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Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate

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Background: Glomerular filtration rate (GFR) estimates facilitate detection of chronic kidney disease but require calibration of the serum creatinine assay to the laboratory that developed the equation. The 4-variable equation from the Modification of Diet in Renal Disease (MDRD) Study has been reexpressed for use with a standardized assay.

Objective: To describe the performance of the revised 4-variable MDRD Study equation and compare it with the performance of the 6-variable MDRD Study and Cockcroft–Gault equations.

Design: Comparison of estimated and measured GFR.

Setting: 15 clinical centers participating in a randomized, controlled trial.

Patients: 1628 patients with chronic kidney disease participating in the MDRD Study.

Measurements: Serum creatinine levels were calibrated to an assay traceable to isotope-dilution mass spectrometry. Glomerular filtration rate was measured as urinary clearance of ^{125}I-iothalamate.

Results: Mean measured GFR was 39.8 mL/min per 1.73 m^2 (SD, 21.2). Accuracy and precision of the revised 4-variable equation were similar to those of the original 6-variable equation and better than in the Cockcroft–Gault equation, even when the latter was corrected for bias, with 90%, 91%, 60%, and 83% of estimates within 30% of measured GFR, respectively. Differences between measured and estimated GFR were greater for all equations when the estimated GFR was 60 mL/min per 1.73 m^2 or greater.

Limitations: The MDRD Study included few patients with a GFR greater than 90 mL/min per 1.73 m^2. Equations were not compared in a separate study sample.

Conclusions: The 4-variable MDRD Study equation provides reasonably accurate GFR estimates in patients with chronic kidney disease and a measured GFR of less than 90 mL/min per 1.73 m^2. By using the reexpressed MDRD Study equation with the standardized serum creatinine assay, clinical laboratories can report more accurate GFR estimates.

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Chronic kidney disease is a recently recognized public health problem. Current guidelines define chronic kidney disease as kidney damage or a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 for 3 months or more, regardless of cause (1–3). Kidney damage is usually ascertained from markers, such as albuminuria. The GFR can be estimated from serum creatinine concentration and demographic and clinical variables, such as age, sex, ethnicity, and body size. The normal mean value for GFR in healthy young men and women is approximately 130 mL/min per 1.73 m^2 and 120 mL/min per 1.73 m^2, respectively, and declines by approximately 1 mL/min per 1.73 m^2 per year after 40 years of age (4). To facilitate detection of chronic kidney disease, guidelines recommend that clinical laboratories compute and report estimated GFR by using estimating equations, such as equations derived from the Modification of Diet in Renal Disease (MDRD) Study (1–3, 5–10).

The original MDRD Study equation was developed by using 1628 patients with predominantly nondiabetic kidney disease. It was based on 6 variables: age; sex; ethnicity; and serum levels of creatinine, urea, and albumin (11). Subsequently, a 4-variable equation consisting of age, sex, ethnicity, and serum creatinine levels was proposed to simplify clinical use (3, 12). This equation is now widely accepted, and many clinical laboratories are using it to report GFR estimates.

Extensive evaluation of the MDRD Study equation shows good performance in populations with lower levels of GFR but variable performance in those with higher levels (13–32). Variability among clinical laboratories in calibration of serum creatinine assays (33, 34) introduces error in GFR estimates, especially at high levels of GFR (35), and may account in part for the poorer performance in this range (13, 14, 16, 18–21, 27, 30). The National Kidney Disease Education Program (NKDEP) has initiated a creatinine standardization program to improve and normalize serum creatinine results used in estimating equations (36).

See also:

Print

Editors' Notes 248
Editorial comment. 299
Related article. 237

Web-Only

Appendix
Conversion of figures and tables into slides

Context

Guidelines recommend that laboratories estimate glomerular filtration rate (GFR) with equations that use serum creatinine level, age, sex, and ethnicity. Standardizing creatinine measurements across clinical laboratories should reduce variability in estimated GFR.

Contribution

Using standardized creatinine assays, the authors calibrated serum creatinine levels in 1628 patients whose GFR had been measured by urinary clearance of ^{125}I-iothalamate. They used these data to derive new equations for estimating GFR and to measure their accuracy. The equations were inaccurate only when kidney function was near-normal.

Cautions

There was no independent sample of patients for measuring accuracy.

Implications

By using this equation and a standardized creatinine assay, different laboratories can report estimated GFR more uniformly and accurately.

