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Performance of Creatinine-Based GFR Estimating Equations in Solid Organ Transplant Recipients

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Abstract

Background—Accurate assessment of kidney function is important for management of solid organ transplant recipients. In other clinical populations, glomerular filtration rate (GFR) is most commonly estimated using the CKD-EPI (Chronic Kidney Disease–Epidemiology Collaboration) creatinine or the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. The accuracy of these equations compared to other GFR estimating equations in transplant recipients has not been carefully studied.

Study Design—Diagnostic test study.

Setting & Participants—Solid organ transplant recipients >6 months post-transplantation from 5 clinical populations [N=3,622, including recipients of kidney (53%), liver (35%) and other or multiple organs (12%)]

Index Test—Estimated GFR (eGFR) using creatinine-based GFR estimating equations identified from a systematic review of the literature. Performance of the CKD-EPI creatinine and MDRD Study equations was compared to alternative equations.

Reference Test—Measured GFR (mGFR) from urinary clearance of iothalamate or plasma clearance of iohexol.

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Measurements—Error (difference between the mGFR and eGFR) expressed as P_{30} (proportion of absolute percent error <30%) and mean absolute error.

Results—We identified 26 GFR estimating equations. Mean mGFR was 55.1 ± 22.7 (SD) ml/min/1.73 m^2. P_{30} and mean absolute error for the CKD-EPI and MDRD Study equations were 78.9% (99.6% CI, 76.9%–80.8%) for both and 10.6 (99.6% CI, 10.1–11.1) vs. 11.0 (99.6% CI, 10.5–11.5) ml/min/1.73 m^2, respectively; these equations were more accurate than any of the alternative equations ($p<0.001$ for all pair-wise comparisons for both measures). They performed better than or as well as the alternative equations in most subgroups defined by demographic and clinical characteristics, including the type of transplanted organ.

Limitations—Study population included few non-whites and people with solid organ transplants other than liver and kidneys.

Conclusions—The CKD-EPI creatinine and MDRD Study equations perform better than the alternative creatinine-based estimating equations in solid organ transplant recipients. They can be used for clinical management.

INDEX WORDS

GFR estimation; renal function; kidney transplantation; solid organ transplant recipient; creatinine-based eGFR equation

Accurate assessment of kidney function is important for the management of solid-organ transplant recipients. Glomerular filtration rate (GFR) is most commonly estimated using serum creatinine-based estimating equations. Numerous equations have been developed, but their performance in transplant recipients has not been systematically and comprehensively evaluated. Clinical practice guidelines recommend monitoring kidney function to detect nephrotoxicity of immunosuppressive medications, to identify early signs of rejection in kidney transplant recipients, to adjust doses of drugs that are excreted by the kidneys, to guide testing and treatment for kidney disease complications, and to estimate prognosis.[1]

Guidelines provide conflicting recommendations about methods for GFR estimation in transplant recipients and there is some concern that currently available equations may be less accurate in transplant recipients than other clinical populations.[2] The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the care of kidney transplant recipients recommends using any one of several creatinine-based equations to estimate GFR.[1] The US Food and Drug Administration (FDA) recommends the use of the Cockcroft-Gault equation for drug development programs and in package inserts.[3] Currently, the National Kidney Disease Education Program (NKDEP) recommends using the isotope-dilution mass spectrometry (IDMS)–traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation for reporting of estimated GFR (eGFR) by clinical laboratories[4,5], but the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has recently been shown to be more accurate than the MDRD Study equation and has begun to replace it in laboratory reports.[6–9] There is a need to determine the accuracy of GFR estimating equations in solid-organ transplant recipients.

We conducted a systematic evaluation of the development methods of all published creatinine-based GFR estimating equations and evaluated their performance in a large and diverse population of solid organ transplant recipients. We compared the performance of the CKD-EPI and the MDRD Study equations with all the other creatinine-based equations.

Methods

Study Overview

We first performed a systematic review of published creatinine-based equations to develop an inventory of eGFR equations and evaluate their development methods. We then performed a study of diagnostic test accuracy to compare the performance of these equations to measured GFR (mGFR) in solid organ transplant recipients.

Systematic Review

We searched MEDLINE for articles that described creatinine-based GFR estimating equations from 1950 until October 2012 with no language restrictions (see Table S1, available as online supplementary material, for search terms). We supplemented this by hand searching the references of relevant articles that reported either a new eGFR equation or compared the performance of existing equations as well as the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines for the laboratory measurements for clinical assessment of kidney disease.[10]

One investigator (S.K.S.) reviewed the articles for inclusion in the systematic review. Inclusion criteria were studies in which a GFR estimating equation (index text) was developed using either GFR measured with an exogenous filtration marker or measured creatinine clearance as a reference test in a population older than 18 years. We excluded studies that: 1) developed a nomogram rather than an equation; 2) developed equations by modifying an existing equation to improve its performance for use in a different clinical population or racial and ethnic subgroup; 3) developed equations that used variables other than age, sex, race, weight, BMI, body surface area, and serum creatinine and urea (or serum urea nitrogen [SUN]) for GFR estimation, as other variables may not be available in routine clinical practice.

We used criteria for developing and validating GFR estimating equations recommended by Earley et al[7] to extract the information on the equation development cohort, index test and the reference test characteristics. Information included the following: year of equation development; development cohort characteristics (overall number, mean GFR, mean age, and type of the population [e.g. inpatient, outpatient or both]); reference test characteristics (filtration marker and clearance method, whether the equation was developed using multiple GFR measurements from the same patients, whether the GFR was scaled to body surface area); index test characteristics (creatinine assay used and its traceability to a standard reference material [SRM]); and whether equations were validated in an external validation cohort.

