9 years, mean measured GFR was 78.8±34.2 mL/min, and 49.5% were female. Performance of the five equations in the whole study population (n=14,804) is shown in Table S4 and illustrated in Appendix Figure 1A and 1B. In comparison to more recent equations, the performance of the CG equation to estimate was worse than for all other equations in terms of bias (with the largest and systematic overestimation) (Appendix Figure 1A), imprecision (with the highest IQR) and accuracy (with the poorest P30)

(Appendix Figure 1B). Among the recent equations, the overall performance of the EFKC and LMR equations were similar and better than the MDRD and CKD-EPI equations. The analysis stratified by mGFR (below 60 mL/min) is shown in Table 1 and Figures 1A and 1B, demonstrating the same results. The CG equation performed systematically worse in terms of bias (Figure 1A), precision and P30 (Figure 1B). Once again, both EFKC and LMR performed better than MDRD and CKD-EPI. In patients with mGFR <60 mL/min, a sub-analysis according to age and BMI is summarized in Table 2-3 and Figures 2. The same ranking among equations can be made in participants younger than 65 years. In older individuals, both bias (but not precision) and P30 of the CG equation were similar to MDRD and CKD-EPI equation, but all had worse performance than LMR and EKFC equations. In patients with BMI higher than 25 kg/m², the performance of the CG was also worse, especially in terms of bias which increased with increasing BMI. In patients with BMI between 18.5 and 25 kg/m², all equations presented with a similar performance. In low BMI (<18.5 kg/m²), both CG and LMR equations had the best results, but all equations shared a relatively poor performance (with P30 of 58.8% and 57.3% for CG and LMR equations, respectively).

As a sensitivity analysis, the same analysis was repeated in the external validation dataset only (see Tables S5 and S6 for the whole external cohort population and stratified by age, mGFR and BMI, respectively). The results and conclusions were not different from the whole cohort.

In comparison with measured GFR under 60 mL/min, subjects were correctly classified in the KDIGO categories in 43.5, 49.8, 48.1, 54.0 and 52.9% with the CG, MDRD, CKD-EPI, LMR and EKFC equations respectively. LMR was slightly better than EKFC. EKFC and LMR were significantly better than MDRD and CKD-EPI. All four equations also performed better than the CG. The difference in categorization between measured and estimated GFR was one stage (for example, stage 3a or 4 with eGFR and 3b with mGFR) in 46.1, 43.1, 43.7, 40.6 and 41.1% with the CG, MDRD, CKD-EPI, LMR and EKFC equations, respectively. Errors of one stage were less frequent in LMR and EFKC compared to MDRD and to CKD-EPI. Errors of one stage were less frequent with all four eGFR equations compared to CG. The difference in categorization between measured and estimated GFR was two stages (for example,

stage 2 or 4 with eGFR and 3b with mGFR) in 9.3, 6.2, 7.2, 5.0 and 5.4% with the CG, MDRD, CKD-EPI, LMR and EKFC equations respectively. Errors of two stage were less frequent in LMR and EFKC compared to MDRD and to CKD-EPI. Errors of two stages were less frequent with all four equations compared to CG.

Discussion

The main objective of this study was to evaluate the performance of the CG to estimate GFR in comparison with four more recent creatinine-based equations [1–3,29]. Originally, the methodology was adapted with regard to drug dosage adjustment, i.e. GFR was expressed in mL/min and we focused on GFR <60 mL/min [9–12]. We showed that the CG equation had the worst performance compared to all other equations to estimate GFR: CG had the largest bias (with a systematic overestimation, especially in high BMI range [30,31]), the lowest precision, and finally the poorest accuracy. Also, the CG equation was associated with a higher number of errors (and larger errors) in terms of GFR classification of patients [27]. Among other equations, both EKFC and LMR performed significantly better than MDRD and CKD-EPI, even if the difference of performance between these equations was much lower than the difference observed between CG and all others. The inferiority of the CG equation compared to others was confirmed in most sub-analyses, i.e. according to GFR, age and BMI. The poor performance of CG has been described in the past but either the methodology was not adapted to drug dosage adjustment or the comparison was only with the MDRD study equation [14–16].

In patients older than 65 years, CG performed as well as the MDRD and CKD-EPI equations. The relatively good performance of CG in the elderly is also described in other cohorts [14,32,33], however we show here that both LMR and EKFC do significantly better in this population [1,34]. Regarding the performance of CG, it was slightly better for patients with low or very low BMI. One can hypothesize that patients in these BMI ranges have abnormally low muscle mass [35]. In these patients, serum creatinine (in the denominator in CG) is falsely low, which results in overestimation of GFR. In the CG

equation, this overestimation due to serum creatinine is counterbalanced by the variable weight (in the numerator) which is, by definition, low in this population. Weight is not directly present in recent equations. Having said that, it remains difficult to recommend CG in a population of very lean individuals as its overall performance remains very poor [29,35]. Consequently, measuring GFR, or using cystatin C-based estimation, are probably to be recommended in such a population [36,37].

In terms of GFR estimation and patients' categorization, we thus confirm the superiority of MDRD and CKD-EPI equations over CG, this superiority being still more obvious when EKFC and LMR are considered for comparison [14,15,38]. In our cohort, this is especially illustrated by errors of more than two stages (for example, stage 2 or 4 with eGFR and 3b with mGFR) which are two times more frequent with CG than with LMR or EKFC.

There are several plausible reasons why CG is inferior to the more recent eGFR equations. First, *sensu stricto,* CG is supposed to estimate creatinine clearance (which is a less precise GFR measure because of errors in urine collection and tubular secretion of creatinine) whereas the four other equations have been developed from "true" GFR measurements [3,21,39]. Second, serum creatinine in the CG equation was not IDMS traceable, as most creatinine assays are now [20,40]. Third, there are several methodologic limitations in the CG study (including its simplistic mathematical model, low sample of development, and lack of female subjects). From a strict "nephrological" point of view, we therefore question why the CG is still used in clinical research and practice to estimate GFR in the context of drug dosage adjustment. Different factors may explain why CG is still used. Several guidelines for drug dosage adaption have been established with the CG equation (or creatinine clearance). Also, adverse events with drugs are particularly frequent in the frail elderly [41]. In this specific population combining low BMI and old age, CG will typically yield a lower GFR result than MDRD and CKD-EPI, which may lead to safer drug dosage. This point explains why CG is still often preferred in the geriatric context. This argument is however spurious because if it is true at the population level, it is not automatically true for the individual (for example, if older adults are obese, CG results will be

higher than other equations)[39,42]. Moreover, one might also consider the risk of under dosing important drugs in elderly people.

