Annals of Internal Medicine | Review

Estimating Equations for Glomerular Filtration Rate in the Era of Creatinine Standardization

A Systematic Review

Amy Earley, BS; Dana Miskulin, MD, MS; Edmund J. Lamb, PhD; Andrew S. Levey, MD; and Katrin Uhlig, MD, MS

Background: Clinical laboratories are increasingly reporting estimated glomerular filtration rate (GFR) by using serum creatinine assays traceable to a standard reference material.

Purpose: To review the performance of GFR estimating equations to inform the selection of a single equation by laboratories and the interpretation of estimated GFR by clinicians.

Data Sources: A systematic search of MEDLINE, without language restriction, between 1999 and 21 October 2011.

Study Selection: Cross-sectional studies in adults that compared the performance of 2 or more creatinine-based GFR estimating equations with a reference GFR measurement. Eligible equations were derived or reexpressed and validated by using creatinine measurements traceable to the standard reference material.

Data Extraction: Reviewers extracted data on study population characteristics, measured GFR, creatinine assay, and equation performance.

Data Synthesis: Eligible studies compared the MDRD (Modification of Diet in Renal Disease) Study and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations or modifications thereof. In 12 studies in North America, Europe, and Australia, the CKD-EPI equation performed better at higher GFRs (approximately >60 mL/min per 1.73 m^2) and the MDRD Study equation performed better at lower GFRs. In 5 of 8 studies in Asia and Africa, the equations were modified to improve their performance by adding a coefficient derived in the local population or removing a coefficient.

Limitation: Methods of GFR measurement and study populations were heterogeneous.

Conclusion: Neither the CKD-EPI nor the MDRD Study equation is optimal for all populations and GFR ranges. Using a single equation for reporting requires a tradeoff to optimize performance at either higher or lower GFR ranges. A general practice and public health perspective favors the CKD-EPI equation.

Primary Funding Source: Kidney Disease: Improving Global Outcomes.

Ann Intern Med. 2012;156:785-795. www.annals.org

For author affiliations, see end of text.

This article was published at www.annals.org on 7 February 2012.

Estimates of glomerular filtration rate (GFR) from serum creatinine levels are now reported by more than 80% of clinical laboratories in the United States (1). Accurate estimation of GFR is important for detecting and staging chronic kidney disease (CKD), determining drug dosages, and stratifying risk (2). The equation from the MDRD (Modification of Diet in Renal Disease) Study is most frequently used but is known to be less accurate at higher GFRs and in racial and ethnic groups outside of North America, Europe, and Australia. Thus, researchers have developed and validated other GFR estimating equations to overcome these limitations.

The increasing use of GFR estimating equations has led to an appreciation of the effect of differences in creatinine assays on the accuracy of GFR estimates (3, 4). In 2006, a serum matrix standard reference material (SRM) was prepared by the National Institute of Standards and Technology and submitted to the Joint Committee for Traceability in Laboratory Medicine (5). Use of this material, in combination with the isotope-dilution mass spectrometry reference method, was intended to assist reagent manufacturers in achieving better consensus among methods (6). By the end of 2009, the calibration of most clinical laboratory methods was traceable to the SRM and isotope-dilution mass spectrometry (1).

Our goal was to systematically review the performance of creatinine-based GFR estimating equations for use with standardized serum creatinine measurements to inform selection of a single equation that laboratories could use to estimate GFR and to help clinicians interpret estimated GFR.

Methods

Data Sources and Searches

We conducted a systematic search in MEDLINE from 1999 (the year before the 4-variable MDRD Study equation was published [7]) to 21 October 2011, with no language restrictions. Because the MDRD Study equation was the first equation to be reexpressed for use with standardized creatinine measurements (8), our search allowed us to identify other equations based on the MDRD Study equation that could also be reexpressed for use with standardized creatinine measurements. We also supplemented our

See also:

Print

Editors' Notes 786

Web-Only

Appendix Tables

CME quiz (preview on page I-29)

Conversion of graphics into slides

Context

Multiple methods are used to estimate glomerular filtration rate (GFR) from serum creatinine level.

Contribution

This review summarized data from cross-sectional studies that compared 2 or more creatinine-based GFR estimating equations to a reference GFR measurement. Studies from North America, Europe, and Australia showed that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation performed better at higher GFRs and the Modification of Diet in Renal Disease (MDRD) Study equation performed better at lower GFRs. Neither equation performed as well in Asian or African populations as it did in North American or European populations.

Implication

The performance of the CKD-EPI and MDRD Study equations varies across populations and GFR ranges.

—The Editors

search with references from 2 previous reviews (9, 10). **Appendix Table 1** (available at www.annals.org) lists our keywords and search strategy.

Study Selection

We included cross-sectional studies in any adult clinical or research population comparing GFR estimates from at least 2 creatinine-based estimating equations with a reference method of GFR measurement. Acceptable reference methods for measuring GFR in the development and validation populations were the urinary or plasma clearance of an exogenous filtration marker. We included equations that were originally developed by using standardized serum creatinine measurements or those for which the coefficients were subsequently recalculated for use with standardized creatinine measurements, which we refer to as *reexpressed*. We also included 1 study for which a conversion factor could be applied post hoc (11). We required evaluation of the equation in a data set that was external to the one in which it was developed, with independent sampling of the development and validation populations. Creatinine assays had to be traceable to the SRM (5). Acceptable assay methods included those standardized against isotope-dilution mass spectrometry of the reference material of the National Institute of Standards of Technology. Studies were also acceptable if they used a conversion factor derived from calibration of samples across the range of creatinine concentrations represented in the study population, with methods traceable to isotope-dilution mass spectrometry. We excluded studies that used an assay that was not traceable to the SRM and those with unclear traceability. In some cases, these studies were developed with assays and analytic material that are no longer available; the performance of the equations described in such studies was considered to be irrelevant to current practice. The minimum size was arbitrarily set at 100. We also looked for results of performance in subgroups by GFR, age, and race that had at least 50 members.

Data Extraction and Quality Assessment

We extracted data on study population characteristics, reference standards, measured GFRs, methods of creatinine calibration, and equation performance (bias, precision, and accuracy). We noted whether participants had conditions that could affect serum creatinine level through non-GFR determinants, such as conditions that alter creatinine generation (chronic illness or steroids), or medications that inhibit creatinine secretion (trimethoprim). Data from each article were systematically extracted by 1 of the authors. Other authors reviewed the methods section of studies describing development and evaluation of an equation to identify the creatinine assays and to confirm the study design and results. Our stringent selection criteria ensured that all reviewed studies were of good methodological quality.

Statistical Analysis

Summary measures of the differences between measured and estimated GFR were compared for each equation. No single metric captures all of the important information for evaluating performance of GFR estimating equations (10). In general, measures on the raw scale tend to emphasize errors at higher GFRs, whereas measures on the percentage or log scale tend to emphasize errors at lower GFRs (10). Bias, an expression of systemic error in estimated GFR, is defined as the median or mean of the differences between estimated and measured GFR. We used bias on the raw scale because it is easier to interpret. Precision is an expression of the random variation or "spread" of estimated GFR values around the measured GFR. The root mean square error of the regression of estimated GFR versus measured GFR, or log estimated GFR versus log measured GFR, is considered to be a direct measure of precision. Indirect measures, such as interquartile range or SD for the differences between estimated GFR and measured GFR, were included if the root mean square error was not provided. Accuracy is affected by both bias and imprecision and was expressed as the percentage of estimated GFR values within 30% of measured GFR (P_{30}). This measure of P_{30} was first reported as a measure of the accuracy of the MDRD Study equation (12) and was subsequently recommended by the National Kidney Foundation Disease Outcomes Quality Initiative in its CKD guidelines (13). An error of 30% is considered large; for example, a 30% error in a patient with measured GFR of 50 mL/min per 1.73 m^2 could lead to an estimated GFR as low as 35 or as high as 65 mL/min per 1.73 m^2. Some have suggested that 20% would be a more appropriate threshold for a large error. We have included alternative values for accuracy (such as P_{10}, P_{15}, or P_{20}) if they were reported. For our conclusions, we focused primarily on P_{30} because it is a measure of large errors that would be important to

clinicians, is less influenced by small bias due to differences in measurement methods or regression to the mean, and was most consistently reported across studies.

We tabulated results separately for adult populations of largely Northern European ancestry (North American, European, and Australian populations) and those from other locations and separated the results for subgroups by GFR range, race or ethnicity, and age. Within each table, we organized the studies first by similar reference measurement method and then by size.

Role of the Funding Source

The authors are members of the evidence review team and 2 workgroup experts of the ongoing Kidney Disease: Improving Global Outcomes (KDIGO) guideline on evaluation and management of CKD. The evidence review team was supported by KDIGO to conduct systematic reviews and provide methods support. The judgments and interpretations in the article are those of the authors. The funding source did not participate in the design, conduct, or reporting of the study.

RESULTS

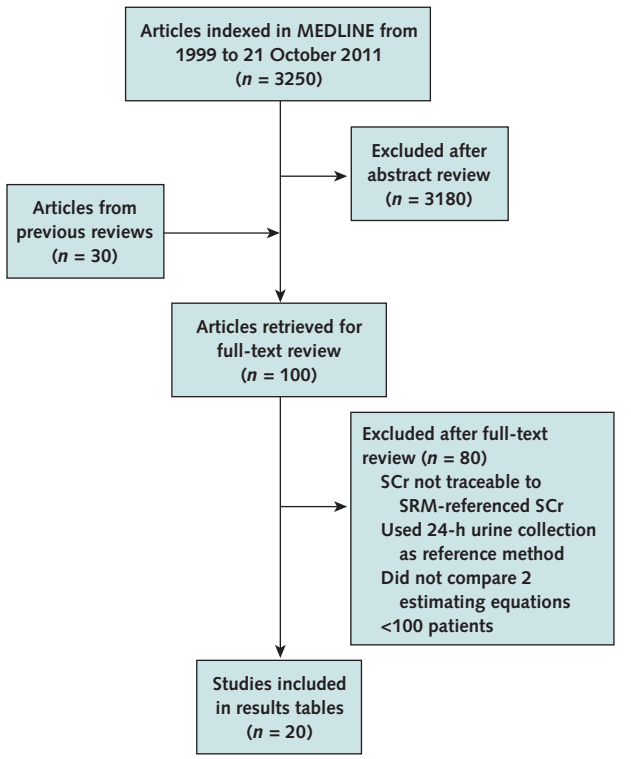
Our search yielded 3250 abstracts; of these, 100 articles were reviewed in full text and 23 met our inclusion criteria (**Figure 1**). The main reason for exclusion was that the equations had not been developed or reexpressed for use with creatinine assays traceable to the SRM. **Appendix Table 2** lists equations that met our criteria, and **Appendix Table 3** (both available at www.annals.org) lists the equations that were not traceable to the SRM.