—The Editors

The MDRD Study equation has now been reexpressed for use with a standardized serum creatinine assay (37), allowing GFR estimates to be reported in clinical practice by using standardized serum creatinine and overcoming this limitation to the current use of GFR estimating equations.

The purpose of this report is to describe the performance of the reexpressed 4-variable MDRD Study equation and compare it with the performance of the reexpressed 6-variable MDRD equation and the Cockcroft–Gault equation (38), with particular attention to the level of GFR. This information should facilitate implementation of reporting and interpreting estimated GFR in clinical practice.

METHODS

Laboratory Methods

Urinary clearances of ^{125}I-iothalamate after subcutaneous infusion were determined at clinical centers participating in the MDRD Study. Serum and urine ^{125}I-iothalamate were assayed in a central laboratory.

All serum creatinine values reported in this study are traceable to primary reference material at the National Institute of Standards and Technology (NIST), with assigned values based on isotope-dilution mass spectrometry. The serum creatinine samples from the MDRD Study were originally assayed from 1988 to 1994 in a central laboratory with the Beckman Synchron CX3 (Global Medical Instrumentation, Inc., Ramsey, Minnesota) by using a kinetic alkaline picrate method. Samples were reassayed in 2004 with the same instrument. The Beckman assay was calibrated to the Roche/Hitachi P module Creatinase Plus enzymatic assay (Roche Diagnostics, Basel, Switzerland), traceable to an isotope-dilution mass spectrometry assay at NIST (37, 39). On the basis of these results, the 4-variable and 6-variable MDRD Study equations were reexpressed for use with standardized serum creatinine assay. The Cockcroft–Gault equation was not reexpressed because the original serum creatinine samples were not available for calibration to standardized serum creatinine assay.

Derivation and Validation of the MDRD Study Equation

The MDRD Study was a multicenter, randomized clinical trial of the effects of reduced dietary protein intake and strict blood pressure control on the progression of chronic kidney disease (40). The derivation of the MDRD Study equation has been described previously (11). Briefly, the equation was developed from data from 1628 patients enrolled during the baseline period. The GFR was computed as urinary clearance of ^{125}I-iothalamate. Creatinine clearance was computed from creatinine excretion in a 24-hour urine collection and a single measurement of serum creatinine. Glomerular filtration rate and creatinine clearance were expressed per 1.73 m^2 of body surface area. Ethnicity was assigned by study personnel, without explicit criteria, probably by examination of skin color.

The MDRD Study equation was developed by using multiple linear regression to determine a set of variables that jointly estimated GFR in a random sample of 1070 patients (development data set). The regressions were performed on log-transformed data to reduce variability in differences between estimated and measured GFR at higher levels. Several equations were developed, and the performance of these equations was compared in the remaining sample of 558 patients (validation data set). To improve the accuracy of the final equations, the regression coefficients derived from the development data set were updated on the basis of data from all 1628 patients (11).

Estimation of GFR

Glomerular filtration rate was estimated by using the following 4 equations: the reexpressed 4-variable MDRD Study equation ($GFR = 175 \times \text{standardized } S_{cr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ [if black] $\times 0.742$ [if female]), the reexpressed 6-variable MDRD Study equation ($GFR = 161.5 \times \text{standardized } S_{cr}^{-0.999} \times \text{age}^{-0.176} \times \text{SUN}^{-0.17} \times \text{albumin}^{0.318} \times 1.18$ [if black] $\times 0.762$ [if female]), the Cockcroft–Gault equation adjusted for body surface area ($C_{cr} = [140 - \text{age}] \times \text{weight} \times 0.85$ [if female] $\times 1.73/72$ standardized $S_{cr} \times \text{BSA}$), and the Cockcroft–Gault equation adjusted for body surface area and corrected for the bias in the MDRD Study sample ($C_{cr} = 0.8 \times [140 - \text{age}] \times \text{weight} \times 0.85$ [if female] $\times 1.73/72$ standardized $S_{cr} \times \text{BSA}$).

In these equations, GFR and creatinine clearance (C_{cr}) are expressed as mL/min per 1.73 m^2, serum creatinine and urea nitrogen (SUN) are expressed as mg/dL, albumin is

expressed as g/dL, weight is expressed as kg, age is expressed as years, and body surface area (BSA) is expressed as m^2. Correction for bias improves performance of the Cockcroft–Gault equation because it adjusts for systematic differences between studies, such as differences in the measures of kidney function (GFR in the MDRD Study and creatinine clearance in the study by Cockcroft and Gault), the serum creatinine assays, and the study samples. Hence, the bias correction for the Cockcroft–Gault equation provided here reexpresses that equation for the estimation of GFR for use with standardized creatinine in study samples similar to that in the MDRD Study.