Our study has several limitations. First, our population was mostly European. The race factor in MDRD and CKD-EPI has recently been extensively questioned [43,44]. As a reminder, no black subjects were included in the seminal CG article. Dedicated studies in patients of African ancestry are urgently needed to assess the performance of the CG equation compared to more recent estimating equations. Second, the EKFC equations were developed from the identical large cohort (in whole or in part). However, the results were similar when the analysis was restricted to the external validation dataset. An external validation performed by independent investigators would further strengthen our results. Third, the performance of new equations like LMR and EKFC is close to 87% (P30 accuracy), not far from the recommended target by the Kidney Disease Outcomes Quality Initiative [45]. However, there is insufficient performance in subgroups, and, in specific patients and situations (for example, for drug dosage adjustment of drugs with narrow therapeutic window, the use of measured GFR must be considered). Fourth, the performance of equations has been studied against different methods of measuring GFR. All these methods are recognized methods [33] but some differences could persist and explain at least in part the results in estimating GFR. Finally, our study remains cross-sectional. Our results could pave the way for a prospective study with patients randomized for drug dosage (based on CG in one group and EKFC or LMR in the other group) with efficacy and safety endpoints definitively answering the question of which equation is the best for drug dosage adjustment.

In conclusion, the older CG equation which is still used for drug dosing purpose is the worst performing equation to estimate GFR and to correctly classify patients in the GFR staging system, in comparison to modern creatinine-based equations. Among these modern equations, EKFC and LMR performed better than CKD-EPI and MDRD equations.

327

328

329

330

331

332

333

Acknowledgement

We sincerely thank Eric P. Cohen, New York for his help in editing the manuscript.

Author contribution: Conception of the study: PD, HP, JB, UN. Analysis and interpretation of data: PD, HP, JB, UN. Collection of data: JB, MC, LC, NE, BOE, RND, LD, FG, CG, AG, LJ, MH, NK, EJL, CL, KL, CM, TM, LR, ADR, ES, POS, UB, KAM, LS, AA, AL, AB, UN. Drafting of the article: PD, HP, JB, UN. All authors critically reviewed the manuscript, have accepted responsibility for the entire content of this manuscript and approved its submission

Conflicts of interest statement

The results presented in this paper have not been published previously in whole or part.

U Nyman has received lecture fees from GE Healthcare AB.

M Courbebaisse has received grant support from BIOPAL, USA.

N Dalton is a Director of and minority shareholder in a University/NHS spin-out company, SpOtOn Clinical Diagnostics and has grant supports from NHS Health Technology Assessment and Juvenile Diabetes Research Foundation.

N Ebert has received lecture fees from Siemens Healthineer and Roche Diagnostics.

BO Eriksen has received lecture fees from Sanofi-Aventis.

N Kamar has received consulting fees or paid advisory boards, lecture fees and travel support from the following companies: Abbvie, Amgen, Astellas, Chiesi, Fresenius Medical care, Gilead, Merck Sharp and Dohme, Neovii, Novartis, Roche, Sanofi and Shire.

C Legendre received consulting fees or paid advisory boards from CSL Behring and Novartis, and lecture fees from Sandoz.

E Schaeffner has received lecture fees from Siemens Healthineers and Fresenius Kabi.

All remaining authors declared no competing interests.

Funding information

Primary funding source: Swedish Research Council (Vetenskapsrådet; grant no. 2019-00198).

Data availability statement

The EKFC dataset used in the present study is hosted by the Lund University Population Research Platform. Legal and ethical restrictions prevent public sharing of the dataset. Data can be made available for collaborations upon request to interested researchers but would generally require a new ethical permission and the permission of each of the data-owners. You can find contact information for the data host at https://www.lupop.lu.se/

References

1. Pottel H, Björk J, Courbebaisse M, et al. Development and Validation of a Modified Full Age Spectrum Creatinine-Based Equation to Estimate Glomerular Filtration Rate. A Cross-sectional Analysis of Pooled Data. *Ann Intern Med*. 2021;174(2):183-191.
2. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
4. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur J Clin Pharmacol*. 2009;65(8):757-773.
5. Dreisbach AW, Flessner MF. Drug metabolism and chronic kidney disease. In: Kimmel PL, Rosenberg, MK, eds. *Chronic Renal Disease*. Vol First Edit. Elsevier; 2014:674-681.
6. Grubb A, Nyman U, Björk J, et al. Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and the Counahan-Barratt prediction equations for children. *Clin Chem*. 2005;51(0009-9147):1420-1431.
7. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20-29.
8. Nyman U, Grubb A, Larsson A, et al. 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.
9. EMA. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162133.pdf.
10. FDA. Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design , Data Analysis , and Impact on Dosing ans Labeling. *FDA*. 2010;(March).
11. Matzke GR, Aronoff GR, Atkinson Jr. AJ, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(11):1122-1137.
12. Delanaye P, Krzesinski J-M. Indexing of renal function parameters by body surface area:

intelligence or folly? *Nephron Clin Pract*. 2011;119(4):c289-c292.
13. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009;(0098-6577 (Print)):S1-130.
14. Froissart M, Rossert J, Jacquot C, et al. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol*. 2005;16(3):763-773.
15. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kidney Dis*. 2009;54(1):33-42.
16. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol*. 2010;5:1003-1009.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-470.
18. Björk J, Nyman U, Delanaye P, et al. A novel method for creatinine adjustment makes the revised Lund–Malmö GFR estimating equation applicable in children. *Scand J Clin Lab Invest*. 2020;80(6):456-463.
19. Pottel H, Delanaye P, Schaeffner ES, et al. Estimating Glomerular Filtration Rate for the Full Age Spectrum from Serum creatinine and cystatin C. *Nephrol Dial Transplant*. 2017;32:497-507.
20. Piéroni L, Delanaye P, Boutten A, et al. A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. *Clin Chim Acta*. 2011;412(23-24):2070-2075. doi:10.1016/j.cca.2011.07.012
21. Soveri I, Berg UB, Björk J, et al. Measuring GFR: a systematic review. *Am J Kidney Dis*. 2014;64(3):411-424.
22. Delanaye P, Ebert N, Melsom T, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research : a review. Part 1 : How to measure glomerular filtration rate with iohexol ? *Clin Kidney J*. 2016;9(5):682-699.
23. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med*. 1916;17:862-871.
24. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1-150.
25. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Clasification and Stratification. *Am J Kidney Dis*. 2002;39((suppl. 1)):1-266. doi:10.1634/theoncologist.2011-S2-45
26. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med*. 2012;156(11):785-795.
27. Luis-Lima S, Escamilla-Cabrera B, Negrín-Mena N, et al. CKD staging with cystatin C or creatinine-based formulas: flipping the coin. *Nephrol Dial Transplant*. 2019;34(2):287-294.
28. Delanaye P, Jager KJ, Bökenkamp A, et al. CKD: A Call for an Age-Adapted Definition. *J Am Soc Nephrol*. 2019;30(10):1785-1805.
29. Björk J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmö Study cohort. *Scand J Clin Lab Invest*. 2011;71(3):232-239.
30. Bouquegneau A, Vidal-Petiot E, Moranne O, et al. Creatinine-based equations for the adjustment of drug dosage in an obese population. *Br J Clin Pharmacol*. 2016;81(2):349-361.
31. Lemoine S, Guebre-Egziabher F, Sens F, et al. Accuracy of GFR estimation in obese patients. *Clin J Am Soc Nephrol*. 2014;9(4):720-727.
32. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med*. 2012;157(7):471-481.
33. Flamant M, Haymann JP, Vidal-Petiot E, et al. GFR Estimation Using the Cockcroft-Gault,