Estimating Equations Developed in Adult Populations in North America, Europe, or Australia

Twelve studies, comprising 12 898 patients, met our criteria (**Table 1**) (14–26). Study populations were the general population in 3 studies (14–17), kidney transplant recipients in 3 studies (18–20), individuals before kidney donation in 1 study (21) and before and after kidney donation in another study (22), patients with cancer in 1 study (23), and a heterogeneous population in 3 studies (24–26). All studies compared the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation with the MDRD Study equation. Methods of measuring GFR included clearance of iothalamate in 5 studies, technetium–diethylenetriamine pentaacetic acid (Tc-DTPA) in 3 studies, inulin in 1 study, iohexol in 1 study, chromium–ethylenediamine tetraacetic acid (Cr-EDTA) in 1 study, and various markers in 1 study.

Across the 12 studies, P_{30} ranged from 59% to 95%. The CKD-EPI equation was more accurate than the MDRD Study equation in 10 studies and less accurate in 2 studies. Bias ranged from 14.6 to −22 mL/min per 1.73 m^2. The CKD-EPI equation was less biased than the MDRD Study equation in 7 studies and more biased in 5 studies. Two studies reported the root mean square error as a measure of precision. In 6 of the 10 studies that reported a measure of precision, the CKD-EPI equation was more precise than the MDRD Study equation; precision for the MDRD Study equation was better or the same in the other 4 studies. In 5 studies (14–17, 25, 26), performance measures were consistently better for the CKD-EPI equation than for the MDRD Study equation. In 2 studies (18, 19), both of which were conducted in kidney transplant recipients, performance measures were better for the MDRD Study equation. In 1 study (18), all patients received trimethoprim.

Figure 1. **Summary of evidence search and selection.**



SCr = serum creatinine; SRM = standard reference material.

Figure 2 shows differences in accuracy and bias according to measured GFR and GFR measurement method. The CKD-EPI equation seems to be more accurate and less biased in studies with higher mean measured GFRs (approximately >60 mL/min per 1.73 m^2), whereas the MDRD Study equation has greater accuracy and less bias at lower GFRs. No clear pattern by GFR measurement method was observed. **Appendix Table 4** (available at www.annals.org) shows subgroups stratified by GFR or clinical characteristics in studies in which these subgroup data were reported (19, 20, 25, 26). Within each study, the differences in accuracy and bias were larger at higher GFRs and smaller at lower GFRs.

One study (27) compared a modification of the CKD-EPI equation that used a 4-level race or ethnicity coeffi-

Table 1. **Performance Comparison of Creatinine-Based GFR Estimating Equations in North America, Europe, and Australia**

Study, Year (Reference)	Country	Population	Patients, *n*	Measured GFR	
				Reference Standard	Value (SD), *mL/min per 1.73 m²*
Murata et al, 2011 (26)	United States	Adults who underwent an outpatient iothalamate clearance at the Mayo Clinic in Rochester, Minnesota (women, 45%; African American, 2%; mean age, 56 y; donor or potential donor, 13%; KTRs, 26%)	5238	^{125}I-Iothalamate (urine)	55.9 (29.7)
Levey et al, 2009 (25)	United States	External validation set comprising 16 studies (women, 45%; white or other, 87%; black, 10%; Hispanic, 2%; Asian, 2%; mean age, 50 y; diabetes, 28%; donor, 16%; KTRs, 29%)	3896	^{125}I-Iothalamate (urine) and others	68 (36)
Lane et al, 2010 (21)	United States	Patients before and after nephrectomy for causes other than donation at the Cleveland Clinic (women, 93%; white, 91%; black, 7%; median age, 58 y)	425	^{125}I-Iothalamate (urine)	50 (IQR, 29 to 69)
Michels et al, 2010 (17)	The Netherlands	Potential kidney donors and adults who underwent GFR measurement for clinical reasons at the Academic Medical Center in Amsterdam (women, 56%; black, 12%; mean age, 44 y)	271	^{125}I-Iothalamate (urine)	78.2 mL/min (33.4)
Tent et al, 2010 (22)	The Netherlands	Living kidney donors who donated from 1996–2007 (women, 57%; white, 100%; mean age, 50 y)	253 before donation 253 after donation	^{125}I-Iothalamate (urine)	115 mL/min (20) 73 mL/min (13)
Kukla et al, 2010 (18)	United States	KTRs receiving immunosuppression (women, 40%; white, 86%; mean age, 49 y; receiving trimethoprim, 100%)	107 on steroid-free immunosuppression early posttransplantation 81 on steroid-free immunosuppression at 1 y	^{125}I-Iothalamate (urine)	55.5 (17.0) 56.8 (17.7)
White et al, 2010 (20)	Canada	Stable KTRs (women, 36%; white, 92%; receiving trimethoprim, 19%)	207	^{99m}Tc-DTPA (plasma)	58 (22)
Pöge et al, 2011 (19)	Germany	Patients with stable renal function after transplantation (women, 40%; white, 99%; mean age, 49 y)	170	^{99m}Tc-DTPA (plasma)	39.6 (IQR, 11.8 to 82.9)
Jones and Imam, 2009 (15), and Jones, 2010 (16)	Australia	Australian patients referred for routine GFR measurements (women, 43%; mean age, 61 y)	169	^{99m}Tc-DTPA (plasma)	75 (IQR, 5 to 150)
Cirillo et al, 2010 (14)	Italy	White adults with and without kidney disease (with kidney disease, 49%; women, 41%; mean age, 47 y; diabetic nephropathy, 26 cases; glomerulonephritis, 40 cases; PKD, 15 cases)	356	Inulin (plasma)	71.5 (36.3)
Eriksen et al, 2010 (24)	Norway	Patients participating in the 6th Tromsø population survey who had no previous myocardial infarction, angina, stroke, diabetes, or renal disease (women, 51%; mean age, 57 y)	1621	Iohexol (plasma)	91.7 (14.4)
Redal-Baigorri et al, 2011 (23)	Denmark	Patients with cancer who were referred for determination of GFR before chemotherapy (women, 57%; mean age, 62 y)	185	^{51}Cr-EDTA (plasma)	85.1 (20.3)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; IDMS = isotope-dilution mass spectrometry; IQR = interquartile range; KTR = kidney transplant recipient; MDRD = Modification of Diet in Renal Disease; ND = not documented; NIST = National Institute of Standards and Technology; P_{30} = percentage of estimated GFR values within 30% of measured GFR; PKD = polycystic kidney disease; SCr = serum creatinine.

* Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.

† Lower values indicate greater precision.

‡ Higher values indicate greater accuracy. Among the 3 studies (14, 18, 19) that reported alternative measures of accuracy, results were consistent with P_{30} in all. In addition to P_{30}, references 14, 18, and 19 reported P_{10}; reference 14 also reported P_{20}.

§ Evaluated as the root mean square error for the regression of estimated GFR on measured GFR.

‖ Evaluated as the IQR for the differences between estimated and measured GFR.

¶ Evaluated as the SD of the differences between estimated and measured GFR.

** Converted to raw scale by multiplying percentage of bias by measured GFR.

Table 1—**Continued**

GFR Estimation		Results		
SCr Calibration and Assay	**Equation**	**Bias (95% CI), *mL/min per 1.73 m²****	**Precision (95% CI)†**	**P_{30} (95% CI), %‡**
Roche Jaffe assay (Roche P- or D-Modular or Roche Cobas C501 with Roche Creatininase Plus assay; Roche Diagnostics, Indianapolis, Indiana) with demonstrated IDMS alignment	MDRD CKD-EPI	−4.1 −0.7	ND	77.6 78.4
Roche enzymatic assay (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffman-La Roche, Basel, Switzerland) recalibrated to standardized SCr at the Cleveland Clinic	MDRD CKD-EPI	−5.5 (−5.0 to −5.9) −2.5 (−2.1 to −2.9)	0.274 (0.265 to 0.283)§ 0.250 (0.241 to 0.259)§	80.6 (79.5 to 82.0) 84.1 (83.0 to 85.3)
Measured at the Cleveland Clinic; assay standardized against NIST	MDRD CKD-EPI	−1.0 −1.7	15.0‖ 13.8‖	75 80
Hitachi enzymatic assay (Hitachi H911; Boehringer Mannheim, Mannheim, Germany) validated against IDMS	MDRD CKD-EPI	14.6 mL/min 12.3 mL/min	19.9¶ 12.1¶	81.2 84.5
Roche enzymatic assay or Jaffe assay on MEGA analyzer (Merck, Darmstadt, Germany); both methods calibrated to reference standard at the Cleveland Clinic	MDRD CKD-EPI MDRD CKD-EPI	−22 mL/min (20 to 25) −14 mL/min (11 to 16) −15 mL/min (14 to 16) −11 mL/min (9 to 11)	20 (14 to 26)‖ 18 (14 to 22)‖ 12 (9 to 15)‖ 12 (10 to 16)‖	73 (68 to 79) 89 (85 to 93) 71 (65 to 76) 89 (85 to 93)
Measured by using a Jaffe CXR Synchron method and, later, an IDMS-traceable assay; Jaffe assay-based SCr converted to IDMS-traceable values	MDRD CKD-EPI MDRD CKD-EPI	8.23 13.30 2.40 6.91	17.9§ 21.1§ 15.8§ 17.3§	71.7 58.5 75.0 66.7
For the reexpressed MDRD Study and CKD-EPI equations, SCr adjusted to IDMS standard	MDRD CKD-EPI	−7.4 −5.2	14.4‖ 15.7‖	79 (73 to 84) 84 (78 to 88)
Jaffe assay on Dimension RxLTM analyzer (Dade Behring, Marburg, Germany); assay adjusted for calibration with the IDMS method	MDRD CKD-EPI	4.49 8.07	10.0¶ 10.9¶	71.8 64.1
Roche Jaffe assay (Roche, Australia) with demonstrated IDMS alignment	MDRD CKD-EPI	−3** −1.5**	ND	81 86
Kinetic Jaffe assay (Bayer Express Plus; Siemens, Munich, Germany) standardized to NIST	MDRD CKD-EPI	−5.2 −0.9	14.9¶ 13.2¶	87.4 88.2
Hitachi enzymatic method (CREA Plus; Roche Diagnostics, Mannheim, Germany) standardized against IDMS	MDRD CKD-EPI	1.3 (0.4 to 2.1) 2.9 (2.2 to 3.5)	18.2 (17.2 to 19.5)‖ 15.4 (14.5 to 16.3)‖	93 (91 to 94) 95 (94 to 96)
Jaffe (Abbott Architect C systems 8000, reagent 7D64; Abbott Laboratories, Abbott Park, Illinois) method standardized to IDMS	MDRD CKD-EPI	0.81 (IQR, −1.56 to 3.19) 1.16 (IQR, −0.76 to 3.09)	16.49¶ 13.37¶	88.6 89.7

cient (black, Asian, and Native American or Hispanic vs. white and other) with a modification that used a 2-level coefficient (black vs. white and other) in racial or ethnic groups in North America and Europe (**Appendix Table 5**, available at www.annals.org). The development data set had few Asian or Native American or Hispanic patients, and the improvements in bias and precision in these groups were not clinically meaningful. Only 2 studies (26, 28) provided results by age subgroups. In both studies, the differences in bias between equations were generally smaller in subgroups of older patients (data not shown).