Measures of Performance

Measures of performance include bias (median difference of measured minus estimated GFR and measured GFR) and percentage bias (percentage of bias divided by measured GFR), precision (interquartile range of the difference between estimated and measured GFR, and percentage of variance in log-measured GFR explained by the regression model [R^2 values]), and accuracy (percentage of estimates within 30% of the measured values). In the overall data set, bias is expected to be close to 0 for equations derived in the MDRD Study database, including the 4-variable and 6-variable equations and the Cockcroft–Gault equation adjusted for bias. The bootstrap method (based on percentiles, with 2000 bootstrap samples) was used to estimate 95% CIs for interquartile ranges and R^2 values. Confidence intervals for the percentage of estimates within 30% of measured values were computed by using the normal approximation to the binomial or exact binomial probabilities, as appropriate. We also computed sensitivity, specificity, positive and negative predictive value of estimated GFR less than 60 mL/min per 1.73 m^2, and receiver-operating characteristic (ROC) curves by using measured GFR less than 60 mL/min per 1.73 m^2 as the criterion standard. Areas under the ROC curves were compared by using the method of DeLong and colleagues (41). R, version 2 (Free Software Foundation, Inc., Boston, Massachusetts), and SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina), were used for statistical analysis. We used the "lowess" function in R to plot smoothed functions in the figures.

Role of the Funding Source

The study was funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) as part of a cooperative agreement that gives the NIDDK substantial involvement in the design of the study and in the collection, analysis, and interpretation of the data. The NIDDK was not required to approve publication of the finished manuscript. The institutional review boards of all participating institutions approved the study.

RESULTS

Clinical characteristics of the 1628 MDRD Study participants from whom the MDRD Study equation was derived are shown in **Table 1** (11). Mean measured GFR was 39.8 mL/min per 1.73 m^2 (SD, 21.2). **Figure 1** shows the difference in measured GFR minus estimated GFR versus the level of estimated GFR using the 4-variable MDRD Study equation and other equations. **Table 2** compares the performance of these equations in the MDRD Study participants according to the level of estimated GFR. For the overall study sample, precision and accuracy for the 4-variable equation are almost as good as for the 6-variable equation. As expected, within the MDRD Study sample, the 4-variable MDRD Study equation has less bias than the Cockcroft–Gault equation, even when the latter is adjusted for body surface area. This equation also has greater precision and accuracy than the Cockcroft–Gault equation, even when the latter is corrected for systematic bias. Percentages of estimates within 30% of measured GFR were 90% and 91% for the 4-variable and 6-variable MDRD Study equations, respectively, and 60% and 83% for the Cockcroft–Gault equation without and with correction for bias, respectively.

Table 1. **Baseline Characteristics of 1628 Participants from the Modification of Diet in Renal Disease Study***