MDRD Study, and CKD-EPI Equations in the Elderly. *Am J Kidney Dis*. 2012;60(5):847-849.
34. Björk J, Grubb A, Gudnason V, et al. Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort. *Nephrol Dial Transplant*. 2018;33(8):1380-1388.
35. Delanaye P, Cavalier E, Radermecker RPP, et al. Estimation of GFR by different creatinine- and cystatin-C-based equations in anorexia nervosa. *Clin Nephrol*. 2009;71(5):482-491.
36. Agarwal R, Delanaye P. Glomerular filtration rate: when to measure and in which patients? *Nephrol Dial Transplant*. 2019;34(12):2001-2007.
37. Delanaye P, Melsom T, Ebert N, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: Why to measure glomerular filtration rate with iohexol? *Clin Kidney J*. 2016;9(5):700-704.
38. Nyman U, Grubb A, Lindstro V, Bjo J. Accuracy of GFR estimating equations in a large Swedish cohort : implications for radiologists in daily routine and research. *Acta Radiol*. 2017;58(3):367-375.
39. Delanaye P. *Kidney Function*.; 2019. doi:10.1016/B978-0-323-54945-5.00010-2
40. Delanaye P, Cavalier E, Pottel H. Serum Creatinine: Not So Simple! *Nephron*. 2017;136(4):302-308.
41. Salvi F, Marchetti A, D'Angelo F, Boemi M, Lattanzio F, Cherubini A. Adverse drug events as a cause of hospitalization in older adults. *Drug Safety*. 2012;35(Supplem 1):29-45.
42. Delanaye P, Guerber F, Scheen A, et al. Discrepancies between the Cockcroft–Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) Equations: Implications for Refining Drug Dosage Adjustment Strategies. *Clin Pharmacokinet*. 2017;56(2):193-205.
43. Delanaye P, Mariat C, Maillard N, et al. Are the creatinine-based equations accurate to estimate glomerular filtration rate in african american populations? *Clin J Am Soc Nephrol*. 2011;6(4):906-912. doi:10.2215/CJN.10931210
44. American Society of Nephrology (ASN); National Kidney Foundation (NKF): Establishing a task force to reassess the inclusion of race in diagnosing kidney disease. https://www.kidneynews.org/view/news/policy-advocacy/leading-edge/asn-and-nkf-establishing-task-force-to-reassess-the-inclusion-of-race-in-diagnosing-kidney-diseases.xml
45. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1-266.

Tables

Table 1: Performance of different equations in subgroups according to measured GFR

	CG	MDRD	CKD-EPI	LMR	EKFC
mGFR<60 mL/min n=4,328					
Median bias (95%CI)	6.1 (5.7; 6.5)	3.9 (3.5; 4.2)	4.4 (4.0; 4.7)	1.5 (1.2; 1.8)	2.9 (2.6; 3.2)
Imprecision	14.8	13.2	14.3	12.0	12.4
P30 (%) (95%CI)	59.4 (57.9; 60.9)	67.3 (65.9; 68.7)	64.9 (63.5; 66.3)	73.8 (72.5; 75.1)	70.3 (68.9; 71.7)
mGFR [45-60[mL/min n=1,490					
Median bias (95%CI)	7.0 (6.1; 7.9)	5.1 (4.3; 6.0)	4.4 (6.4; 8.1)	1.5 (1.9; 3.3)	2.9 (2.8; 4.4)
Imprecision	20.3	18.6	20.6	16.4	17.2
P30 (%) (95%CI)	67.1 (64.7; 69.5)	73.2 (70.9; 75.4)	67.1 (64.7; 69.5)	78.4 (76.3; 80.5)	76.6 (74.4; 78.7)
mGFR [30-45[mL/min n=1,299					
Median bias (95%CI)	6.5 (5.5; 7.2)	4.3 (3.5; 5.0)	5.3 (4.4; 5.8)	0.9 (0.1; 1.7)	3.1 (2.4; 3.8)
Imprecision	16.4	13.8	15.0	14.7	13.5
P30 (%) (95%CI)	63.5 (60.9; 66.1)	68.8 (66.3; 71.3)	67.2 (4.7; 69.8)	72.5 (70.1;74.9)	71.7 (69.2;74.1)
mGFR [15-30[mL/min n=1,207					
Median bias (95%CI)	6.0 (5.4; 6.5)	3.5 (2.9; 4.0)	3.0 (2.5; 3.6)	0.7 (0.3; 1.4)	2.7 (2.2; 3.2)
Imprecision	11.1	9.9	10.3	7.9	9.6
P30 (%) (95%CI)	49.5 (46.7; 52.4)	62.1 (59.4; 64.9)	61.9 (59.1; 64.6)	72.8 (70.3; 75.3)	64.7 (62.0; 67.4)
mGFR <15 mL/min n=332					
Median bias (95%CI)	4.2 (3.4; 4.7)	2.3 (1.8; 3.2)	1.8 (1.1; 2.3)	2.2 (1.8; 2.5)	2.0 (1.6; 2.5)
Imprecision	6.6	6.2	6.4	5.0	6.2
P30 (%) (95%CI)	44.6 (39.2; 49.4)	536 (48.3;59.0)	56.6 (51.3;61.9)	62.0 (56.8; 67.3)	57.2 (51.9; 62.5)

Bias (estimated GFR – measured GFR) and imprecision (interquartile range) expressed in mL/min.
P30: percentage of estimated GFR within ±30% of measured GFR. CI: confidence interval.
CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases.
mGFR: measured glomerular filtration rate.