Estimating Equations Developed in Adult Populations Outside North America, Europe, or Australia

Eight studies met our criteria (**Table 2**) (29–34). The study populations were from Asia and Africa, including Japanese, Chinese, Thai, Korean, South African black, or multiethnic Singapore populations and included general

Table 2. **Performance Comparison of Creatinine-Based GFR Estimating Equations Outside of North America, Europe, and Australia**

Study, Year (Reference)	Country	Population	Patients, *n*	Measured GFR	
				Reference Standard	Value (SD), *mL/min per 1.73 m²*
Stevens et al, 2011 (27)	China, Japan, and South Africa	Populations from 3 studies in China, Japan, and South Africa (women, 48%; Asian, 90%; black, 10%; mean age, 49 y; diabetes, 6%; KTRs, 0%)	99 black patients (South Africa)	^{125}I-Iothalamate (urine) and other filtration markers	61 (32)
			248 Asian patients (Japan)		55 (35)
			675 Asian patients (China)		53 (31)
Matsuo et al, 2009 (34)	Japan	Hospitalized Japanese patients; external validation set (women, 42%; mean age, 54 y; diabetes, 44 cases; donors, 10; KTRs, 2; glomerulonephritis, 176 cases; PKD, 0 cases; lupus, 3 cases)	350	Inulin (urine)	57.2 (34.7) (GFR ≥60, 41%; GFR <60, 59%)
Horio et al, 2010 (29)	Japan	Japanese patients (women, 42%; mean age, 54 y; diabetes, 22%; donors, 3%; KTRs, 1%; hypertension, 58%)	350	Inulin (urine)	45 (25)
Yeo et al, 2010 (33)	Korea	Korean KTRs in the early postoperative period (women, 43%; mean age, 42 y; diabetes, 16%)	102	^{51}Cr-EDTA (plasma)	76.8 (17.0)
van Deventer et al, 2008 (30)	South Africa	Black South African patients (women, 49%; median age, 47 y; diabetes, 25%; donors, 7%; HIV, 20%; hypertension, 36%)	100	^{51}Cr-EDTA (plasma)	61.5 (49.6)
Teo et al, 2011 (32)	Singapore	Outpatients with CKD in the nephrology clinic at National University Hospital, Singapore (women, 48%; Chinese, 41%; Malay, 31%; Indian or other, 28%; median age, 58 y; diabetes, 23%; hypertension, 50%)	232	^{99}Tc-DTPA (plasma)	51.7 (27.5) (GFR ≥60, 69%; GFR <60, 31%)
Ma et al, 2006 (11)	China	Patients with CKD from 9 renal institutes at university hospitals located in 9 geographic regions of China	230	^{99}Tc-DTPA (plasma)	ND
Praditpornsilpa et al, 2011 (31)	Thailand	Thai patients with CKD who were in stable condition	100	^{99}Tc-DTPA (plasma)	51.1 (28.4)

CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; IDMS = isotope-dilution mass spectrometry; JSN-CKDI = Japanese Society of Nephrology-Chronic Kidney Disease Initiatives; KTR = kidney transplant recipient; MDRD = Modification of Diet in Renal Disease; ND = not documented; NIST = National Institute of Standards and Technology; P_{30} = percentage of estimated GFR values within 30% of measured GFR; PKD = polycystic kidney disease; SCr = serum creatinine; SRM = standard reference material.

* Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.

† Lower values indicate greater precision.

‡ Higher values indicate greater accuracy. Among the 5 studies (11, 31–34) that reported alternative measures of accuracy, results were consistent with P_{30} in 3. Of the studies reporting results consistent with P_{30}, reference 31 reported P_{10} and P_{15}, reference 33 reported P_{10}, and reference 34 reported P_{15}. References 11 and 32 reported inconsistent results between P_{15} and P_{30}.

§ Evaluated as the interquartile range for the differences between estimated and measured GFR.

‖ Evaluated as the root mean square error for the regression of estimated GFR on measured GFR.

¶ Evaluated as the SD of the differences between estimated and measured GFR.

** African American coefficient of the MDRD equation.

†† Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the 186 coefficient should be replaced with the 175 coefficient from the reexpressed MDRD equation.

‡‡ Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the SCr should be replaced by SCr × 0.95, which represents the calibration factor relating the SCr assay in the Cleveland Clinic laboratory to the standardized SCr assay.

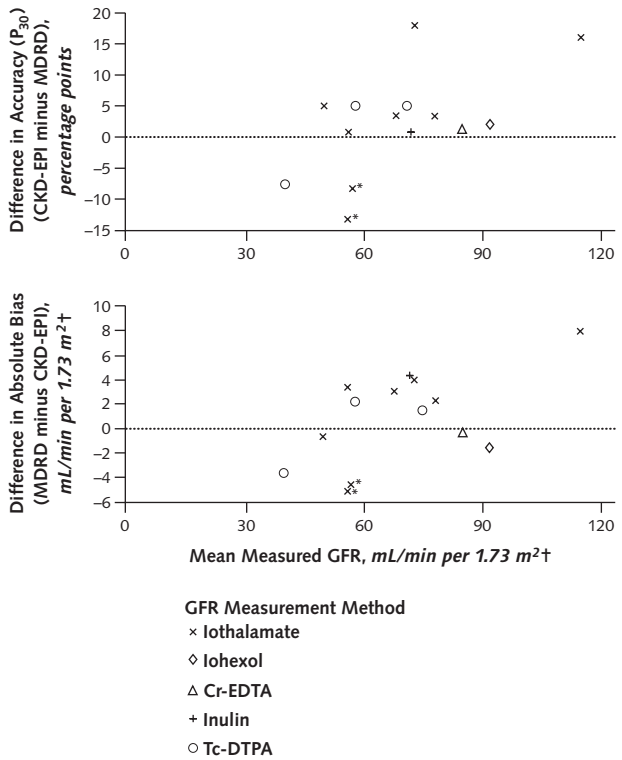
Table 2—**Continued**

GFR Estimation		Results		
SCr Calibration and Assay	**Equation**	**Bias (95% CI), *mL/min per 1.73 m²****	**Precision (95% CI)†**	**P_{30} (95% CI), %‡**
Calibrated to standardized SCr measurements by using Roche (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffmann-La Roche, Basel, Switzerland) enzymatic assay at the Cleveland Clinic	CKD-EPI equation with 2-level race or ethnicity coefficient	12.4 (7.6 to 18.3)	0.326 (0.292 to 0.361)‖	55.6 (46.5 to 64.6)
	CKD-EPI equation with 4-level race or ethnicity coefficient	12.5 (7.6 to 18.4)	0.327 (0.292 to 0.362)‖	55.6 (46.5 to 64.6)
	CKD-EPI equation with 2-level race or ethnicity coefficient	17.8 (14.7 to 20.1)	0.469 (0.424 to 0.515)‖	29.4 (23.8 to 35.1)
	CKD-EPI equation with 4-level race or ethnicity coefficient	21.4 (18.2 to 23.3)	0.507 (0.463 to 0.553)‖	36.3 (30.6 to 42.3)
	CKD-EPI equation with 2-level race or ethnicity coefficient	−2.7 (−3.7 to −1.9)	0.325 (0.302 to 0.348)‖	73.2 (69.9 to 76.6)
	CKD-EPI equation with 4-level race or ethnicity coefficient	−1.3 (−2.2 to −0.6)	0.318 (0.295 to 0.343)‖	72.1 (68.7 to 75.7)
Hitachi enzymatic assay (Hitachi, Tokyo, Japan) with excellent agreement against the Cleveland Clinic methods	MDRD	12.0	25.2‖	59 (54 to 64)
	Japanese-modified MDRD (equation 1)	−5.9	19.9‖	72 (67 to 76)
	JSN-CKDI equation (equation 2)	−7.9	20.3‖	73 (69 to 78)
	MDRD with Japanese coefficient (equation 3)	−1.3	19.4‖	73 (59 to 78)
	3-variable Japanese equation (equation 4)	−2.1	19.1‖	75 (70 to 79)
Enzymatic assay validated by using the calibration panel of the Cleveland Clinic	MDRD with Japanese coefficient	−1.3	19.4‖	73 (69 to 78)
	CKD-EPI with Japanese coefficient	−0.4	17.8‖	75 (70 to 79)
Rate-blanked, Toshiba-compensated, kinetic Jaffe assay (Toshiba Medical Systems, Tokyo, Japan) using a Roche calibrator (Roche Diagnostics, Indianapolis, Indiana) traceable to the IDMS reference method	MDRD	−0.33	12.57¶	94.1
	Japanese-modified MDRD	17.95	11.06¶	68.6
Rate-blanked, Roche-compensated, kinetic Jaffe assay (Roche Modular analyzer; Roche Diagnostics, Indianapolis, Indiana) with calibration traceable to IDMS, compared with Roche enzymatic assay (Creatinine Plus; Roche Diagnostics, Indianapolis, Indiana) at the Cleveland Clinic with values adjusted by regression	MDRD with race or ethnicity factor**	13.1 (5.5 to 18.3)	28.5‖	52
	MDRD without race or ethnicity factor**	1.9 (−0.8 to 4.5)	16.6‖	74
Siemens enzymatic assay (Siemens Advia 2400; Siemens, Munich, Germany) calibrated with manufacturer-provided materials traceable to standardized creatinine (NIST SRM 967) measured by using IDMS	MDRD	−3.0 (−4.2 to −1.7)	12.2 (10.0 to 14.4)§	79.7 (74.6 to 84.9)
	CKD-EPI	−1.2 (−2.7 to 0.3)	12.1 (9.0 to 15.1)§	82.8 (77.9 to 87.6)
Hitachi kinetic Jaffe assay with values adjusted by regression analysis to Cleveland Clinic Beckman CX3 assay (Beckman Coulter, Fullerton, California)	Original MDRD equation, calibrated to the Cleveland Clinic creatinine measurements (study equation 2)††	−7.8 (−21.5 to −1.8)	ND	66.1
	Original MDRD equation, calibrated to Cleveland Clinic creatinine measurements, with Chinese coefficient (study equation 4)††	−0.9 (−9.6 to 7.4)		77.8
	Chinese equation (study equation 6)‡‡	−0.8 (−9.7 to 7.4)		79.6
Roche enzymatic assay (Roche Diagnostics, Indianapolis, Indiana) with values adjusted to IDMS reference serum SRM 967	MDRD	−11.9	8.8¶	62.7
	CKD-EPI	−10.9	7.8¶	68.0
	MDRD equation with Thai racial factor correction	−10.3	8.5¶	73.3
	Thai estimated GFR equation	−7.2	6.3¶	90.0