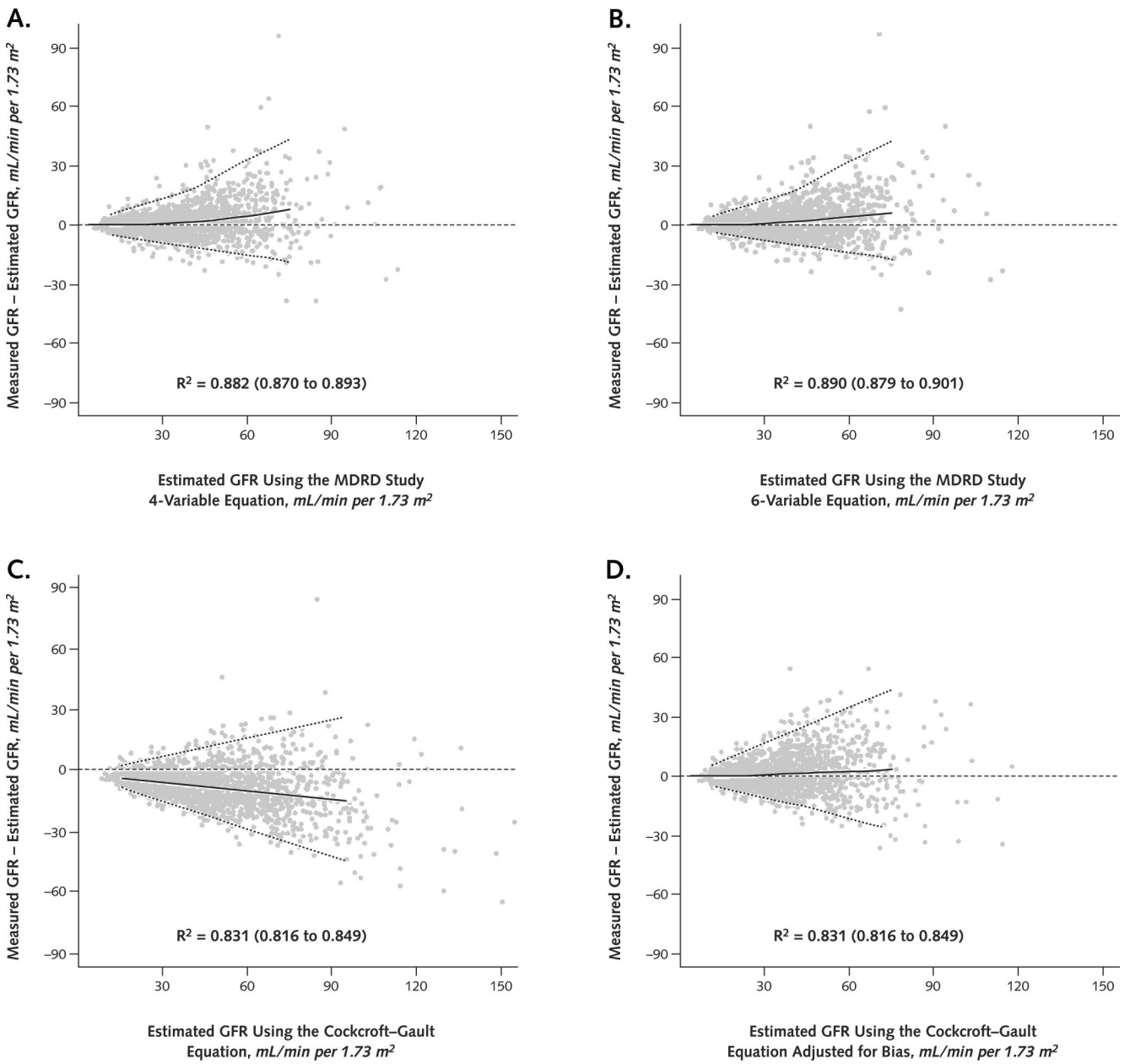
Characteristic	Value
Men, *n (%)*	983 (60)
African American, *n (%)*	197 (12)
Diabetes, *n (%)*	99 (6)
Cause of kidney disease, *n (%)*	
Glomerular disease	525 (32)
Polycystic kidney disease	364 (22)
Tubulointerstitial disease	121 (7)
Other or unknown	618 (40)
Mean age (SD), *y*	50.6 (12.7)
Mean weight (SD), *kg*	79.6 (16.8)
Mean body surface area (SD), m^2	1.91 (0.23)
Mean arterial pressure (SD), *mm Hg*	99.4 (12.7)
Mean dietary protein intake (SD), *g/kg per d*	0.99 (0.24)
Mean GFR (SD), *mL/min per 1.73 m^2*	39.8 (21.2)
Mean creatinine clearance (SD), *mL/min per 1.73 m^2*	48.6 (24.5)
Mean standardized serum creatinine concentration	
μmol/L	189.2 (98.1)
mg/dL	2.14 (1.11)
GFR range, *n (%)*	
>90 mL/min per 1.73 m^2	34 (2.0)
60–89 mL/min per 1.73 m^2	226 (13.9)
30–59 mL/min per 1.73 m^2	747 (45.9)
15–29 mL/min per 1.73 m^2	465 (28.6)
<15 mL/min per 1.73 m^2	156 (9.6)

* GFR = glomerular filtration rate.

For all equations, differences between measured and estimated GFR (**Figure 1**) and interquartile range (**Table 2**) increase at higher levels of estimated GFR when expressed on the absolute scale. On a percentage basis, these differences are relatively constant. Data are limited for higher levels of GFR, particularly for an estimated GFR greater than 90 mL/min per 1.73 m^2.