Table 2: Performance of different equations in patients with mGFR <60 mL/min according to age

age [18-40[years n=567	CG	MDRD	CKD-EPI	LMR	EKFC
Median bias (95%CI)	16.7 (15.4; 18.0)	7.2 (5.7; 9.3)	13.5 (11.6; 15.9)	5.9 (4.4; 7.1)	8.7 (7.4; 10.2)
Imprecision	17.2	16.7	20.0	15.9	15.7
P30 (%) (95%CI)	35.1 (31.2; 39.0)	61.6 (57.6; 65.6)	46.4 (42.3; 50.5)	65.6 (61.7; 69.5)	57.5 (53.4; 61.6)
age [40-65[years n=1,077					
Median bias (95%CI)	10.0 (9.1; 11.2)	2.0 (1.3; 2.8)	3.8 (3.2; 5.3)	2.3 (1.7; 3.4)	4.6 (3.8; 5.6)
Imprecision	15.1	13.6	14.8	13.5	14.0
P30 (%) (95%CI)	47.8 (44.8; 50.8)	70.1 (67.4; 72.8)	65.7 (62.9; 68.6)	70.5 (67.7; 73.2)	66.7 (63.9; 69.5)
age ≥65 years n=2,684					
Median bias (95%CI)	3.0 (2.6; 3.4)	4.0 (3.6; 4.4)	3.4 (2.9; 3.8)	0.6 (0.2; 1.0)	1.6 (1.2; 2.0)
Imprecision	11.7	12.2	12.1	10.6	10.9
P30 (%) (95%CI)	69.2 (67.4; 70.9)	67.4 (65.6; 69.1)	68.4 (66.7; 70.2)	76.9 (75.3; 78.5)	74.5 (72.8; 76.1)

Bias (estimated GFR – measured GFR) and imprecision (interquartile range) expressed in mL/min.
P30: percentage of estimated GFR within ±30% of measured GFR. CI: confidence interval.
BMI: body mass index. CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases. mGFR: measured glomerular filtration rate.

Table 3: Performance of different equations in patients with mGFR <60 mL/min according to body mass index.

BMI <18.5 kg/m² n=262	CG	MDRD	CKD-EPI	LMR	EKFC
Median bias (95%CI)	7.5 (6.1; 9.5)	11.2 (9.5;12.4)	15.8 (12.7; 17.4)	8.8 (6.8; 11.0)	10.8 (9.1; 12.9)
Imprecision	13.9	16.9	20.1	14.8	15.9
P30 (%) (95%CI)	58.8 (52.8; 64.7)	49.2 (43.2; 55.3)	36.6 (30.8; 42.5)	57.3 (51.3; 63.2)	50.0 (43.9; 56.1)
BMI [18.5-25[kg/m² n=1,713					
Median bias (95%CI)	3.9 (3.3; 4.6)	4.6 (4.0; 5.1)	5.6 (5.0; 6.0)	2.1 (1.7; 2.4)	3.6 (3.1;4.2)
Imprecision	14.9	13.0	15.0	12.4	12.7
P30 (%) (95%CI)	65.6 (63.4; 67.9)	66.1 (63.9; 68.4)	63.1 (60.8; 65.4)	72.9 (70.8; 75.0)	68.7 (66.5; 70.8)
BMI [25-30[kg/m² n=1,415					
Median bias (95%CI)	5.2 (4.7; 6.0)	3.0 (2.3; 3.5)	3.0 (2.5; 3.6)	0.4 (-0.1; 0.9)	1.9 (1.5; 2.4)
Imprecision	12.8	11.7	12.2	10.7	11.0
P30 (%) (95%CI)	62.0 (59.5; 64.6)	71.0 (68.7; 73.4)	69.8 (67.4; 72.1)	77.5 (75.4; 79.7)	74.6 (72.4; 76.9)
BMI [30-35[kg/m² n=643					
Median bias (95%CI)	8.5 (7.7; 9.5)	2.7 (1.9; 3.7)	2.5 (1.4; 3.5)	0.2 (-0.6; 1.1)	1.7 (0.8; 2.5)
Imprecision	14.1	12.3	12.3	11.0	11.1
P30 (%) (95%CI)	50.1 (46.2; 53.9)	68.7 (65.2; 72.3)	69.1 (65.5; 72.6)	76.2 (72.9; 79.5)	73.9 (70.5; 77.3)
BMI [35-40[kg/m² n=203					
Median bias (95%CI)	15.4 (13.6; 17.4)	3.4 (1.3; 4.9)	3.7 (2.0; 5.4)	1.3 (-0.1; 3.2)	3.0 (1.2; 5.3)
Imprecision	17.9	14.4	14.5	13.4	12.9
P30 (%) (95%CI)	33.5 (27.0; 40.0)	68.5 (62.1; 74.9)	68.0 (61.6; 74.4)	73.8 (67.3; 79.5)	70.3 (63.1; 75.8)
BMI ≥40 kg/m² n=92					
Median bias (95%CI)	17.2 (14.2; 21.0)	-0.5 (-2.8; 1.9)	0.1 (-2.4; 2.9)	-1.4 (-3.5; 0.2)	-0.1 (-2.4; 2.1)
Imprecision	19.3	13.7	14.9	13.7	14.9
P30 (%) (95%CI)	27.2 (18.1; 36.3)	69.6 (60.2; 79.0)	67.4 (57.8; 77.0)	65.2 (55.5; 74.9)	69.6 (60.2; 79.0)

Bias (estimated GFR – measured GFR) and imprecision (interquartile range) expressed in mL/min.
P30: percentage of estimated GFR within ±30% of measured GFR. CI: confidence interval.
BMI: body mass index. CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases. mGFR: measured glomerular filtration rate.