Comparison of Equation Performance

Data Source—The study population included subjects with one measurement of GFR, using urinary or plasma clearance of an exogenous filtration marker, and serum creatinine using assays that were standardized to the SRM.[11] We included a total of 3,622 subjects from five clinical populations (studies).[8,12] Data from four studies (Baylor, Groningen, Lund, Cleveland Clinic) comprised all solid organ transplant recipients from the CKD-EPI 2009 creatinine equation external validation cohort (n=1,112).[8] Additional subjects from one of the study sites (Groningen; n=586) and data from the Mayo Clinic (n=1,924) were also included.[12] Inclusion and exclusion criteria of study populations have been previously described [8,12] and are shown in Item S1 and Figure S1. One of the equations we tested required serum urea. Serum urea or SUN was not available in 764 subjects; therefore, we included 2,858 subjects for GFR estimation using that equation. None of the patients included were receiving trimethoprim/sulfamethoxazole. All studies were approved by the institutional review boards at the participating medical centers and Tufts Medical Center.

Reference and Index Tests—We considered mGFR as the reference test and eGFR computed by the equations identified in the systematic review as the index tests. We compared the performance of the CKD-EPI creatinine and MDRD Study equations to the alternative equations.

Statistical Analysis

We evaluated the distribution of continuous variables by assessing the mean ± standard deviation and categorical variables by number (percentage) in the whole data set as well as in subgroups according to the study population characteristics and transplant organ type. We defined error as mGFR minus eGFR (*mGFR – eGFR*) for each subject and percent error as this difference relative to mGFR, ie, *(mGFR-eGFR)/mGFR*. We computed bias as the average error and percent error, with mean or median used as appropriate for the distribution. We computed accuracy as the mean absolute error and proportion of subjects with absolute percent error less than 30% (P_{30}). [13] We used P_{30} as the primary outcome as it is a commonly used metric of accuracy in GFR estimating equations, and used mean absolute error as the secondary outcome.

We performed pair wise comparisons of the CKD-EPI and MDRD Study equations with alternative equations. A priori, we decided to perform pairwise comparisons for only those alternative equations that had a P_{30} of ≥60% and mean absolute error of ≤20 ml/min/1.73 m^2 to ensure that the comparisons are clinically meaningful. To overcome the problem of non-independence of the observations, we used generalized estimating equation models to calculate the point estimates and confidence intervals (CIs) for the difference between the P_{30} or mean absolute error of the CKD-EPI or the MDRD Study equations and each of the alternative equations (see Item S2 for further details). We obtained the point estimates and CIs for median percent and absolute percent error by the bootstrap method (2000 bootstraps). To circumvent the problem of inflated type I error rate due to 12 pairwise comparisons, we used Bonferroni's approach to set the α for each comparison at 0.004 to achieve an overall α of 0.05 and reported 99.6% CIs. We also compared the performance (P_{30} and mean absolute error) of the CKD-EPI equation with the MDRD Study equation.

Since both equations were derived on the log scale, in sensitivity analyses, for this comparison, we also computed percent error on the log scale. Finally, we used interaction terms in the model to assess whether the difference in the performance of the CKD-EPI or the MDRD Study equation and the alternative equations was similar across the levels of the following clinical and demographic variables: age (≤55, >55 years), sex, race (non-white, white), weight (<75, 75–100, >100 kg), level of mGFR (< 60, ≥60 ml/min/1.73 m^2), study, and transplant organs (kidneys, liver, lungs, heart and pancreas). We had complete data on these variables on all subjects. We based our conclusions on clinical and statistical significance.

Results

Systematic Review

Our search for creatinine-based GFR estimating equation revealed 4,947 articles (Figure 1). After initial screening, we selected 78 articles for full text review, of which 36 articles reported 37 eGFR equations. We identified an additional 14 equations based on hand searches of the articles and the KDOQI clinical practice guideline for chronic kidney disease. Of the 51 equations, a total of 26 equations met our criteria for inclusion in the systematic review.[8,14–37] The equations and their characteristics are shown in Tables 1 and S2. For equations not specifically named in the literature, we simply use the first author's last name. The first equation (Edwards) was reported in 1959 while the most recent equation (Berlin Initiative Study [BIS] 1) was reported in 2012.[14,37] Only 2 equations (CKD-EPI and MDRD Study) had a development cohort comprising greater than 1000 subjects.[8,28] Five equations had transplant recipients in their development cohort; of these, 2 equations were developed exclusively in organ transplant recipients (Nankivell in kidney transplant recipients and Nankivell-SPK in simultaneous pancreas and kidney transplant recipients),[23,24] and three equations were developed using both transplant recipients and the other populations (CKD-EPI, Gates, and Mayo).[8,19,32] Twelve equations used creatinine as the filtration marker for the reference test with the remainder using iothalamate, inulin, ethylenediaminetetraacetic acid (EDTA) or diethylenetriaminepentaacetic acid (DTPA). In most of the equations (n=19), GFR was measured by urinary clearance of the filtration marker. The mean mGFR in the development cohort was 57 ml/min/1.73 m^2 for the equations that reported GFR scaled to body surface area of 1.73 m^2 (n=12), and 62 ml/min for the equations that did not scale eGFR to body size (n=11). A total of 2 equations did not report the mean GFR in the development cohort and 1 equation reported eGFR scaled to body surface area of 3 m^2. Five equations used a creatinine assay that was traceable to SRM.[5,8,34,36,37] Sixteen equations were developed in a population in which serum creatinine was in a steady state. Age, sex and race were used in 19, 20, and 2 equations, respectively. Fifteen equations were evaluated in a validation cohort in the original publication.

Comparison of Equation Performance

Clinical and Demographic Characteristics—The clinical and demographic characteristics of the 3622 subjects who were used for evaluation of equation performance are shown by study in Table 2. Of the overall study population, the mean age was 54 years, 98% of the subjects were white and 57% were males. The mean mGFR was 55 ml/min/1.73

m^2. Kidney (53%) and liver (35%) transplant recipients were most common, with recipients of heart, lung, pancreas or more than one organ constituting the remainder (12%). There was a wide variation in clinical and demographic variables among recipients of different organs (Table S3) and by availability of SUN concentrations (Table S4).