population in 3 studies (27, 29, 30), patients with CKD in 3 studies (11, 31, 32), kidney transplant recipients in 1 study (33), and a heterogeneous population in 1 study (34). All studies examined the MDRD Study and CKD-EPI equations or modifications thereof. In 6 studies (11, 28–31, 34), the MDRD Study or CKD-EPI equations were modified by adding or removing a coefficient to improve the performance of the equation in the development data set or a new equation was developed by using the same variables (**Appendix Table 2**). Methods for measuring GFR included Tc-DTPA in 3 studies, inulin in 2 studies, Cr-EDTA in 2 studies, and iothalamate in 1 study.

Comparing the performance of equations across studies is limited because locally derived equations were generally not tested in other studies or populations. In these studies, the unmodified MDRD Study and CKD-EPI equations were less accurate (P_{30} ranging from 29% to 94%) than in the studies of populations in North America, Europe, and Australia. In 5 studies, adding (11, 29, 31, 34) or removing (30) a coefficient improved the accuracy of

Figure 2. **Differences in accuracy and bias between estimated GFR by CKD-EPI and MDRD Study equations in North America, Europe, and Australia.**



Difference in accuracy (*top*), as measured by P_{30} (P_{30} for CKD-EPI minus P_{30} for MDRD), is plotted against mean measured GFR in the study population. Difference in bias (*bottom*) (absolute value for bias for estimated GFR by MDRD Study equation minus absolute value for bias for estimated GFR by CKD-EPI equation) is plotted against mean measured GFR in the study population. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; P_{30} = percentage of estimated GFR values within 30% of measured GFR.
* Denotes study in which all patients received trimethoprim.
† Could be reported in mL/min.

GFR estimation (11, 29–31, 34). However, in 1 study (27), modifying the CKD-EPI equation by substituting a 4-level race or ethnicity coefficient derived in a North American and European population for the 2-level coefficient did not significantly improve accuracy in Chinese, Japanese, or South African black populations. Coefficients developed in 1 study of an ethnic or racial population did not improve equation accuracy in a study of another ethnic or racial population (30, 33). The Japanese and Chinese coefficients also vary widely (**Appendix Table 2**) (29, 34). In 3 studies that compared the CKD-EPI and MDRD Study equations (29, 31, 32) (with or without modification), the CKD-EPI equation was more accurate.

Three studies examined the performance of estimating equations by GFR strata (**Appendix Table 6**, available at www.annals.org) (29, 30, 32). In 2 studies, the differences in accuracy and bias were larger at higher GFRs and smaller at lower GFRs. In 1 study (29), the differences in bias between equations were smaller in older subgroups than in younger subgroups (data not shown).

Discussion

Only the MDRD Study and CKD-EPI equations and modifications thereof have been expressed for use with creatinine assays traceable to the SRM and concurrently compared with measured GFR in adults. In studies of North American, European, or Australian populations, the CKD-EPI equation was more accurate (had a higher P_{30}) than the MDRD Study equation in 10 of 12 studies. The comparison of bias was more variable. For both accuracy and bias, the CKD-EPI equation performed better at higher GFRs (approximately >60 mL/min per 1.73 m^2) and the MDRD Study equation performed better at lower GFRs. Within studies, the differences in bias were greater at higher GFRs than at lower GFRs.

Data on adults outside of North America, Europe, and Australia are more limited. Neither the MDRD Study nor the CKD-EPI equation performs as well in these locations as it does in North America and Europe. Equation performance can be improved by deriving local "race/ethnicity" coefficients; however, the modified or new equations generally do not exhibit the same level of accuracy as the CKD-EPI or MDRD Study equations do in North American, European, or Australian populations. The coefficients also do not seem to be generalizable beyond the local population, possibly because of differences in GFR measurement methods or differences in populations in addition to race or ethnicity (35).

Despite estimating GFR from the same variables (age, sex, race, and serum creatinine level), the CKD-EPI equation generally yields higher values for estimated GFR than does the MDRD Study equation. The difference in equation performance can be explained by differences in the development populations. The MDRD Study equation was developed in a study population with CKD and a mean GFR of 40 mL/min per 1.73 m^2, whereas the CKD-EPI equation was developed in a more diverse study population, including participants with and without CKD, with a mean GFR of 68 mL/min per 1.73 m^2. Our observation of differences in equation performance in various GFR ranges probably reflects differences in non-GFR determinants of creatinine (in particular, creatinine generation due to muscle mass and diet) and regression to the mean. Our observation of larger differences in estimated GFR between the equations at higher GFRs probably reflects equation development on the logarithmic scale.

Other differences in equation performance can be explained by differences between the development and the validation populations. The CKD-EPI and MDRD Study equations were developed in North American and European populations that mainly consisted of black and white

persons. Our observation that both equations perform less well in other racial and ethnic groups is consistent with known racial and ethnic differences in muscle mass and diet (35). No participants were receiving trimethoprim in either development population. Our observation of marked underestimation of GFR with both equations in persons receiving trimethoprim is consistent with the known inhibition of creatinine secretion by this drug (36).

Both the MDRD Study and CKD-EPI equations were developed by using iothalamate clearance as the reference standard for GFR. The validation studies used various filtration markers, with small differences in clearance compared with iothalamate (37). Use of filtration markers other than iothalamate in validation studies of these equations would introduce a systematic bias. The observation of variation in differences in equation performance among studies with similar mean GFRs may be due in part to differences in GFR measurement method.

The observed and expected differences in performance by range of GFR suggest that we cannot optimize the performance of any equation for all clinical populations across a wide range of GFRs. Because the goal is to select a single estimating equation for routine use by clinical laboratories, the tradeoff of optimizing performance at either higher or lower GFR ranges must be accepted. Because the difference in bias (on the raw scale) between the equations is greater at higher GFRs, using the CKD-EPI equation would lead to smaller average bias in clinical populations with a wide range of GFRs.

As in diagnostic test evaluation, the magnitude of differences in performance between the CKD-EPI and MDRD Study equations are best appreciated by considering the implications for clinical practice. Reporting estimated GFR by using the MDRD Study equation is widespread, so a change in the estimating equation used by clinical laboratories would have profound implications. Because the differences between the equations are greater at higher GFRs, the implications of introducing the CKD-EPI equation would be larger for public health and general clinical practice than for nephrology practices. Applying the CKD-EPI rather than the MDRD Study equation to the U.S. adult population would lead to a higher average estimated GFR, less sensitivity but more specificity for detecting a GFR less than 60 mL/min per 1.73 m^2, and a lower prevalence estimate but a higher risk profile for persons with an estimated GFR in this range (25, 38–40). This would potentially enable more efficient use of resources in caring for patients with decreased estimated GFR. Another consequence of using the CKD-EPI equation would be to allow reporting of estimated GFR as a numerical value throughout the full range, rather than limit it to lower values (for example, <60 mL/min per 1.73 m^2, as currently recommended for the MDRD Study equation in the United States) (1). However, using the CKD-EPI equation would slightly increase bias (overestimation) at lower GFRs. Nephrologists and others caring for patients with low GFR would need to be aware of this limitation.

Estimation methods need to be further improved. Even in North America, Europe, and Australia, the CKD-EPI equation does not meet the 2002 KDOQI benchmark of P_{30} greater than 90% (13). This level of performance may be beyond expectation for creatinine-based equations. Standardization has reduced but not eliminated bias due to differences in creatinine assays, and differences among GFR measurement methods remain another source of bias. Imprecision in estimating equations is quantitatively more important, probably because of variation in non-GFR determinants of serum creatinine level and imprecision in measured GFR. The former reflects the large number of factors affecting creatinine generation and reducing imprecision may require including additional variables, such as measures of muscle mass or diet; the latter reflects the fallibility of the reference standard rather than errors in the estimating equations and can be improved only by more precise measures of GFR. Although urinary clearance of inulin is the gold standard, it is difficult to use, and studies are needed to compare the bias and precision of alternative methods to enable calibration of GFR measurement methods. In addition, statistical adjustment for measurement error may allow more accurate evaluation of estimated GFR (41).

Outside North America, Europe, and Australia, bias remains an issue because of systematic variation in differences in creatinine generation. Incorporating locally derived coefficients can minimize this bias. However, the lack of generalizability of these coefficients probably reflects the contributions of multiple factors that differ across populations in various locations. Developing or reexpressing existing equations for local populations requires significant resources and may not be feasible in all locations.

The accuracy and worldwide generalizability of GFR estimating equations might be improved by using such alternative filtration markers as cystatin C, which is less dependent on muscle mass. However, all filtration markers have non-GFR determinants, so it is unlikely that imprecision will be eliminated by any single marker. Using multiple markers can improve precision by minimizing the contribution of any 1 non-GFR determinant (42). In June 2010, the Institute for Reference Materials and Measurements released a reference material for cystatin C measurement (43–45). Reagent manufacturers are in the process of recalibrating their assays against this standard, and estimating equations for use with standardized cystatin C measurements are being evaluated (46).