Performance of equations was also compared by using a cutoff value for a measured GFR less than 60 mL/min per 1.73 m^2, the threshold value for the definition of chronic kidney disease. **Figure 2** shows ROC curves and sensitivity, specificity, predictive values, and area under the

Figure 1. **Differences between measured and estimated glomerular filtration rate (*GFR*) for 4 estimating equations, according to the level of estimated GFR.**



A. Four-variable Modification of Diet in Renal Disease (*MDRD*) Study equation. **B.** 6-variable MDRD Study equation. **C.** Cockcroft–Gault equation adjusted for body surface area. **D.** Cockcroft–Gault equation adjusted for body surface area and corrected for bias. Points indicate individual patients. Patients with differences between measured and estimated GFR greater than 60 mL/min per 1.73 m^2 are not shown. The dashed horizontal line is the reference line. The solid black line is the smooth estimate of the mean difference, and the 2 dotted lines represent the 95% of the population of differences across the range of estimated GFR. Curves are drawn through the 2.5% to 97.5% of the range of GFR estimates. Values for R^2 (95% CIs) are for the regression of measured GFR versus estimated GFR.

curve for each equation for detection of a GFR less than 60 mL/min per 1.73 m^2. The 4-variable and 6-variable equations were comparable and were better than the Cockcroft–Gault equation, even after adjustment for body surface area and correction for bias.

DISCUSSION

Accurate GFR estimation requires standardized serum creatinine assays and estimating equations expressed for use with standardized assays. The NKDEP has begun a program for national creatinine standardization (36), analo-

gous to cholesterol standardization as the first step of the National Cholesterol Education Program in the 1980s. Once standardization is complete (expected in 2008), clinical laboratories can use standardized serum creatinine values to report estimated GFR. The MDRD Study laboratory has now been calibrated to a standardized serum creatinine assay, and the 4-variable MDRD Study equation has now been reexpressed for use with standardized serum creatinine assays.

In the MDRD Study sample, with a GFR range of approximately 5 mL/min per 1.73 m^2 to 90 mL/min per 1.73 m^2, we found that the 4-variable MDRD Study equation was nearly as accurate as the 6-variable equation. For both equations, differences between measured and estimated GFR were greater in subgroups with estimated GFR of 60 mL/min per 1.73 m^2 or greater when expressed on the raw scale but were similar across the range of estimated GFR when expressed as a percentage.

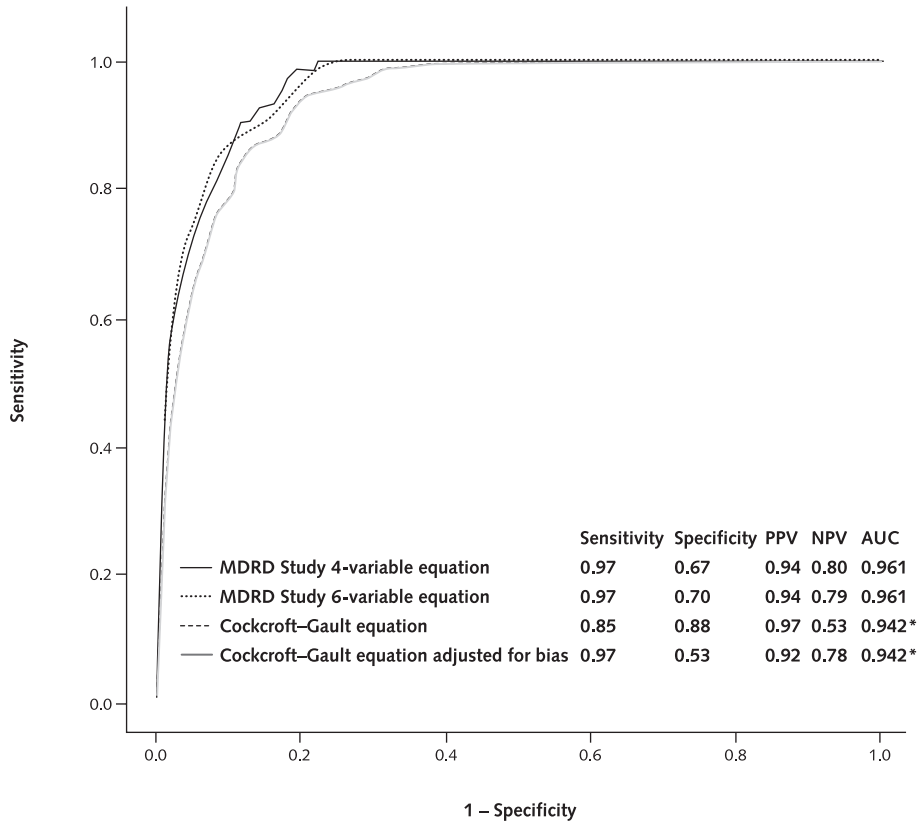
Sensitivity and specificity of the 4-variable and 6-variable MDRD Study equations for detection of a GFR less than 60 mL/min per 1.73 m^2, the threshold GFR level for the definition of chronic kidney disease, were nearly identical (96% to 97% and 67% to 70%, respectively), as were areas under the ROC curves (0.96098 and 0.96091, respectively). However, interpretation of sensitivity and specificity of GFR measurements is difficult for 3 reasons. First, measured and estimated GFR are continuous variables. Sensitivity and specificity can be affected by the distribution of values near the cutoff value, and ROC analysis treats small and large errors as equal. Second, we suspect that measurement error in the GFR assay may be greater than other criterion standards used to evaluate test perfor-