Performance in the Whole Cohort—Table 3 shows the performance of the 26 equations. The CKD-EPI equation had a mean error of 0.4 (99.6% CI, −0.3 to 1.1) ml/min/1.73 m^2, P_{30} of 78.9% (99.6% CI, 76.9%–80.8%) and mean absolute error of 10.6 (99.6% CI, 10.1–11.1) ml/min/1.73 m^2. The MDRD Study equation had a mean error of 4 (99.6% CI, 3.3–4.7) ml/min/1.73 m^2, P_{30} of 78.9% (99.6% CI, 76.9%–80.8%), and mean absolute error of 11.0 (99.6% CI, 10.5–11.5) ml/min/1.73 m^2. There was a wide range in the performance of the other equations, with mean error ranging between −67.3 and 24.1 ml/min/1.73 m^2 and P_{30} between 4.9% and 78.9%. Only 12 other equations (including the Gates and the Nankivell-SPK equations) met the criteria of a P_{30} ≥60% and absolute error ≤20 ml/min/1.73 m^2 for further comparison to the CKD-EPI and the MDRD Study equations (Figure 1).

For P_{30}, the CKD-EPI and the MDRD Study equations outperformed all alternative equations (difference in P_{30} ranged from 2.4%–17.2% [p <0.001 for all pairwise comparisons with the CKD-EPI equation] and 2.5%–17.3% [p <0.001 for all pairwise comparison with the MDRD Study equation]; Figure 2). Similarly, the CKD-EPI and the MDRD Study equations had lower mean absolute errors than all the alternative equations (difference in mean absolute error ranged from −6.2 to −1.0 ml/min/1.73 m^2 [p <0.001 for all pairwise comparisons with the CKD-EPI equation] and −5.8 to −0.6 ml/min/1.73 m^2 [p <0.001 for all pairwise comparisons with the MDRD Study equation]; Figure 2).

The CKD-EPI and MDRD Study equations had similar performance (difference [CKD-EPI – MDRD Study] in P_{30} of −0.05% [99.6% CI, −1.4% to 1.5] and difference in mean absolute error of −0.4 [99.6% CI, −0.6 to −0.2] ml/min/1.73 m^2).

Performance in Subgroups—There were significant pairwise differences in equation performance for many subgroups based on organ, demographic and clinical characteristics, and study (Figure 3 and Figures S2–S7). For all subgroups with significant differences, including organ, the performance of the CKD-EPI equation was either superior or similar to the alternative equations, with the exception of the subgroups with mGFR <60 ml/min/1.73 m^2 where the Walser equation performed better (difference in P_{30} of −3.5% [99.6% CI, −5% to −1.9%]), and with mGFR ≥60 ml/min/1.73 m^2 where some other equations performed better (differences in P_{30} of −5.0% [99.6% CI, −8.1% to −2.0%], −3.7% [99.6% CI, −5.5% to −1.9%], −3.0% [99.6% CI, −5.5% to −0.6%], −4.8% (99.6% CI, −7.4% to −2.2%], and −2.6% [99.6% CI, −4.8% to −0.5%] for Cockcroft-Gault, Virga, Edwards, Yukawa, and Wright equations, respectively (Figure S6). We observed similar findings for interactions of subject level covariates and equations in comparisons with the MDRD Study equation (Figures S2–S7). Comparisons of performance of CKD-EPI and MDRD Study equations by study, organ and level of mGFR are shown in Tables S5 and S6 and Figure S8, respectively. Performance of the CKD-EPI equation was better at higher GFR and performance of the MDRD Study equation was better at lower GFR (Figure S8).

Discussion

Clinicians monitor serum creatinine frequently in organ transplant recipients to detect immunologic rejection, infection or toxicity of medications. Most US clinical laboratories report eGFR using the CKD-EPI or MDRD Study equation whenever serum creatinine is ordered.[6] However, no single GFR estimating equation is optimal for all populations and GFR ranges,[7] and there has been some reluctance by transplant physicians to use GFR estimates in the day-to-day management of solid organ transplant recipients because of the concern that the equations might be less accurate in transplant recipients than in other clinical populations.[2] Our systematic review of creatinine-based GFR estimating equations revealed substantial variability in equation development methods and showed that the newer equations were more thorough in their reporting of development methods. Our evaluation of equation performance in a large cohort of solid organ transplant recipients revealed that the CKD-EPI creatinine and IDMS-traceable 4-variable MDRD Study equations were more accurate than the alternative equations (even those equations developed in populations of only transplant recipients) and as accurate as observed in other clinical populations (P_{30} of approximately 80%). [7] In addition, they performed either better than or as well as any other equation in almost all the subgroups that we examined, including type of organ.

Several prior studies have compared the performance of creatinine-based GFR estimating equations in kidney, liver and heart transplant recipients and have shown conflicting results.[12,38–49] The majority of the studies showed that the CKD-EPI and the MDRD Study equations performed better than other equations, whereas a few studies showed some of the alternative equations performed better. Prior to the publication of the CKD-EPI equation, White et al performed a systematic review of studies to compare the performance of some of the creatinine-based equations and concluded that the MDRD Study equation was the most accurate. [50] The authors pointed out that the studies included in the systematic review were limited by the heterogeneity among test populations, use of non-standardized creatinine assays, incomplete reporting of the equation performance metrics and inclusion of multiple GFR measurements on the same patients. Studies directly comparing the performance of the CKD-EPI and MDRD Study equations have also shown conflicting results. [2,12,47,50] We did not find a difference between these two equations in the overall study population, but showed better performance of the CKD-EPI equation at higher levels of GFR and better performance of the MDRD Study equation at lower levels of GFR, which is consistent with the systematic review by Earley et al [7] based on an analysis of group data.