A strength of our review is that the stringent selection criteria eliminated older and smaller studies. This generated an evidence base of good-quality studies and makes the conclusions directly relevant to the current era of creatinine assays. Our review also highlights the shortcomings of the existing literature. We propose criteria for studies that are developing and validating GFR estimating equa-

Table 3. **Suggested Criteria for Developing and Validating GFR Estimating Equations**

The equation should be developed and validated in separate populations. Both populations should be representative of the population of intended use. A study should have sufficient sample size to detect a substantial improvement in equation performance, which we suggest is a relative reduction in bias of 50% or RMSE of 20% in relevant age and GFR strata. These values correspond to the improvements found in performance of the CKD-EPI over the MDRD Study equation.
The measured GFR should be based on urine or plasma clearance of an exogenous filtration marker. The clearance method and filtration marker assay, including typical performance characteristics, should be stated. The accuracy of the GFR measurement procedure compared with urinary inulin clearance should be documented if not already known.
The serum creatinine assay used in both the development and validation data sets should be standardized against SRM. The method, reagent manufacturer, and analytic platform should be stated together with typical performance characteristics of the assay (such as imprecision). When available, traceability data should be provided from robust crossover studies against the reference method. These same recommendations apply to other filtration markers, including cystatin C.
Measures of equation performance should include bias, precision, and accuracy. Accuracy is probably the best single measure for comparing equations because it incorporates bias and precision. Studies should report P_{30} and P_{20}. For precision, RMSE should be reported. However, the best measure may vary depending on the particular population and study hypotheses.
Validation should include comparison of a newly developed estimating equation with ≥1 previously developed equation in the population of interest to identify which equation is superior. To facilitate comparison of equations across studies in heterogeneous populations, we suggest including a common comparator. We currently suggest comparing the performance of any new or adapted equations with that of the unmodified CKD-EPI equation.

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; RMSE = root mean square error; SRM = standard reference material.

tions (**Table 3**) to enhance the quality and comparability of future studies.

Our review has limitations. It was restricted to studies that compared at least 2 equations. Although this omits studies that developed and validated a single GFR estimating equation, it probably did not alter our conclusions because such equations are unlikely to have been developed in large populations and tested as widely as the equations that we included. We may also have inadvertently excluded studies that did use creatinine assays standardized against SRM. This emphasizes the importance of our recommendation that investigators provide full information about their methods.

In summary, neither the CKD-EPI nor the MDRD Study equation is optimal across all populations and GFR ranges. Using a single equation for reporting estimated GFR requires a tradeoff to optimize performance at either higher or lower GFR ranges. A general practice and public health perspective favors adopting the CKD-EPI equation in North America, Europe, and Australia and using it as a comparator for new equations in all locations. Whether the precision of creatinine-based equations can be substantially improved without adding other variables is uncertain. Equations using other filtration markers instead of or in addition to creatinine hold promise in this regard. Going forward, new equations should be rigorously developed, validated, and reported.

From Tufts Medical Center, Boston, Massachusetts, and Kent and Canterbury Hospital, Canterbury, Kent, United Kingdom.

Grant Support: By KDIGO.

Potential Conflicts of Interest: Ms. Earley and Drs. Miskulin and Uhlig report the following: *Grant (money to institution):* National Kidney Foundation; *Support for travel to meetings for the study or other purposes:* National Kidney Foundation. Ms. Earley and Dr. Uhlig further report: *Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like (money to institution):* National Kidney Foundation. Dr. Miskulin further reports: *Grant:* National Kidney Foundation; *Employment:* Dialysis Clinic. Dr. Lamb: *Support for travel to meetings for the study or other purposes:* Kidney Disease: Improving Global Outcomes; *Grants/grants pending (money to institution):* National Institutes of Health. Dr. Levey: *Support for travel to meetings for the study or other purposes (money to institution):* National Kidney Foundation; *Board membership (money to institution):* National Kidney Foundation; *Grants/grants pending (money to institution):* National Kidney Foundation. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-2267.

Requests for Single Reprints: Katrin Uhlig, MD, MS, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02111; e-mail, kuhlig@tuftsmedicalcenter.org.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Miller WG.** Estimating glomerular filtration rate [Editorial]. Clin Chem Lab Med. 2009;47:1017-9. [PMID: 19728841]
2. **Stevens LA, Coresh J, Greene T, Levey AS.** Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med. 2006;354:2473-83. [PMID: 16760447]
3. **Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al.** Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis. 2002;39:920-9. [PMID: 11979335]
4. **Vickery S, Stevens PE, Dalton RN, van Lente F, Lamb EJ.** Does the ID-MS traceable MDRD equation work and is it suitable for use with compensated Jaffe and enzymatic creatinine assays? Nephrol Dial Transplant. 2006;21:2439-45. [PMID: 16720592]
5. **Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al; National Kidney Disease Education Program Laboratory Working Group.** Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem. 2006;52:5-18. [PMID: 16332993]
6. **Panteghini M, Myers GL, Miller WG, Greenberg N; International Federation of Clinical Chemistry and Laboratory Medicine.** The importance of metrological traceability on the validity of creatinine measurement as an index of renal function. Clin Chem Lab Med. 2006;44:1287-92. [PMID: 17032144]
7. **Levey AS, Greene T, Kusek J, Beck G.** A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. J Am Soc Nephrol. 2000;11:155A.
8. **Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al; Chronic Kidney Disease Epidemiology Collaboration.** Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247-54. [PMID: 16908915]
9. **Coresh J, Stevens LA.** Kidney function estimating equations: where do we stand? Curr Opin Nephrol Hypertens. 2006;15:276-84. [PMID: 16609295]

10. **Stevens LA, Zhang Y, Schmid CH.** Evaluating the performance of equations for estimating glomerular filtration rate. J Nephrol. 2008;21:797-807. [PMID: 19034863]
11. **Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al.** Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17:2937-44. [PMID: 16988059]
12. **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;130:461-70. [PMID: 10075613]
13. **National Kidney Foundation.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266. [PMID: 11904577]
14. **Cirillo M, Lombardi C, Luciano MG, Bilancio G, Anastasio P, De Santo NG.** Estimation of GFR: a comparison of new and established equations [Letter]. Am J Kidney Dis. 2010;56:802-4. [PMID: 20801570]
15. **Jones GR, Imam SK.** Validation of the revised MDRD formula and the original Cockcroft and Gault formula for estimation of the glomerular filtration rate using Australian data. Pathology. 2009;41:379-82. [PMID: 19404852]
16. **Jones GR.** Use of the CKD-EPI equation for estimation of GFR in an Australian cohort [Letter]. Pathology. 2010;42:487-8. [PMID: 20632832]
17. **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; 5:1003-9. [PMID: 20299365]
18. **Kukla A, El-Shahawi Y, Leister E, Kasiske B, Mauer M, Matas A, et al.** GFR-estimating models in kidney transplant recipients on a steroid-free regimen. Nephrol Dial Transplant. 2010;25:1653-61. [PMID: 20118486]
19. **Pöge U, Gerhardt T, Stoffel-Wagner B, Sauerbruch T, Woitas RP.** Validation of the CKD-EPI formula in patients after renal transplantation. Nephrol Dial Transplant. 2011;26:4104-8. [PMID: 21551088]
20. **White CA, Akbari A, Doucette S, Fergusson D, Knoll GA.** Estimating glomerular filtration rate in kidney transplantation: is the new chronic kidney disease epidemiology collaboration equation any better? Clin Chem. 2010;56: 474-7. [PMID: 19959620]
21. **Lane BR, Demirjian S, Weight CJ, Larson BT, Poggio ED, Campbell SC.** Performance of the chronic kidney disease-epidemiology study equations for estimating glomerular filtration rate before and after nephrectomy. J Urol. 2010; 183:896-901. [PMID: 20083272]
22. **Tent H, Rook M, Stevens LA, van Son WJ, van Pelt LJ, Hofker HS, et al.** Renal function equations before and after living kidney donation: a within-individual comparison of performance at different levels of renal function. Clin J Am Soc Nephrol. 2010;5:1960-8. [PMID: 20616162]
23. **Redal-Baigorri B, Stokholm KH, Rasmussen K, Jeppesen N.** Estimation of kidney function in cancer patients. Dan Med Bull. 2011;58:A4236. [PMID: 21299923]
24. **Eriksen BO, Mathisen UD, Melsom T, Ingebretsen OC, Jenssen TG, Njølstad I, et al.** Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. Kidney Int. 2010;78:1305-11. [PMID: 20844470]
25. **Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).** A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150: 604-12. [PMID: 19414839]
26. **Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC.** Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. Clin J Am Soc Nephrol. 2011;6:1963-72. [PMID: 21737852]
27. **Stevens LA, Claybon MA, Schmid CH, Chen J, Horio M, Imai E, et al.** Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. Kidney Int. 2011;79:555-62. [PMID: 21107446]
28. **Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, et al.** Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m^2. Am J Kidney Dis. 2010;56: 486-95. [PMID: 20557989]
29. **Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S.** Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis. 2010;56:32-8. [PMID: 20416999]
30. **van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ.** Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft–Gault equations. Clin Chem. 2008;54:1197-202. [PMID: 18487286]
31. **Praditpornsilpa K, Townamchai N, Chaiwatanarat T, Tiranathanagul K, Katawatin P, Susantitaphong P, et al.** The need for robust validation for MDRD-based glomerular filtration rate estimation in various CKD populations. Nephrol Dial Transplant. 2011;26:2780-5. [PMID: 21357214]
32. **Teo BW, Xu H, Wang D, Li J, Sinha AK, Shuter B, et al.** GFR estimating equations in a multiethnic Asian population. Am J Kidney Dis. 2011;58:56-63. [PMID: 21601325]
33. **Yeo Y, Han DJ, Moon DH, Park JS, Yang WS, Chang JW, et al.** Suitability of the IDMS-traceable MDRD equation method to estimate GFR in early post-operative renal transplant recipients. Nephron Clin Pract. 2010;114:c108-17. [PMID: 19887831]
34. **Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al; Collaborators developing the Japanese equation for estimated GFR.** Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53: 982-92. [PMID: 19339088]
35. **Rule AD, Teo BW.** GFR estimation in Japan and China: what accounts for the difference? [Editorial]. Am J Kidney Dis. 2009;53:932-5. [PMID: 19463761]
36. **Berglund F, Killander J, Pompeius R.** Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. J Urol. 1975;114: 802-8. [PMID: 1195454]
37. **Stevens LA, Levey AS.** Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol. 2009;20:2305-13. [PMID: 19833901]
38. **Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J.** Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2010;55:648-59. [PMID: 20189275]
39. **Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD.** Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. Am Heart J. 2011;162:548-54. [PMID: 21884875]
40. **White SL, Polkinghorne KR, Atkins RC, Chadban SJ.** Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. Am J Kidney Dis. 2010;55:660-70. [PMID: 20138414]
41. **Kwong YT, Stevens LA, Selvin E, Zhang YL, Greene T, Van Lente F, et al.** Imprecision of urinary iothalamate clearance as a gold-standard measure of GFR decreases the diagnostic accuracy of kidney function estimating equations. Am J Kidney Dis. 2010;56:39-49. [PMID: 20537455]
42. **Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, et al.** Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51:395-406. [PMID: 18295055]
43. **Blirup-Jensen S, Grubb A, Lindstrom V, Schmidt C, Althaus H.** Standardization of Cystatin C: development of primary and secondary reference preparations. Scand J Clin Lab Invest Suppl. 2008;241:67-70. [PMID: 18569968]
44. **Grubb A, Blirup-Jensen S, Lindström V, Schmidt C, Althaus H, Zegers I; IFCC Working Group on Standardisation of Cystatin C (WG-SCC).** First certified reference material for cystatin C in human serum ERM-DA471/IFCC. Clin Chem Lab Med. 2010;48:1619-21. [PMID: 21034257]
45. **Zegers I, Auclair G, Schimmel H, Emons H, Blirup-Jensen S, Schmidt C, et al.** Certification of Cystatin C in the Human Serum. Reference Material ERM-DA471/IFCC. Luxembourg: Publications Office of the European Union; 2010.
46. **Inker LA, Eckfeldt J, Levey AS, Leiendecker-Foster C, Rynders G, Manzi J, et al.** Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values [Letter]. Am J Kidney Dis. 2011;58:682-4. [PMID: 21855190]