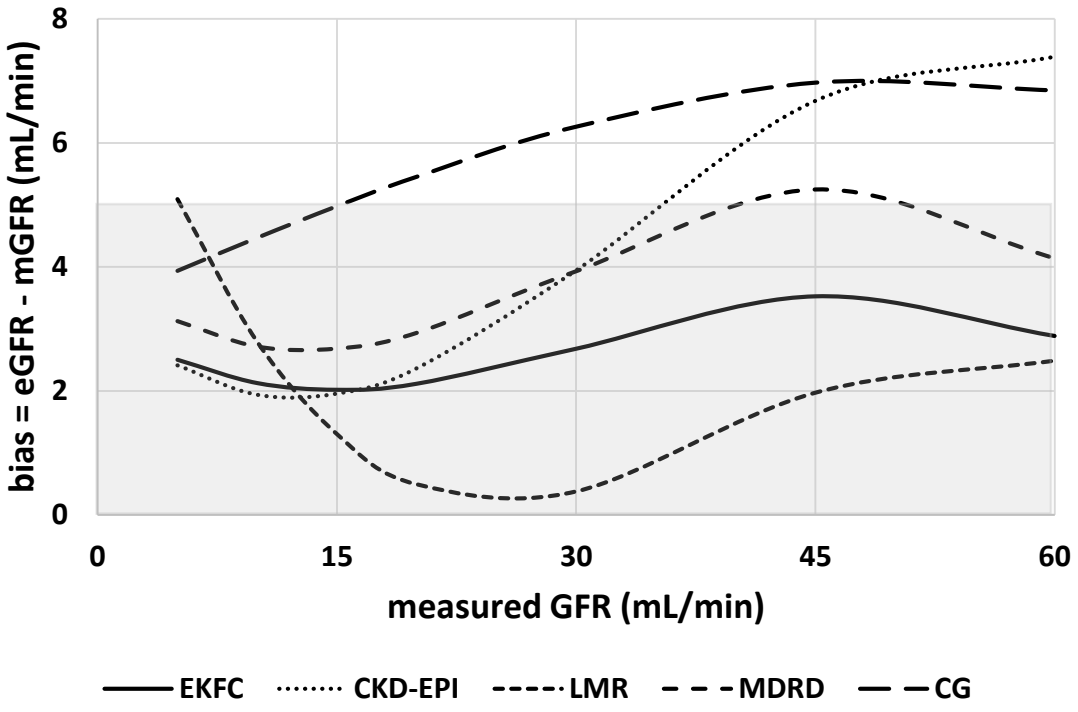
Figures legends

Figure 1: A: Bias = eGFR – mGFR against measured GFR for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR <60 mL/min. Positive bias indicates overestimation; negative bias indicates underestimation. Grey zone is corresponding to a bias of +/- 5mL/min. B: P30 against measured GFR for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR <60 mL/min (n=4,328).

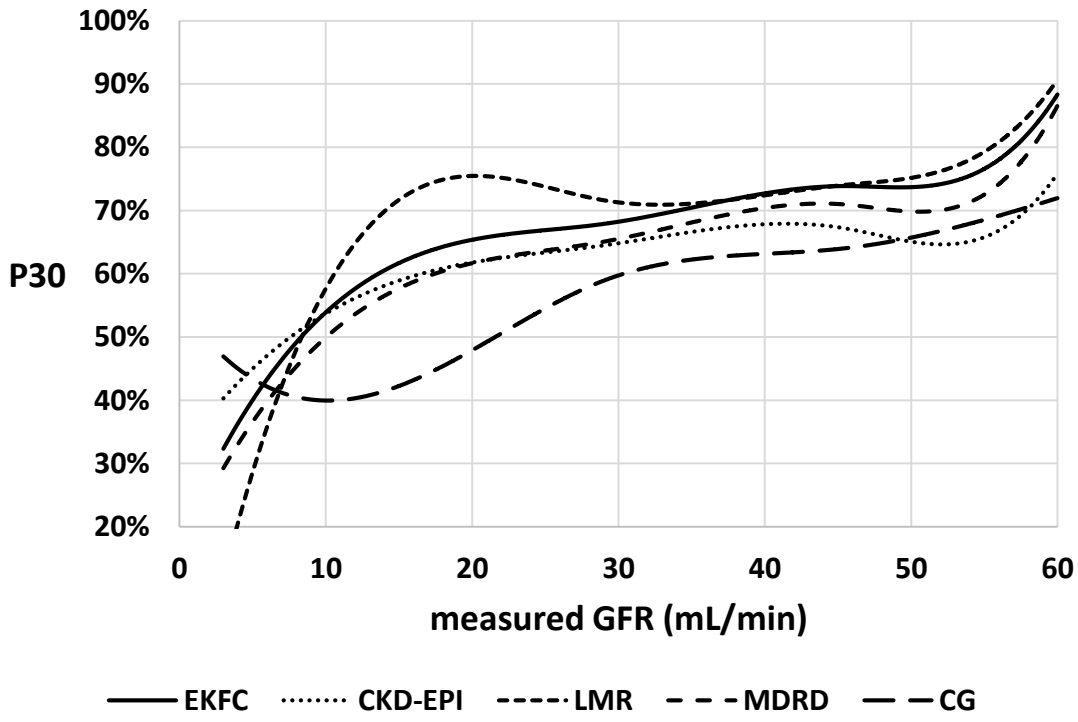
Figure 2: A: Bias = eGFR – mGFR against age for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR <60 mL/min. Positive bias indicates overestimation; negative bias indicates underestimation. Grey zone is corresponding to a bias of +/- 5mL/min. B: P30 against age for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR <60 mL/min. C: Bias = eGFR – mGFR against weight for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR <60 mL/min. Positive bias indicates overestimation; negative bias indicates underestimation. Grey zone is corresponding to a bias of +/- 5mL/min. D: P30 against weight for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations in patients with mGFR <60 mL/min (n=4,328).

Appendix Figure 1: A: Bias = eGFR – mGFR against measured GFR for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations on the whole GFR range (n=14,804). Positive bias indicates overestimation; negative bias indicates underestimation. Grey zone is corresponding to a bias of +/- 5mL/min. B: P30 against measured GFR for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations on the whole GFR range (n=14,804).