Creatinine has long been used as a filtration marker, but its serum levels are affected by factors besides GFR, such as creatinine generation by muscle mass and diet.[51] GFR estimating equations use readily available clinical and demographic variables as surrogates for this and other non-GFR determinants. It has been suggested that muscle mass in solid organ transplant recipients may differ systematically from that in patients with other clinical conditions because of use of corticosteroids and immunosuppressive medications, periods of prolonged dialysis prior to kidney transplantation, chronic inflammatory state due to prolonged illness, bouts of rejection and infections. Our finding that the CKD-EPI and MDRD Study equations perform better than or as well as they do in non-transplant populations suggests that the non-GFR determinants of serum creatinine may not differ

systematically between solid organ transplant recipients and other patients.[52] Possibly, there are differences in non-GFR determinants among recipients of types of organs which account for some of the variability in performance of equations across subgroups of types of organs.

The better performance of the CKD-EPI and MDRD Study equations compared to the other equations is likely due to their development in a large study population, use of mGFR instead of creatinine clearance as the reference test in the equation development cohort, use of standardized creatinine and robust statistical methods and inclusion of a variable for race, [7] and, for the CKD-EPI equation, development in a cohort made up of subjects with diverse clinical characteristics and a wide range of GFRs. Use of urinary clearance of iothalamate to measure GFR in the vast majority of our study population (98.8%), as in the development population for the CKD-EPI and MDRD Study equations, may also contribute to the better performance of these equations in our study.

The results of this study have important clinical implications. Our findings that the CKD-EPI and the MDRD Study equations are the two most accurate equations in solid organ transplant recipients as in other clinical populations enables transplant physicians to use the GFR estimates that are routinely reported by the laboratories for clinical purposes. Estimated GFR provides similar information to serum creatinine for monitoring changes in kidney function, as the relative change in eGFR is proportional to the relative change in serum creatinine.[1] However, serum creatinine alone cannot be used to determine the level of eGFR, which is essential for detection and staging of chronic kidney disease and for management of its various complications, including anemia, mineral and bone disease [1] and some recent studies suggest worse stage-based management in kidney transplant recipients compared with patients with native kidney diseases. [53,54] Furthermore, transplant recipients require a large number of medications and eGFR is required for accurate dosing. Moreover, the level of eGFR has been shown to be a predictor of patient and allograft survival as well as health care expenditure in several large well-conducted studies. [55,56] Finally, quantification of the change in kidney function may be facilitated by the use of eGFR, since it does not require computation of relative changes, which may be difficult for some physicians to recognize, particularly at the extremes of serum creatinine.[13] Nonetheless, as in other clinical populations, GFR estimates based on serum creatinine are limited by imprecision and there is a need for further improvement [12]. Recent studies show that the use of cystatin C and creatinine in combination can improve the precision of GFR estimates, both in the general population and kidney transplant recipients. [47,57] Further work is required to evaluate these equations in kidney and other solid organ transplant recipients.

Our study has several strengths. Our study population included recipients of various types of solid organs with a wide range of kidney function from multiple centers, which enhances its generalizability. Our methods were comprehensive and rigorous. We examined all published creatinine-based equations. The GFR was measured using well-accepted methods and serum creatinine assays were standardized to reference methods. We used robust statistical methods to circumvent the problems of non-independence of observations and multiple hypothesis testing. To our knowledge, this is the first instance of the use of generalized estimating equations for assessing the performance of GFR estimating equations and this technique can be used for future studies of diagnostic accuracy.

Our study has some limitations. We pooled data from 5 studies and clinical populations which could have led to heterogeneity of study population, however, the CKD-EPI and the MDRD Study equation performed either similarly to or better than the alternative equations when we assessed the equation performance in each population. Urinary clearance of inulin is considered the gold standard for measuring GFR. However, urinary clearance of iothalamate and inulin demonstrate good co-linearity.[58] The GFR was measured by plasma clearance of iohexol in a minority of patients (1.2%), all of whom were in the Lund study, but our results did not differ substantially among studies. We had few non-Caucasians and subjects with solid organ transplants other than liver and kidneys; therefore our assessment of the equation performance in these subgroups is limited. The results may not apply to recipients taking trimethoprim/sulfamethoxazole, which causes systematic underestimation of mGFR by all equations. We did not have information on the immunosuppressive medications. Finally, imprecision in GFR measurements contributes to error between GFR estimates versus measurements, but this should not systematically bias the comparisons between GFR estimating equations.