Current Author Addresses: Ms. Earley and Drs. Miskulin, Levey, and Uhlig: Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02111.
Dr. Lamb: East Kent Hospitals University National Health Service Trust, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent CT1 3NG, United Kingdom.

Author Contributions: Conception and design: A. Earley, E.J. Lamb, A.S. Levey, K. Uhlig.
Analysis and interpretation of the data: A. Earley, D. Miskulin, E.J. Lamb, A.S. Levey, K. Uhlig.
Drafting of the article: A. Earley, D. Miskulin, E.J. Lamb, A.S. Levey, K. Uhlig.
Critical revision of the article for important intellectual content: A. Earley, D. Miskulin, E.J. Lamb, A.S. Levey, K. Uhlig.
Final approval of the article: A. Earley, E.J. Lamb, A.S. Levey, K. Uhlig.
Statistical expertise: K. Uhlig.
Obtaining of funding: K. Uhlig.
Administrative, technical, or logistic support: A. Earley, E.J. Lamb, K. Uhlig.
Collection and assembly of data: A. Earley, D. Miskulin, E.J. Lamb, A.S. Levey, K. Uhlig.

47. **Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al.** Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007;11:41-50. [PMID: 17384997]
48. **Cockcroft DW, Gault MH.** Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41. [PMID: 1244564]
49. **Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG.** Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med. 2004;141:929-37. [PMID: 15611490]
50. **Jelliffe RW.** Estimation of creatinine clearance when urine cannot be collected. Lancet. 1971;1:975-6. [PMID: 4102307]
51. **Jelliffe RW.** Letter: Creatinine clearance: bedside estimate. Ann Intern Med. 1973;79:604-5. [PMID: 4748282]
52. **Mawer GE, Lucas SB, Knowles BR, Stirland RM.** Computer-assisted prescribing of kanamycin for patients with renal insufficiency. Lancet. 1972;1:12-5. [PMID: 4108815]
53. **Hull JH, Hak LJ, Koch GG, Wargin WA, Chi SL, Mattocks AM.** Influence of range of renal function and liver disease on predictability of creatinine clearance. Clin Pharmacol Ther. 1981;29:516-21. [PMID: 7471619]
54. **Gates GF.** Creatinine clearance estimation from serum creatinine values: an analysis of three mathematical models of glomerular function. Am J Kidney Dis. 1985;5:199-205. [PMID: 3838415]
55. **Bjornsson TD, Cocchetto DM, McGowan FX, Verghese CP, Sedor F.** Nomogram for estimating creatinine clearance. Clin Pharmacokinet. 1983;8:365-9. [PMID: 6617044]
56. **Walser M, Drew HH, Guldan JL.** Prediction of glomerular filtration rate from serum creatinine concentration in advanced chronic renal failure. Kidney Int. 1993;44:1145-8. [PMID: 8264148]
57. **Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR.** Predicting glomerular filtration rate after kidney transplantation. Transplantation. 1995;59:1683-9. [PMID: 7604438]

Appendix Table 1. **Search Strategy**

1. exp kidney glomerulus/
2. exp kidney disease/
3. exp kidney function tests/
4. exp renal replacement therapy/
5. exp kidney transplantation/
6. exp kidney, artificial/
7. renal.af. or renal.tw.
8. kidney.af. or kidney.tw.
9. or/1-8
10. limit 9 to humans
11. limit 9 to (guideline or meta analysis or practice guideline or "review")
12. 10 not 11
13. glomerular filtration rate.af. or glomerular filtration rate.tw.
14. gfr.af.
15. exp kidney function tests/
16. serum creatin$.af. or serum creatin$.tw.
17. creatin$.af. or creatin.tw.
18. cystat$.af. or cystat$.tw.
19. or/13-18
20. predict$.af.
21. formula.af.
22. equation.af.
23. exp regression analysis/ or regression analysis.mp.
24. 20 or 21 or 22 or 23
25. 12 and 19 and 24
26. limit 25 to yr="1999-2011"

Appendix Table 2. **Information on Development of Equations Based on Serum Creatinine Assays That Are Traceable to the Standard Reference Material**

Study, Year (Reference)	Equation Name	Equation	Development and Internal Validation Population	GFR Measurement Method (Mean GFR)	SCr Assay Method
North America, Europe, and Australia					
Levey et al, 2006 (8)	MDRD equation MDRD equation without ethnicity factor*	$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black) $175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	1628 patients enrolled in the MDRD study (mean age, 50.6 y)	^{125}I-Iothalamate (urine); GFR measured in mL/min per 1.73 m^2 (39.8 mL/min per 1.73 m^2 SD, 21.2])	Samples from MDRD Study were assayed from 1988 to 1994 with the Beckman Synchron CX3 kinetic Jaffe assay (Global Medical Instrumentation, Ramsey, Minnesota). Samples were reassayed in 2004 with the same instrument. The Beckman assay was calibrated to the Roche enzymatic assay (Roche Diagnostics, Basel, Switzerland), which is traceable to an IDMS assay at NIST.
Levey et al, 2009 (25)	CKD-EPI equation	$141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) $\times$ 1.159 (if black), where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1	8254 participants from 6 research studies and 4 clinical populations (mean age, 47 y)	^{125}I-Iothalamate (urine); GFR measured in mL/min per 1.73 m^2 (68 mL/min per 1.73 m^2 [SD, 40])	Values of SCr were recalibrated to standardized SCr measurements at the Cleveland Clinic by using a Roche enzymatic assay (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffman-La Roche, Basel, Switzerland).
Outside of North America, Europe, and Australia					
Horio et al, 2010 (29)	MDRD equation with Japanese coefficient	$0.808 \times 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	413 Japanese patients in 80 medical centers (mean age, 51.4 y)	Inulin (urine); GFR measured in mL/min per 1.73 m^2 (ND for development or internal validation set)	Levels of SCr were measured by using a Hitachi enzymatic creatinine assay and the values obtained were compared with those of the Cleveland Clinic.
Imai et al, 2007 (47)	Japanese-modified MDRD equation	$0.741 \times 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	248 inpatients with CKD for estimating and determining the coefficient of the MDRD Study equation for Japanese patients (mean age, 50.1 y)	Inulin (urine); GFR measured in mL/min per 1.73 m^2 (ND for development or internal validation set)	Levels of SCr were assayed by both enzymatic and noncompensated kinetic Jaffe methods for the 116 patients in the inulin clinical study and by an enzymatic method for the 132 inpatients at Tokyo Women's Medical University between 2003 and 2004 and the 168 patients with CKD at the University of Tsukuba Hospital from 1988 to 1994. The SCr levels of the samples from the 101 patients from Tokyo Women's Medical University between 2001 and 2002 were measured by a noncompensated kinetic Jaffe method. The SCr levels used in the inulin clinical trial were simultaneously measured by both the noncompensated kinetic Jaffe method and the enzymatic method at the International Organization for Standardization–approved central laboratory. The SCr values from the noncompensated Jaffe method were 0.207 higher than those from the enzymatic method throughout the measured range, based on calibrated standards that were indirectly calibrated with IDMS.
Praditpornsilpa et al, 2011 (31)	MDRD equation with Thai coefficient	$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.129 (if Thai)	250 cases of Thai patients with CKD who were in stable condition (mean age, 59.5 y)	^{99m}Tc-DTPA; GFR measured in mL/min per 1.73 m^2 (plasma) (ND for development or internal validation set)	Fasting SCr levels measured by using a Roche enzymatic assay (Roche Diagnostics, Indianapolis, Indiana), and values adjusted by using IDMS reference SCr (SRM 967) from NIST. Levels of SCr also measured by a Roche kinetic Jaffe assay (Roche Diagnostics) without adjustments to IDMS reference. The SCr levels obtained from enzymatic and Jaffe assays were used in each estimated GFR equation accordingly.