A


8
6
4
2
0
bias = eGFR - mGFR (mL/min)
0
15
30
45
60
measured GFR (mL/min)
EKFC
CKD-EPI
LMR
MDRD
CG

B


100%
90%
80%
70%
60%
50%
40%
30%
20%
P30
0
10
20
30
40
50
60
measured GFR (mL/min)
EKFC
CKD-EPI
LMR
MDRD
CG

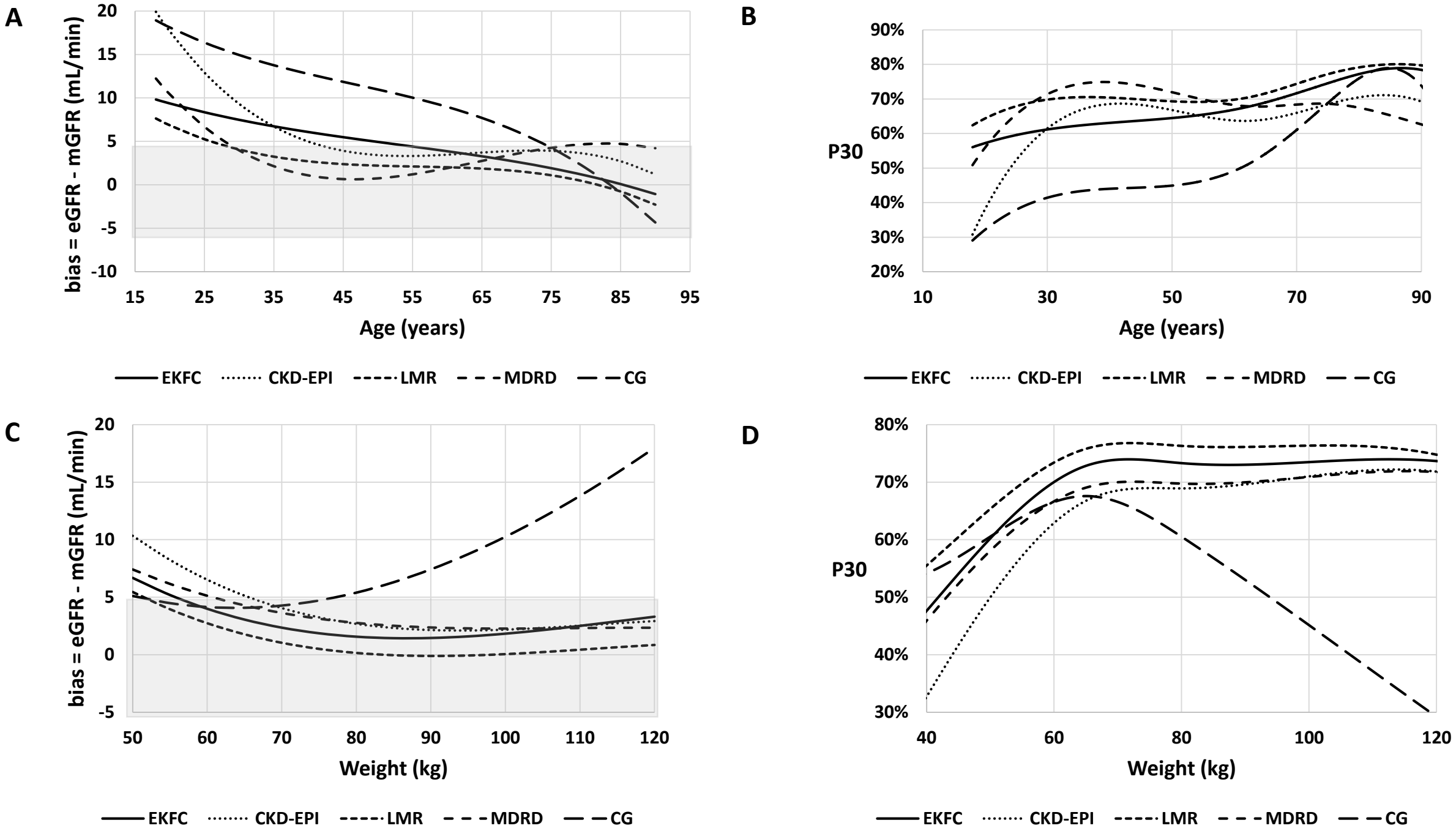

A
bias = eGFR - mGFR (mL/min)
20
15
10
5
0
-5
-10
15
25
35
45
55
65
75
85
95
Age (years)
EKFC
CKD-EPI
LMR
MDRD
CG
B
P30
90%
80%
70%
60%
50%
40%
30%
20%
10
30
50
70
90
Age (years)
EKFC
CKD-EPI
LMR
MDRD
CG
C
bias = eGFR - mGFR (mL/min)
20
15
10
5
0
-5
50
60
70
80
90
100
110
120
Weight (kg)
EKFC
CKD-EPI
LMR
MDRD
CG
D
P30
80%
70%
60%
50%
40%
30%
40
60
80
100
120
Weight (kg)
EKFC
CKD-EPI
LMR
MDRD
CG

Table S1: Creatinine-based equations

Cockcroft-Gault equation (mL/min)[3]

[(140-age)/(72×SCr)]×weight (kg) ×(0.85 for female)

MDRD study equation (mL/min/1.73 m²)[17]

175 x SCr (mg/dL) $^{-1.154}$ x age $^{-0.203}$ x 0.742 (for female)

CKD-EPI equation (mL/min/1.73 m2)[2]

Female
SCr≤0.7 mg/dL
144 x (SCr/0.7) $^{-0.329}$ x 0.993^{age}
SCr>0.7 mg/dL
144 x (SCr/0.7) $^{-1.209}$ x 0.993^{age}
Male
SCr≤0.9 mg/dL
141 x (SCr/0.9) $^{-0.411}$ x 0.993^{age}
SCr>0.9 mg/dL
141 x (SCr/0.9) $^{-1.209}$ x 0.993^{age}

LMR equation[29]

$e^{X - 0.0158 \times age + 0.438 \times \ln(age)}$

Female and SCr<1.71 mg/dL
X=3.43+0.0121x(1.71-SCr)
Female and SCr≥1.71 mg/dL
X=3.43-0.926xln(SCr/1.71)
Male and SCr<2.05 mg/dL
X=3.37+0.00968x(2.05-SCr)
Female and SCr≥2.05 mg/dL
X=3.37-0.926xln(SCr/2.05)

EKFC equation[1]

2-40 years
SCr/Q<1
107.3 x $(SCr/Q)^{-0.322}$
SCr/Q≥1
107.3 x $(SCr/Q)^{-1.132}$
>40 years
SCr/Q<1
107.3 x $(SCr/Q)^{-0.322}$ x $0.99^{(age-40)}$
SCr/Q≥1
107.3 x $(SCr/Q)^{-1.132}$ x $0.99^{(age-40)}$

Q values[18]
For ages 2-25 years
Males
$Ln(Q)=3.2 + 0.259 \times age - 0.543 \times \ln(age) - 0.00763 \times age^2 + 0.000079 \times age^3$
Females
$Ln(Q)=3.08 + 0.177 \times age - 0.223 \times \ln(age) - 0.00596 \times age^2 + 0.0000686 \times age^3$
For ages ≥ 25 years
Males
Q=0.9 mg/dL
Females
Q=0.7 mg/dL

CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases. SCr = serum creatinine.
Results in mL/min/1.73m² were "de-indexed" for body surface area. Scr and Q in mg/dL (to convert from mg/dL to µmol/L, multiply by 88.4)

Table S2: Basic participants characteristics. Descriptive measures given as median values (2.5; 97.5 percentiles) if not stated otherwise.