In conclusion, we showed that the CKD-EPI and the MDRD Study equations are more accurate than any other currently available GFR estimating equations in solid organ transplant recipients, and are as accurate in this population as they are in other clinical populations. These equations can be used for routine monitoring of kidney function in solid organ transplant recipients as they are in other clinical populations. Future studies should focus on developing more accurate GFR estimating equations in this and other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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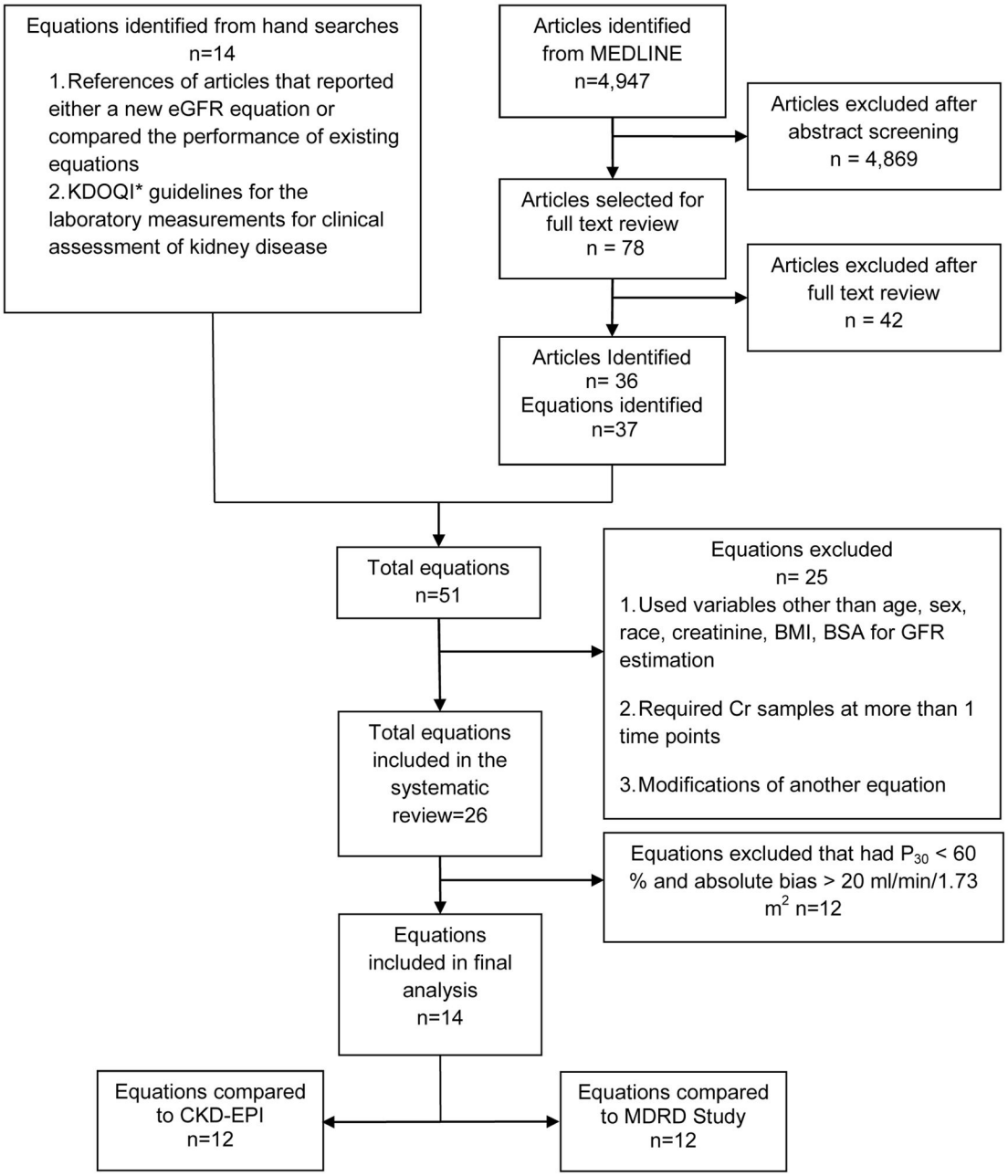

Fig 1.

Search strategy to identify eGFR equations

*KDOQI; Kidney Disease Outcomes Quality Initiative

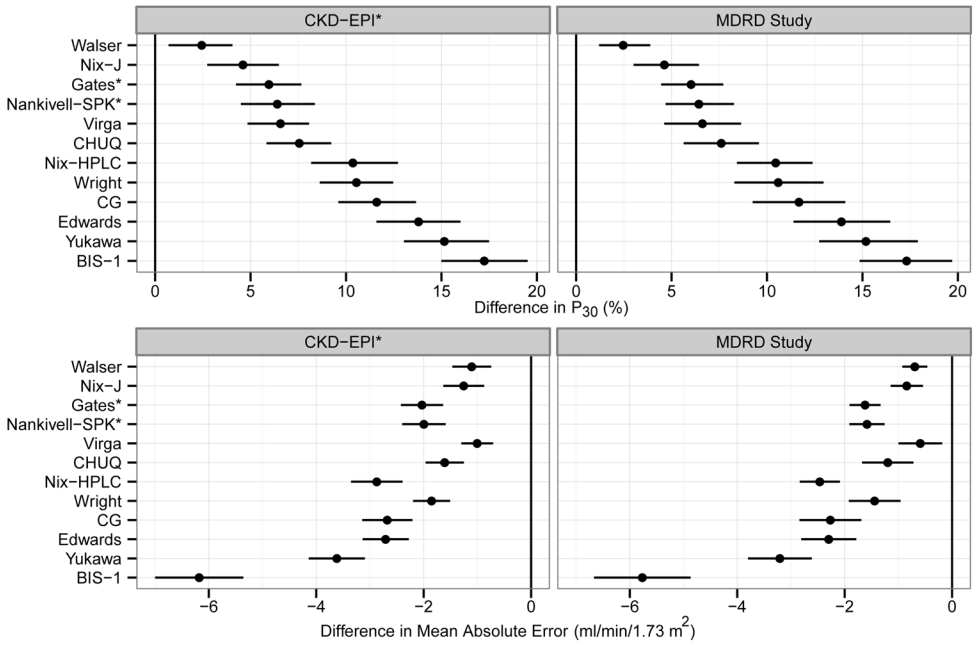

Fig 2.

The performance of the CKD-EPI or the MDRD Study equation vs. the alternative equations Difference in P_{30} (upper panels) and the mean absolute error (lower panels) of the CKD-EPI or the MDRD Study equation and the alternative equations along with their 99.6 % CIs are shown. For the metric of P_{30}, a difference of >0 indicates that CKD-EPI or the MDRD Study equation is superior to the alternative equations. For mean absolute error, a difference of <0 indicates that the CKD-EPI or the MDRD Study equation has a lower mean absolute error than the alternative equations. P values for all pair wise comparisons with the CKD-EPI or the MDRD Study equation are < 0.004.

*Equations that had transplant recipients in the development cohort

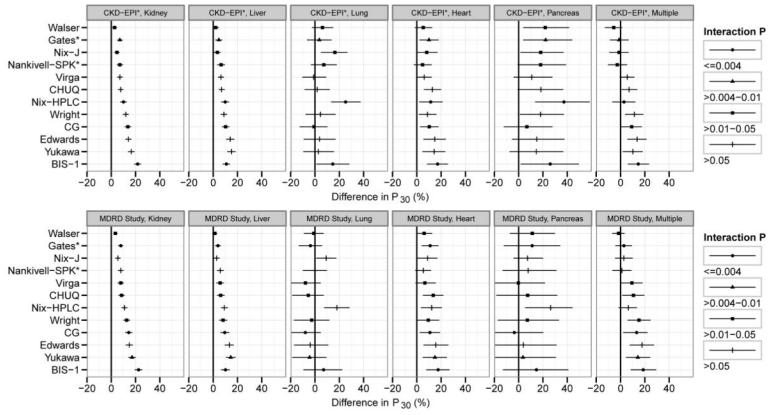

Fig 3.