Continued on following page

Appendix Table 2—**Continued**

Study, Year (Reference)	Equation Name	Equation	Development and Internal Validation Population	GFR Measurement Method (Mean GFR)	SCr Assay Method
Horio et al, 2010 (29)	CKD-EPI equation with Japanese coefficient	$0.813 \times 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) $\times$ 1.159 (if black), where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1	413 Japanese patients in 80 medical centers (mean age, 51.4 y)	Inulin (urine); GFR measured in mL/min per 1.73 m^2 (ND for development or internal validation set)	Levels of SCr measured by Hitachi enzymatic assay and values obtained compared with those of the Cleveland Clinic.
Matsuo et al, 2009 (34)	JSN-CKDI equation (equation 2) 3-variable Japanese equation (equation 4)	$171 \times SCr^{-1.004} \times age^{-0.287} \times 0.782$ (if female) $194 \times SCr^{-1.094} \times age^{-0.287} \times 0.739$ (if female)	413 Japanese patients in 80 medical centers; data collected from 1 December 2006 to 20 April 2007 (mean age, 51.4 y)	Inulin (urine) (59.1 mL/min per 1.73 m^2 [SD, 35.4])	Levels of SCr measured by using a Hitachi enzymatic assay (Hitachi, Tokyo, Japan) and values obtained compared with those of the Cleveland Clinic.
Levey et al, 2000 (7)	Original MDRD equation, calibrated to the Cleveland Clinic creatinine measurements (study equation 2)†	$186 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	1628 patients whose GFR was measured as part of the MDRD Study (mean age, 50.6 y)	^{125}I-Iothalamate (urine) GFR measured in mL/min per 1.73 m^2 (39.8 mL/min per 1.73 m^2 [SD, 21.2])	Serum and urine creatinine levels measured by using kinetic Jaffe assay.
Ma et al, 2006 (11)	Original MDRD equation, calibrated to Cleveland Clinic creatinine measurements, with Chinese coefficient (study equation 4)† Chinese equation (study equation 6)‡	$186 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.227 (if Chinese), with SCr calibrated to the Cleveland Clinic $206 \times SCr^{-1.234} \times age^{-0.227} \times 0.803$ (if female), with SCr calibrated to the Cleveland Clinic	454 patients from 9 renal institutes of university hospitals located in 9 geographic regions of China (mean age, 49.9 y)	^{99m}Tc-DTPA (plasma); GFR measured in mL/min per 1.73 m^2 (ND for development or internal validation set)	Levels of SCr measured by using a Hitachi kinetic Jaffe assay and values calibrated to the Cleveland Clinic Laboratory.
Praditpornsilpa et al, 2011 (31)	Thai estimated GFR equation	$375.5 \times SCr^{-0.848} \times age^{-0.364} \times 0.712$ (if female); $r^2 = 0.869$	250 Thai patients with CKD who were in stable condition (mean age, 59.5 y)	^{99m}Tc-DTPA (plasma); GFR measured in mL/min per 1.73 m^2 (ND for development or internal validation set)	Fasting SCr levels measured by using a Roche enzymatic assay (Roche Diagnostics) and values adjusted by using IDMS reference SCr (SRM 967) from NIST. Levels of SCr were also measured by using a Roche kinetic Jaffe assay (Roche Diagnostics) without adjustments to IDMS reference. The SCr levels obtained from enzymatic and Jaffe assays were used in each estimated GFR equation accordingly.

CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; IDMS = isotope-dilution mass spectrometry; JPN-CKDI = Japanese Society of Nephrology-Chronic Kidney Disease Initiatives; MDRD = Modification of Diet in Renal Disease; ND = not documented; NIST = National Institute of Standards and Technology; SCr = serum creatinine; SRM = standard reference material.

*African American coefficient of the MDRD equation.

† Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the 186 coefficient should be replaced with the 175 coefficient from the reexpressed MDRD equation.

‡ Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the SCr should be replaced by SCr × 0.95, which represents the calibration factor relating the SCr assay in the Cleveland Clinic laboratory to the standardized SCr assay.

Appendix Table 3. **Overview Table of Equations Developed to Predict GFR Based on Serum Creatinine Assays Not Traceable to the Standard Reference Material**

Study, Year (Reference)	Equation Name	Expression	Formula
Cockcroft and Gault, 1976 (48)	Cockcroft–Gault	CrCl in mL/min	$(140 - \text{age}) \times \text{weight}/(72 \times \text{SCr}) \times 0.85$ (if female) SCr in mg/dL
Levey et al, 2006 (8)	4-variable MDRD	GFR in mL/min per 1.73 m^2	$186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) SCr in mg/dL
Levey et al, 1999 (12)	6-variable MDRD	GFR in mL/min per 1.73 m^2	$170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times 1.180$ (if black) $\times 0.762$ (if female) $\times \text{BUN}^{-0.170} \times \text{albumin}^{0.318}$ SCr in mg/dL, BUN in mg/dL, and albumin in g/dL
Ma et al, 2006 (11)	Chinese-modified MDRD	GFR in mL/min per 1.73 m^2	$1.233 \times 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times (0.742$ if female) SCr in mg/dL
Rule et al, 2004 (49)	Quadratic equation by Rule	GFR in mL/min per 1.73 m^2	$\exp[1.911 + (5.249/\text{SCr}) - (2.114/\text{SCr}^2) - 0.00686 \times \text{age} - 0.205$ (if female)] SCr in mg/dL
Jelliffe, 1971 (50)	Jelliffe, 1971	CrCl in mL/min	Men: $(100/\text{SCr}) - 12$ Women: $(80/\text{SCr}) - 7$ SCr in mg/dL
Jelliffe, 1973 (51)	Jelliffe, 1973	CrCl in mL/min	$[98 - 0.8 \times (\text{age} - 20)]/\text{SCr} \times (0.9$ if female) SCr in mg/dL
Mawer et al, 1972 (52)	Mawer	CrCl in mL/min	Men: weight $\times [29.3 - (0.203 \times \text{age})] \times [1 - (0.03 \times \text{SCr})]/(14.4 \times \text{SCr}) \times \text{weight}/70$ Women: weight $\times [25.3 - (0.175 \times \text{age})] \times [1 - (0.03 \times \text{SCr})]/(14.4 \times \text{SCr}) \times \text{weight}/70$ SCr in mg/dL
Hull et al, 1981 (53)	Hull	CrCl in mL/min	$[(145 - \text{age})/\text{SCr} - 3] \times (\text{weight}/70) \times 0.85$ (if female) SCr in mg/dL
Gates, 1985 (54)	Gates	CrCl in mL/min	Men: $(89.4 \times \text{SCr}^{-1.2}) + [(55 - \text{age}) \times (0.447 \times \text{SCr}^{-1.1})]$ Women: $(60 \times \text{SCr}^{-1.1}) + [(56 - \text{age}) \times (0.3 \times \text{SCr}^{-1.1})]$ SCr in mg/dL
Bjornsson et al, 1983 (55)	Bjornsson	CrCl in mL/min	Men: $[27 - (0.173 \times \text{age})] \times \text{weight} \times 0.007/\text{SCr}$ Women: $[25 - (0.175 \times \text{age})] \times \text{weight} \times 0.007/\text{SCr}]$ SCr in mg/dL
Walser et al, 1993 (56)	Walser	GFR in mL/min	Men: $7.57/\text{SCr} - 0.103 \times \text{age}) + (0.096 \times \text{weight}) - 6.66$ Women: $6.05/\text{SCr} - (0.08 \times \text{age}) + (0.08 \times \text{weight}) - 4.81$ SCr in μmol/L
Nankivell et al, 1995 (57)	Nankivell	GFR in mL/min	$(6.7/\text{SCr}) + (\text{weight}/4) - (\text{BUN}/2) - (100/\text{height}^2) + (35$ if male or 25 if female) SCr in μmol/L and BUN in mmol/L
Imai et al, 2007 (47)	JSN-CKDI	GFR in mL/min per 1.73 m^2	$1.223 \times 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) SCr in mg/dL

BUN = blood urea nitrogen; CrCl = creatinine clearance; GFR = glomerular filtration rate; JSN-CKDI = Japanese Society of Nephrology-Chronic Kidney Disease Initiatives; MDRD = Modification of Diet in Renal Disease; SCr = serum creatinine.

Appendix Table 4. **Performance of Creatinine-Based GFR Estimating Equations in North America, Europe, and Australia in Subgroups by GFR**

Study, Year (Reference)	Country	Population	Patients, *n*	Measured GFR	
				Reference Standard	Value (SD), *mL/min per 1.73 m²*
Murata et al, 2011 (26)	United States	5238 adults who underwent an outpatient iothalamate clearance at the Mayo Clinic in Rochester, Minnesota (women, 45%; African American, 2%; mean age, 56 y; donor or potential donor, 13%; KTRs, 26%)	583	^{125}I-Iothalamate (urine)	98.9 (20.1)
			97		65.8 (17.4)
			2324		57.3 (24.1)
			1375		52.3 (19.5)
			859		46.2 (29.5)
Levey et al, 2009 (25)	United States	External validation set comprising 16 studies (women, 45%; white or other, 87%; black, 10%; Hispanic, 2%; Asian, 2%; mean age, 50 y; diabetes, 28%; donor, 16%; KTRs, 29%)	3896	^{125}I-Iothalamate (urine) and others	68 (36)
White et al, 2010 (20)	Canada	Stable KTRs (women, 36%; white, 92%; receiving trimethoprim, 19%)	109	^{99m}Tc-DTPA (plasma)	58 (22)
			98		
Pöge et al, 2011 (19)	Germany	Patients with stable renal function after transplantation (women, 40%; white, 99%; mean age, 49 y)	150	^{99m}Tc-DTPA (plasma)	35.9
			20		67.9

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; IDMS = isotope-dilution mass spectrometry; KTR = kidney transplant recipient; MDRD = Modification of Diet in Renal Disease; P_{30} = percentage of estimated GFR values within 30% of measured GFR; SCr = serum creatinine.
* Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.
† The difference between the absolute values for bias.
‡ Lower values indicate greater precision.
§ Higher values indicate greater accuracy.
‖ The difference between the P_{30} values for accuracy (CKD-EPI minus MDRD).
¶ Evaluated as the root mean square error for the regression of estimated GFR on measured GFR.
** Evaluated as the interquartile range for the differences between estimated and measured GFR.
†† Evaluated as the SD of the differences between estimated and measured GFR.