Characteristic	All (n = 14,804)	mGFR <60 mL/min (n = 4,328)
Age (years)	58.5 (18.6; 84.0)	71.0 (19.0; 88.7)
Females (percent)	49.5	47.4
BMI (kg/m²)	25.6 (17.6; 38.4)	25.5 (16.8; 39.2)
BSA (m²)	1.84 (1.43; 2.31)	1.82 (1.38; 2.31)
Plasma/serum creatinine (mg/dL)	0.89 (0.52; 3.53)	1.62 (0.71; 5.07)
Measured GFR (mL/min)	81.5 (15.3; 142.1)	37.7 (10.0; 58.9)
GFR estimated by CG equation (mL/min)	87.6 (18.9; 175.3)	43.2 (12.4; 92.5)
GFR estimated by MDRD equation (mL/min)	82.5 (16.9; 151.3)	41.4 (11.0; 86.2)
GFR estimated by CKD-EPI equation (mL/min)	88.7 (16.2; 140.6)	42.0 (10.4; 88.2)
GFR estimated by LMR equation (mL/min)	79.1 (16.3; 122.8)	38.2 (11.4; 78.4)
GFR estimated by EKFC equation (mL/min)	82.9 (16.4; 129.4)	40.3 (10.9; 82.6)

BMI: body mass index. BSA: body surface area. CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. mGFR: measured glomerular filtration rate. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases. Plasma/serum creatinine in mg/dL (to convert from mg/dL to μmol/L, multiply by 88.4)

Table S3: Method and patients characteristics

Center	Country	Cohort	n	Method	Exogenous marker	Age	mGFR (mL/min)	% of female
Amsterdam	The Netherlands	CAPA-study[46] + referrals	48	Plasma clearance	Inulin	18.7±0.9	93.7±27.9	25.0
Berlin	Germany	BIS-Study[32]	657	Plasma clearance	Iohexol	78.4±6.1	60.3±21.5	41.7
France	France	Kidney Donor Study[48]	2,572	Plasma/renal clearance	Iohexol/^{51}Cr-EDTA/inulin	50.4±11.8	100.1±22.2	61.9
Kent	UK	GFR in old adults[49]	394	Plasma clearance	Iohexol	80.4±4.6	55.3±20.5	52.0
Leuven	Belgium	Referrals	21	Plasma clearance	^{51}Cr-EDTA	19.1±1.2	78.2±23.1	47.6
Lund	Sweden	CAPA-study[46]	2,847	Plasma clearance	Iohexol	60.1±16.5	62.5±34.1	48.5
Lyon	France	Referrals	2,435	Plasma/renal clearance	Iohexol/inulin	31.3±16.7	84.5±32.7	46.8
Örebro	Sweden	Referrals	2,051	Plasma clearance	Iohexol	56.5±16.3	64.3±36.0	41.7
Rochester	USA	ECEC/GENOA study[50]	1,093	Renal clearance	Iothalamate	65.2±8.9	90.2±26.8	56.6
Saint-Etienne	France	HIV-study[51]	203	Plasma clearance	Iohexol	48.7±10.3	100.3±27.3	48.7
Stockholm	Sweden	Referrals	856	Plasma clearance	Iohexol	72.9±14.1	48.7±27.6	44.2
Tromsø	Norway	RENIS-T6 study[52]	1,627	Plasma clerance	Iohexol	58.1±3.8	101.5±19.9	50.8

*Referrals = referred for plasma or renal clearance measurement on clinical grounds. Results mean±SD.

Table S4: Performance of different equations in the whole population

N=14,804	**CG**	**MDRD**	**CKD-EPI**	**LMR**	**EKFC**
Median bias (95%CI)	6.5 (6.2; 6.8)	1.6 (1.3; 1.9)	4.0 (3.8; 4.3)	-3.4 (-3.7; -3.2)	-0.1 (-0.4; 0.1)
Imprecision	22.2	19.6	18.0	17.1	16.6
P30 (%) (95%CI)	73.7 (73.0; 74.4)	80.9 (80.3; 81.6)	82.3 (81.6; 82.9)	87.8 (87.3; 88.3)	86.9 (86.4; 87.5)

Bias (estimated GFR – measured GFR) and imprecision (interquartile range) expressed in mL/min.
P30: percentage of estimated GFR within ±30% of measured GFR. CI: confidence interval.
CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. GFR: glomerular filtration rate. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases. Results in mL/min.

Table S5: Performance of different equations in the whole population from the external validation cohort

N=6,975	**CG**	**MDRD**	**CKD-EPI**	**LMR**	**EKFC**
Median bias (95%CI)	5.3 (4.8; 7.7)	0.5 (0.1;0.9)	3.1 (2.8; 3.4)	-3.9 (-4.3; -3.6)	-0.6 (-1.0; -0.2)
Imprecision	22.4	19.5	16.8	16.9	16.4
P30 (%) (95%CI)	75.2 (74.2; 76.2)	82.8 (81.9;83.7)	84.8 (83.9; 85.6)	88.5 (87.8; 89.3)	87.8 (87.1; 88.6)

Bias (estimated GFR – measured GFR) and imprecision (interquartile range) expressed in mL/min. P30: percentage of estimated GFR within ±30% of measured GFR. CI: confidence interval.
CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. GFR: glomerular filtration rate. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases.