The difference between the P_{30} (99.6% CI) of the CKD-EPI or the MDRD Study equation and each of the alternative equations in subgroups by organ [Kidney, Liver, Lung, Heart, Pancreas, and Multiple organs(Heart/Kidney, Heart/Liver, Kidney/Liver, Kidney/Lung, Kidney/Pancreas, Lung/Liver or Lung/Herat)]

A significant global p value (≤0.004) indicates that the difference in the performance of the CKD-EPI (upper panels) or the MDRD Study equation (lower panels) and the alternative equations is different across studies. A difference of >0 indicates that the P_{30} of the alternative equation is less than the CKD-EPI or the MDRD Study equation. If the lower margin of the 99.6% CI is above 0, then the alternative equation is inferior; if the margin includes 0, then the alternative equation is similar. For the difference in P_{30}, only the values that are >−20% and < 60% are shown for ease of representation.

Interaction P values represent 4 categories; P≤0.004, P>0.004–0.01, P>0.01–0.05, and P>0.05

*Equations that had transplant recipients in the development cohort

Table 1

Characteristics of creatinine-based equations identified by the systematic review according to year of publication

Equation	Development Population					Reference Test					Index Test						Validation Cohort
	Year	N	Mean Age (y)	Population	Transplant Recipients Included	Clearance	Filtration marker	Scaled to BSA	Multiple measurements	Mean GFR	Cr assay	SRM	Cr in Steady State	Age Variable	Sex Variable	Race Variable	
Edwards [14]	1959	44	U	OP/IP	N	U	Cr	Y	Y	?	PK	N	B	N	Y	N	N
Cockcroft-Gault[15]	1974	249	55	OP	N	U	Cr	N	Y	55*	PK	N	Y	Y	Y	N	Y
Rowe [16]	1976	548	U	OP	N	U	Cr	Y	N	79*	PK	N	Y	Y	N	N	Y
Mogensen[17]	1980	9	U	?	?	U	Iothal	?	?	?	PK	N	?	N	N	N	?
Taylor [18]	1982	169	U	OP/IP	N	P	Cr	Y	N	69	PU	N	?	Y	N	N	N
Gates [19]	1985	90	56	IP	B	U	Cr	Y	Y	37	?	N	Y	Y	Y	N	Y
Kaji [20]	1990	18	55	?	N	U	Cr	N	N	32*	PK	N	Y	N	N	N	Y
Robinson [21]	1990	106	U	IP	N	U	Cr	N	Y	102*	PU	N	N	Y	Y	N	Y
Walser [22]	1993	85	U	IP	N	U	DTPA	O	Y	13†	PK	N	Y	Y	Y	N	N
Nankivell-SPK[23]	1995	33	42	OP	E	P	DTPA	N	Y	55*	PK	N	Y	Y	Y	N	Y
Nankivell [24]	1995	146	43	OP/IP	E	P	DTPA	N	Y	52*	PU	N	B	N	Y	N	Y
AASK-pilot [25]	1996	193	53	OP	N	U	Iothal	Y	?	69	PK	N	Y	Y	Y	N	N
Baracskay [26]	1997	41	73	OP	N	P	Iothal	N	N	71*	?	N	Y	Y	N	N	N
Martin [27]	1998	80	62	?	N	P	EDTA	N	N	66*	EN	N	?	N	Y	N	Y
MDRD Study [5,28]	1999	1070	51	OP	N	U	Iothal	Y	N	40	PK	Y	Y	Y	Y	Y	Y
Yukawa [29]	1999	179	60	IP	N	U	Cr	N	Y	44*	PK	N	?	Y	N	N	N
AASK-main [30]	2001	1703	54	IP	N	U	Iothal	Y	N	57	PK	N	Y	Y	Y	N	N
Wright [31]	2001	62	58	IP	N	U	EDTA	N	N	73*	EN	N	N	Y	Y	N	Y
Mayo[32]	2004	900	45	OP	B	U	Iothal	Y	N	82	PK	N	Y	Y	Y	N	N
Virga [33]	2005	530	57	?	N	U	Cr	N	N	55*	PK	N	Y	Y	Y	N	Y
Nix-HPLC [34]	2006	27	51	OP	N	U	Cr	N	N	71*	HPLC	Y	Y	N	Y	N	N
Nix-J [34]	2006	27	51	OP	N	U	Cr	N	N	71*	PK	N	Y	N	Y	N	N

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Equation	Development Population					Reference Test					Index Test						Validation Cohort
	Year	N	Mean Age (y)	Population	Transplant Recipients Included	Clearance	Filtration marker	Scaled to BSA	Multiple measurements	Mean GFR	Cr assay	SRM	Cr in Steady State	Age Variable	Sex Variable	Race Variable	
CHUQ [35]	2008	773	54	OP/IP	N	U	Cr	Y	N	67	PK	N	B	Y	Y	N	Y
CKD-EPI [8]	2009	5504	47	OP	B	U	Iothal	Y	N	68	EN	Y	Y	Y	Y	Y	Y
Matsuo [36]	2009	413	51	IP	?	U	Inulin	Y	N	59	EN	Y	B	Y	Y	N	Y
BIS-1[37]	2012	570	78	OP	N	P	Iohex	Y	N	60	EN	Y	Y	Y	Y	N	Y

Note: N=26 equations. Unless otherwise indicated, GFR is expressed in mL/min/1.73 m^2.