Appendix Table 4—**Continued**

GFR Estimation			Results				
SCr Calibration and Assay	**Subgroup**	**Equation**	**Bias (95% CI), *mL/min per 1.73 m²****	**Difference in Bias, *mL/min per 1.73 m²*†**	**Precision (95% CI)‡**	**P_{30} (95% CI), %§**	**Difference in Accuracy, *percentage points*‖**
Roche Jaffe assay (Roche P- or D-Modular or Roche Cobas C501 with Roche Creatininase Plus assay; Roche Diagnostics, Indianapolis, Indiana) with demonstrated IDMS alignment	Potential kidney donors	MDRD	−19.2	9	ND	75.8	12.9
		CKD-EPI	−10.2			88.7	
	Postnephrectomy kidney donors	MDRD	−11	5.3		82.5	11.3
		CKD-EPI	−5.7			93.8	
	Other organ recipients	MDRD	−1.5	−0.5		80.6	−2.1
		CKD-EPI	2.0			78.5	
	Kidney recipient	MDRD	−1.9	0.3		80.1	−1.7
		CKD-EPI	1.6			78.4	
	Native patients with CKD	MDRD	−2.3	1.9		75.2	−0.2
		CKD-EPI	−0.4			75.0	
Roche enzymatic assay (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffman-La Roche, Basel, Switzerland) recalibrated to standardized SCr at the Cleveland Clinic	GFR ≥60 mL/min per 1.73 m²	MDRD	−10.6 (−9.8 to −11.3)	7.1	0.248 (0.238 to 0.258)¶	84.7 (83.0 to 86.3)	3.6
		CKD-EPI	−3.5 (−2.6 to −4.5)		0.213 (0.203 to 0.223)¶	88.3 (86.9 to 89.7)	
	GFR <60 mL/min per 1.73 m²	MDRD	−3.4 (−2.9 to −4.0)	1.3	0.294 (0.280 to 0.308)¶	77.2 (75.5 to 79.0)	2.7
		CKD-EPI	−2.1 (−1.7 to −2.4)		0.284 (0.270 to 0.298)¶	79.9 (78.1 to 81.7)	
For the reexpressed MDRD Study and CKD-EPI equations, SCr adjusted to IDMS standard	GFR >60 mL/min per 1.73 m²	MDRD	−14.0	5.8	15.8**	79 (69 to 86)	10
		CKD-EPI	−8.2		17.9**	89 (81 to 94)	
	GFR <60 mL/min per 1.73 m²	MDRD	−4.0	1.9	11.6**	80 (71 to 86)	−1
		CKD-EPI	−2.1		12.3**	79 (70 to 85)	
Jaffe assay on Dimension RxLTM analyzer (Dade Behring, Marburg, Germany); assay adjusted for calibration with the IDMS method	GFR >60 mL/min per 1.73 m²	MDRD	1.23	−5.77	16.3††	85.0	−15
		CKD-EPI	7.00		15.2††	70.0	
	GFR <60 mL/min per 1.73 m²	MDRD	4.93	−3.29	8.75††	70.0	−6.7
		CKD-EPI	8.22		10.1††	63.3	

Appendix Table 5. **Performance of Creatinine-Based GFR Estimating Equations in North America, Europe, and Australia in Subgroups by Race**

Study, Year (Reference)	Country	Population	Patients, *n*	Measured GFR		GFR Estimation		Results		
				Reference Standard	Value (SD), *mL/min per 1.73 m²*	SCr Calibration and Assay	Equation	Bias (95% CI), *mL/min per 1.73 m²**	Precision (95% CI)†	P_{30} (95% CI), %‡
Stevens et al, 2011 (27)	United States and Europe	External validation set comprising 16 studies (women, 45%; white or other, 87%; black, 10%; Hispanic, 2%; Asian, 2%; mean age, 50 y; diabetes, 28%; donor, 16%; KTRs, 29%)	384 black patients	^{125}I-Iothalamate (urine) and other filtration markers	62 (34)	Calibrated to standardized SCr measurements by using Roche (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffmann-La Roche, Basel, Switzerland) enzymatic assay at the Cleveland Clinic	CKD-EPI equation with 2-level race or ethnicity coefficient	0.8 (−0.6 to 2.0)	0.242 (0.221 to 0.265)†	82 (78 to 85)
							CKD-EPI equation with 4-level race or ethnicity coefficient	0.9 (−0.6 to 2.0)	0.243 (0.221 to 0.266)†	82 (80 to 85)
			185 Native American and Hispanic patients		105 (47)		CKD-EPI equation with 2-level race or ethnicity coefficient	−2.3 (−5.1 to 2.1)	0.265 (0.223 to 0.310)†	80 (74 to 85)
							CKD-EPI equation with 4-level race or ethnicity coefficient	−1.6 (−4.2 to 3.0)	0.264 (0.222 to 0.310)†	81 (76 to 87)
			67 Asian patients		53 (31)		CKD-EPI equation with 2-level race or ethnicity coefficient	−2.1 (−1.1 to −0.3)	0.302 (0.188 to 0.436)†	85 (76 to 93)
							CKD-EPI equation with 4-level race or ethnicity coefficient	−0.8 (−2.6 to 2.2)	0.293 (0.178 to 0.424)†	85 (76 to 93)
			3378 white or other patients		69 (36)		CKD-EPI equation with 2-level race or ethnicity coefficient	−2.8 (−3.2 to −2.4)	0.250 (0.240 to 0.258)†	84 (83 to 86)
							CKD-EPI equation with 4-level race or ethnicity coefficient	−2.9 (−3.4 to −2.5)	0.250 (0.240 to 0.259)†	84 (83 to 85)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; KTR = kidney transplant recipient; P_{30} = percentage of estimated GFR values within 30% of measured GFR; SCr = serum creatinine.

* Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.

† Lower values indicate greater precision. Evaluated as the root mean square error for the regression of estimated GFR on measured GFR.

‡ Higher values indicate greater accuracy.

Appendix Table 6. **Performance of Creatinine-Based GFR Estimating Equations Outside North America, Europe, and Australia in Subgroups by GFR**

Study, Year (Reference)	Country	Population	Patients, *n*	Measured GFR	
				Reference Standard	Value (SD), *mL/min per 1.73 m²*
Horio et al, 2010 (29)	Japan	Japanese patients (women, 42%; mean age, 54 y; diabetes, 22%; donors, 3%; KTRs, 1%; hypertension, 58%)	206	Inulin (urine)	45 (25)
			144		
Teo et al, 2011 (32)	Singapore	Outpatients with CKD in the nephrology clinic at National University Hospital, Singapore (women, 48%; Chinese, 41%; Malay, 31%; Indian or other, 28%; median age, 58 y; diabetes, 23%; hypertension, 50%)	160	^{99}Tc-DTPA (plasma)	36 (14)
			72		86 (19)
van Deventer et al, 2008 (30)	South Africa	Black South African patients (women, 49%; median age, 47 y; diabetes, 25%; donors, 7%; HIV, 20%; hypertension, 36%)	41	^{51}Cr-EDTA (plasma)	61.5 (49.6)
			39		
			120		

CKD-chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; IDMS = isotope-dilution mass spectrometry; KTR = kidney transplant recipient; MDRD = Modification of Diet in Renal Disease; NIST = National Institute of Standards and Technology; P_{30} = percentage of estimated GFR values within 30% of measured GFR; SCr = serum creatinine; SRM = standard reference material.

* Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.

† The difference between the absolute values for bias (MDRD minus CKD-EPI).

‡ Lower values indicate greater precision.

§ Higher values indicate greater accuracy.

‖ The difference between the P_{30} values for accuracy (CKD-EPI minus MDRD).

¶ Evaluated as the root mean square error for the regression of estimated GFR on measured GFR.

** Evaluated as the interquartile range for the differences between estimated and measured GFR.

†† African American coefficient of the MDRD equation.

Appendix Table 6—**Continued**

GFR Estimation			Results				
SCr Calibration and Assay	**Subgroup**	**Equation**	**Bias (95% CI), *mL/min per 1.73 m²****	**Difference in Bias, *mL/min per 1.73 m²*†**	**Precision (95% CI)‡**	**P_{30} (95% CI), %§**	**Difference in Accuracy, *percentage points*‖**
Enzymatic assay validated by using the calibration panel of the Cleveland Clinic	GFR >60 mL/min per 1.73 m²	MDRD with Japanese coefficient	−7.8	0.5	23.5¶	82 (75 to 87)	6
		CKD-EPI with Japanese coefficient	−7.3		21.8¶	88 (82 to 92)	
	GFR <60 mL/min per 1.73 m²	MDRD with Japanese coefficient	3.3	−1.1	15.9¶	67 (61 to 74)	−2
		CKD-EPI with Japanese coefficient	4.4		14.4¶	65 (58 to 71)	
Siemens enzymatic assay (Siemens Advia 2400; Siemens, Munich, Germany) calibrated with manufacturer-provided materials traceable to standardized creatinine (NIST SRM 967) measured by using IDMS	GFR >60 mL/min per 1.73 m²	MDRD	−5.3 (−9.5 to −1.2)	4.4	18.3 (10.3 to 26.4)**	81.9 (73.1 to 90.8)	9.8
		CKD-EPI	0.9 (−4.1 to 5.9)		22.0 (16.7 to 27.2)**	91.7 (85.3 to 98.1)	
	GFR <60 mL/min per 1.73 m²	MDRD	−2.4 (−3.7 to −1.1)	0.9	9.2 (7.0 to 11.4)**	78.8 (72.4 to 85.1)	0
		CKD-EPI	−1.5 (−2.8 to −0.1)		9.3 (7.0 to 11.6)**	78.8 (72.4 to 85.1)	
Rate-blanked, Roche-compensated, kinetic Jaffe assay (Roche Modular analyzer; Roche Diagnostics, Indianapolis, Indiana) with calibration traceable to IDMS; compared with Roche enzymatic assay (Creatinine Plus; Roche Diagnostics, Indianapolis, Indiana) at the Cleveland Clinic with values adjusted by regression	Estimated GFR, >60 mL/min per 1.73 m²	MDRD with ethnicity factor††	20.4 (17.6 to 28)	15.3	35.1¶	51	25
		MDRD without ethnicity factor††	5.1 (−0.3 to 17.0)		26.8¶	76	
	Estimated GFR, 30 to 60 mL/min per 1.73 m²	MDRD with ethnicity factor††	8.8 (−2.2 to 14.8)	8.4	18.0¶	53	22
		MDRD without ethnicity factor††	0.4 (−6.4 to 5.1)		11.8¶	75	
	Estimated GFR <30 mL/min per 1.73 m²	MDRD with ethnicity factor††	1.7 (−1.7 to 4.4)	0.3	7.2¶	55	12
		MDRD without ethnicity factor††	−1.4 (−4.0 to 2.2)		7.0¶	67	