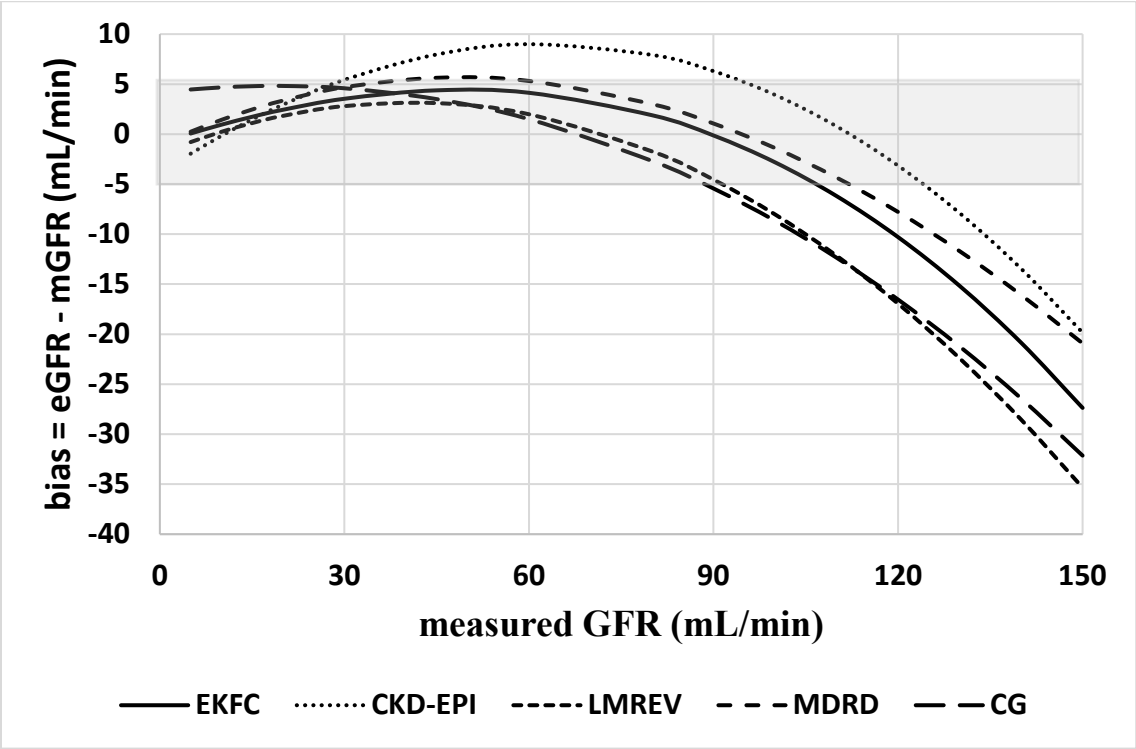
Table S6: Performance of different equations in subgroups according to measured GFR (mGFR), age and BMI from the external validation set

	CG	MDRD	CKD-EPI	LMR	EKFC
mGFR<60 mL/min n=1,779					
Median bias	5.8	3.8	4.2	1.6	3.0
Imprecision	14.7	11.8	13.1	11.7	11.7
P30 (%)	58.5	69.4	67.1	75.0	71.4
mGFR<15 mL/min n=185					
Median bias	3.9	1.8	1.0	2.0	1.5
Imprecision	6.6	5.9	5.9	5.3	6.0
P30 (%)	46.5	55.1	59.5	63.8	60.0
mGFR [15-30[mL/min n=470					
Median bias	5.7	3.3	3.1	0.9	2.7
Imprecision	11.2	9.1	9.4	7.7	9.1
P30 (%)	51.5	64.3	64.7	74.9	67.2
mGFR [30-45[mL/min n=515					
Median bias	6.0	3.8	4.5	0.4	3.1
Imprecision	17.0	12.9	14.1	14.0	12.8
P30 (%)	61.0	71.7	68.7	74.0	72.6
mGFR [45-60[mL/min n=609					
Median bias	6.9	5.8	7.3	3.2	3.9
Imprecision	21.5	16.2	17.9	16.0	16.6
P30 (%)	65.4	75.9	69.8	79.5	77.0
mGFR<60 mL/min and age [18-40[years n=100					
Median bias	19.2	4.6	10.6	4.1	5.5
Imprecision	17.1	13.6	18.7	14.9	17.5
P30 (%)	30.0	73.0	60.0	71.0	62.0
mGFR<60 mL/min and age [40-65[years n=487					
Median bias	11.0	2.9	5.3	3.4	5.6
Imprecision	14.6	12.0	14.0	12.1	12.7
P30 (%)	42.9	72.7	65.3	72.7	65.9
mGFR<60 mL/min and age ≥65 years n=1,192					
Median bias	3.2	4.2	3.4	0.7	1.4
Imprecision	12.6	11.7	11.9	10.9	10.7
P30 (%)	67.2	67.8	68.4	76.3	74.4
mGFR<60 mL/min and BMI<18.5 kg/m^2 n=72					
Median bias	2.9	8.8	10.2	7.8	6.7
Imprecision	10.6	14.4	17.2	13.2	14.5
P30 (%)	63.9	54.2	43.1	59.7	51.4
mGFR<60 mL/min and BMI [18.5-25[kg/m^2 n=641					
Median bias	2.5	3.9	4.3	1.5	3.1
Imprecision	13.0	12.1	13.8	11.8	11.7
P30 (%)	70.0	68.6	67.1	74.6	70.8
mGFR<60 mL/min and BMI [25-30[kg/m^2 n=660					
Median bias	5.2	3.1	3.2	0.6	1.9
Imprecision	13.4	10.0	11.9	10.8	11.1
P30 (%)	60.2	73.6	71.4	78.0	75.0
mGFR<60 mL/min and BMI [30-35[kg/m^2 n=284					
Median bias	9.7	4.1	3.6	1.6	2.8
Imprecision	14.6	12.4	13.5	11.4	11.5
P30 (%)	45.4	68.0	66.9	75.4	72.9

mGFR<60 mL/min and BMI [35-40[kg/m^2 n=93					
Median bias	19.3	7.0	7.1	3.9	5.8
Imprecision	20.0	12.0	13.2	10.9	12.8
P30 (%)	21.5	66.7	60.2	76.3	65.6
mGFR<60 mL/min and BMI ≥40 kg/m^2 n=40					
Median bias	24.9	1.9	3.3	1.6	3.9
Imprecision (IQR)	18.6	12.6	15.3	14.2	15.2
P30 (%)	17.1	65.9	65.9	63.4	65.9

Bias (estimated GFR – measured GFR) and imprecision (interquartile range) expressed in mL/min. P30: percentage of estimated GFR within ±30% of measured GFR. CI: confidence interval.
BMI: body mass index. CG: Cockcroft and Gault. CKD-EPI: Chronic Kidney Disease Epidemiology. EKFC: European Kidney Function Consortium. LMR: Lund Malmö Revised. MDRD: Modification of Diet in Renal Diseases. mGFR: measured glomerular filtration rate.

Supplement Figure 1A: Bias = eGFR – mGFR against measured GFR for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations on the whole GFR range (n=14,804).



Positive bias indicates overestimation; negative bias indicates underestimation. Grey zone is corresponding to a bias of +/- 5mL/min.

Supplement Figure 1B: P30 against measured GFR for the Cockcroft and Gault, MDRD, CKD-EPI, LMR and EKFC equations on the whole GFR range (n=14,804).