Abbreviations and definitions: Year; Year of publication, SRM; Traceable to standardized reference material, Y; Yes, N; No, ?; Unknown, B; Both, OP; Outpatient, IP; Inpatient, E; Exclusive, U; Urinary, P; Plasma, Cr; Creatinine, Iothal; Iothalamate, Iohex; Iohexol, DTPA; Diethylenetriaminepentaacetic acid, GFR; glomerular filtration rate, PK; Picrate kinetic, PU; Picrate non-modified, EN; Enzymatic, HPLC; High-performance liquid chromatography; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; BIS, Berlin Initiative Study; CHUQ, Le Centre hospitalier universitaire de Québec; AASK, African American Study of Kidney Disease and Hypertension; SPK, simultaneous pancreas and kidney; BSA, body surface area; SRM, standard reference material; J, Jaffe;

*Units are ml/min,

†Units are ml/min/3 m^2

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Table 2

Clinical and demographic variables of the population subdivided according to the study

	Total	Mayo	Groningen	Baylor	Lund	CCFP
No. (row %)	3622 (100.0)	1924 (53.1)	953 (26.3)	686 (18.9)	44 (1.2)	15 (0.4)
Age (y)	54.0 (13.0)	55.9 (13.4)	50.6 (12.9)	53.9 (10.7)	51.5 (14.1)	41.3 (16.0)
Female sex	1541 (42.6)	812 (42.2)	397 (41.7)	308 (44.9)	20 (45.5)	4 (26.7)
Black race	72 (2.0)	23 (1.2)	3 (0.3)	44 (6.4)	0 (0.0)	2 (13.3)
Height (cm)	172.1 (10.4)	171.5 (10.4)	173.8 (9.8)	171.4 (10.9)	169.8 (9.9)	175.9 (9.2)
Weight (kg)	83.7 (20.2)	85.4 (21.8)	80.6 (15.8)	84.2 (20.3)	73.6 (17.1)	81.5 (17.0)
BSA (m^2)	1.96 (0.25)	1.97 (0.27)	1.95 (0.21)	1.96 (0.26)	1.84 (0.23)	1.97 (0.20)
BMI (kg/m^2)	28.2 (5.9)	28.9 (6.4)	26.6 (4.5)	28.6 (6.0)	25.4 (4.9)	26.4 (5.5)
Scr (mg/dl)	1.49 (0.64)	1.45 (0.60)	1.56 (0.61)	1.47 (0.63)	1.93 (1.63)	2.07 (1.19)
SUN* (mg/dl)	27.7 (12.8)	27.7 (12.8)	33.5 (25.9)	28.1 (13.9)	27.9 (21.9)	36.3 (27.7)
GFR (ml/min/1.73 m^2)	55.1 (22.7)	54.1 (21.6)	54.6 (20.4)	59.3 (27.7)	43.6 (17.1)	47.0 (28.4)
Diabetes	733 (20.3)	419 (21.8)	127 (13.3)	173 (25.2)	12 (27.3)	2 (13.3)
Marker						
Iohexol	44 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	44 (100.0)	0 (0.0)
Iothalamate	3578 (98.9)	1924 (100.0)	953 (100.0)	686 (100.0)	0 (0.0)	15 (100.0)
Organ						
Kidney	1905 (52.7)	1027 (53.4)	869 (91.2)	0 (0.0)	0 (0.0)	9 (60.0)
Liver	1251 (34.6)	520 (27.0)	0 (0.0)	686 (100.0)	44 (100.0)	1 (6.7)
Lung	147 (4.1)	147 (7.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart	110 (3.0)	33 (1.7)	74 (7.8)	0 (0.0)	0 (0.0)	3 (20.0)
Pancreas	26 (0.7)	26 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple organs	183 (5.1)	171 (8.9)	10 (1.0)	0 (0.0)	0 (0.0)	2 (13.3)

Note: Unless otherwise indicated, values for categorical variables are given as number (column percentage); values for continuous variables, as mean ± standard deviation.

Abbreviation: Mayo; Mayo Clinic, Rochester, Minnesota: Baylor; Baylor University Medical Center, Dallas, Texas, US: Groningen; Groningen Institute for Kidney Diseases, Groningen, Netherlands: Lund; Division of Nephrology, Lund University, Lund, Sweden: CCFP; Cleveland Clinic Foundation Prospective Cohort, Cleveland, Ohio; SUN; serum urea nitrogen; BSA, body surface area; BMI, body mass index; Scr, serum creatinine; GFR, glomerular filtration rate;

* SUN reported on 2,858 patients. See Figure S1 for details of patients missing SUN.

Table 3

Performance of eGFR equations (n=26) according to P_{30}

Equation	Mean GFR (ml/min/1.73 m2)	Mean Error (ml/min/1.73 m^2)	Median Percent Error (%)	Mean Absolute Error (ml/min/1.73 m^2)	Median Absolute Percent Error (%)	P_{30} (%)
CKD-EPI	54.6 (53.6, 55.6)	0.4 (−0.3, 1.1)	0.8 (−0.4, 2.0)	10.6 (10.1, 11.1)	15.9 (15.0, 16.8)	78.9 (76.9, 80.8)
MDRD Study	51.1 (50.1, 52.0)	4.0 (3.3, 4.7)	6.8 (5.7, 7.9)	11.0 (10.5, 11.5)	16.6 (15.7, 17.3)	78.9 (76.9, 80.8)
Virga	49.5 (48.7, 50.4)	5.5 (4.8, 6.2)	8.6 (7.2, 10.0)	11.7 (11.2, 12.2)	17.9 (17.1, 18.9)	76.4 (74.4, 78.4)
Walser	51.2 (50.3, 52.1)	3.9 (3.1, 4.6)	5.5 (4.0, 6.4)	11.8 (11.3, 12.4)	18.0 (17.1, 18.9)	74.3 (72.2, 76.3)
Nix-J	49.8 (48.8, 50.8)	5.3 (4.5, 6.1)	9.9 (8.6, 11.3)	12.6 (12.0, 13.2)	19.4 (18.6, 20.3)	72.9 (70.7, 75.0)
CHUQ	49.6 (48.8, 50.4)	5.5 (4.7, 6.3)	9.4 (8.3, 10.6)	12.6 (12.0, 13.2)	19.9 (19.1, 21.1)	72.5 (70.3, 74.6)
Wright	59.8 (58.8, 60.8)	−4.8 (−5.5, −4.0)	−9.7 (−10.9, −8.5)	11.6 (11.1, 12.1)	17.4 (16.4, 18.3)	72.3 (70.1, 74.4)
Gates	60.8 (59.7, 62.0)	−5.8 (−6.6, −5.0)	−10.5 (−11.9, −9.0)	12.2 (11.6, 12.8)	17.7 (16.9, 18.6)	71.3 (69.1, 73.5)
Nankivell-SPK	46.4 (45.6, 47.2)	8.6 (7.9, 9.4)	14.3 (12.9, 15.7)	13.5 (12.9, 14.1)	21.4 (20.6, 22.4)	68.5 (66.2, 70.7)
Cockcroft-Gault	61.8 (60.8, 62.9)	−6.8 (−7.5, −6.1)	−14.1 (−15.7, −12.9)	12.4 (11.9, 13.0)	18.9 (17.8, 20.1)	68.3 (66.0, 70.5)
Edwards	61.6 (60.5, 62.7)	−6.5 (−7.3, −5.7)	−12.1 (−13.6, −10.7)	13.3 (12.7, 13.9)	19.4 (18.3, 20.5)	67.3 (65.0, 69.5)
Nix-HPLC	63.0 (62.0, 64.0)	−8.0 (−8.7, −7.2)	−17.2 (−19.1, −15.5)	13.3 (12.8, 13.8)	20.9 (19.8, 22.0)	65.1 (62.8, 67.3)
Yukawa	62.4 (61.5, 63.2)	−7.3 (−8.1, −6.5)	−15.1 (−16.8, −13.1)	14.2 (13.6, 14.8)	21.3 (19.9, 22.6)	63.7 (61.4, 66.0)
BIS1	65.2 (63.8, 66.6)	−10.1 (−11.3, −9.0)	−14.9 (−16.8, −13.2)	16.8 (15.8, 17.7)	21.7 (20.8, 23.0)	61.6 (59.3, 63.9)
AASK-main	66.0 (64.7, 67.3)	−10.9 (−11.8, −10.1)	−19.3 (−20.7, −17.8)	15.7 (15.1, 16.4)	23.9 (22.8, 25.5)	59.9 (57.5, 62.2)
Mayo	41.0 (40.2, 41.7)	14.1 (13.4, 14.8)	25.0 (24.1, 25.8)	15.8 (15.1, 16.4)	26.6 (25.8, 27.4)	59.0 (56.7, 61.4)
Matsuo	67.4 (66.2, 68.6)	−12.4 (−13.2, −11.6)	−23.5 (−24.9, −22.0)	15.7 (15.0, 16.3)	24.7 (23.3, 25.9)	57.6 (55.3, 60.0)
Nankivell*	66.2 (65.0, 67.4)	−11.2 (−12.1, −10.3)	−23.1 (−24.8, −21.3)	16.0 (15.3, 16.7)	25.9 (23.8, 27.2)	54.8 (52.1, 57.4)
Baracskay	64.9 (64.0, 65.9)	−9.9 (−10.9, −8.8)	−19.6 (−21.8, −16.9)	18.7 (18.0, 19.5)	27.8 (26.5, 29.1)	53.4 (51.0, 55.7)
Taylor	52.1 (50.9, 53.4)	2.9 (1.8, 4.0)	3.3 (1.3, 5.5)	18.0 (17.3, 18.7)	29.6 (27.9, 30.9)	50.6 (48.2, 53.0)
Robinson	73.0 (71.4, 74.7)	−18.0 (−19.3, −16.7)	−29.3 (−32.0, −26.3)	23.7 (22.6, 24.8)	33.6 (31.5, 35.3)	46.1 (43.7, 48.5)
Mogensen	71.1 (69.8, 72.4)	−16.0 (−17.0, −15.1)	−30.1 (−32.3, −28.2)	20.4 (19.7, 21.2)	33.7 (32.0, 35.5)	45.5 (43.1, 47.9)
AASK-pilot	76.3 (74.9, 77.6)	−21.2 (−22.2, −20.2)	−38.9 (−41.6, −36.6)	23.9 (23.0, 24.8)	40.0 (37.7, 41.9)	38.9 (36.6, 41.2)
Kaji	31.0 (30.4, 31.6)	24.1 (23.2, 24.9)	43.8 (42.7, 45.0)	24.9 (24.0, 25.8)	44.4 (43.5, 45.6)	26.9 (24.9, 29.1)
Martin	98.6 (97.0, 100.2)	−43.5 (−44.7, −42.4)	−80.7 (−83.5, −78.2)	44.0 (42.8, 45.1)	80.7 (78.1, 83.5)	9.6 (8.3, 11.1)
Rowe	122.4 (121.9, 122.9)	−67.3 (−68.4, −66.2)	−129.6 (−134.1, −125.6)	67.5 (66.5, 68.6)	129.6 (125.5, 134.1)	4.9 (4.0, 6.0)

Note: Data given as value (99.6% confidence interval). All estimates are scaled to 1.73 m^2 for validity of comparisons. Equations are ranked by P_{30} in descending order. The equations that had a P_{30} ≥60% and mean absolute error ≤20 ml/min/1.73m^2 are highlighted in bold and were included in the final analysis where we compared the performance of the CKD-EPI equation or the MDRD Study equations with the alternative equations

P_{30}: Percentage of patients who have absolute percent error ≤30%.; eGFR, estimated glomerular filtration rate; GFR; glomerular filtration rate, MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; BIS, Berlin Initiative Study; CHUQ, Le Centre hospitalier universitaire de Québec; AASK, African American Study of Kidney Disease and Hypertension; SPK, simultaneous pancreas and kidney; BSA, body surface area; SRM, standard reference material; J, Jaffe

*eGFR estimated on 2858 patients on whom serum urea/serum urea nitrogen was available and was in steady state