Table 2. **Performance of the Equations Using Standardized Creatinine Values in Subgroups of the Modification of Diet in Renal Disease Study Cohort Defined by Level of Estimated Glomerular Filtration Rate***

Subgroups Defined by GFR_{est} Range	Patients, *n*	$GFR_{meas} - GFR_{est}$, *mL/min per 1.73 m²*		$GFR_{meas} - GFR_{est}/GFR_{meas}$, %		GFR_{est} within 30% of GFR_{meas} (95% CI), %
		Median	IQR (95% CI)	Median	IQR (95% CI)	
Four-variable MDRD Study equation						
Overall	1628	0.2	7.7 (7.2 to 8.2)	0.6	23.6 (22.2 to 25.2)	90 (89 to 91)
>90 mL/min per 1.73 m^2	18	−3.0	21.5 (8.5 to 51.5)	−3.3	21.0 (9.0 to 56.4)	78 (59 to 97)
60 to 89 mL/min per 1.73 m^2	201	0.5	20.1 (16.3 to 22.4)	0.8	26.7 (22.8 to 30.4)	86 (81 to 91)
30 to 59 mL/min per 1.73 m^2	822	0.1	9.0 (8.3 to 10.0)	0.2	21.9 (19.6 to 23.4)	92 (90 to 94)
15 to 29 mL/min per 1.73 m^2	455	0.1	5.7 (5.2 to 6.2)	0.5	26.5 (23.7 to 29.1)	87 (84 to 90)
<15 mL/min per 1.73 m^2	132	0.3	3.3 (2.6 to 3.9)	2.2	25.1 (20.2 to 29.8)	91 (86 to 96)
Six-variable MDRD Study equation						
Overall†	1628	0.2	7.4 (6.9 to 7.8)	0.5	22.5 (21.1 to 24.0)	91 (90 to 92)
>90 mL/min per 1.73 m^2	15	0.4	31.8 (15.7 to 60.4)	0.4	31.8 (14.0 to 61.0)	73 (51 to 95)
60 to 89 mL/min per 1.73 m^2	214	0.8	17.0 (14.3 to 19.9)	1.2	23.7 (20.0 to 27.4)	90 (86 to 94)
30 to 59 mL/min per 1.73 m^2	795	0.2	9.1 (8.3 to 9.9)	0.4	21.0 (19.2 to 23.0)	92 (90 to 94)
15 to 29 mL/min per 1.73 m^2	470	0.0	5.1 (4.6 to 5.6)	0.2	24.3 (21.5 to 26.2)	90 (87 to 93)
<15 mL/min per 1.73 m^2	134	0.2	3.1 (2.4 to 4.2)	2.1	24.5 (19.4 to 30.4)	93 (89 to 97)
Cockcroft–Gault equation, with adjustment for body surface area§						
Overall	1628	−7.3	10.9 (10.3 to 11.6)	−24.3	37.8 (35.2 to 39.7)	60 (58 to 62)
>90 mL/min per 1.73 m^2	66	−21.8	28.5 (17.8 to 34.0)	−28.4	43.4 (27.6 to 54.8)	56(44 to 68)
60 to 89 mL/min per 1.73 m^2	365	−12.0	15.9 (13.8 to 18.1)	−20.3	32.5 (28.5 to 37.5)	65 (60 to 70)
30 to 59 mL/min per 1.73 m^2	817	−7.9	10.3 (9.4 to 11.3)	−23.8	35.7 (32.5 to 39.0)	59 (56 to 62)
15 to 29 mL/min per 1.73 m^2	350	−5.2	5.9 (4.9 to 6.6)	−30.0	45.1 (38.1 to 50.5)	49 (44 to 54)
<15 mL/min per 1.73 m^2	30	−2.9	2.2 (1.4 to 3.5)	−28.5	33.3 (16.2 to 47.7)	50 (32 to 68)
Cockcroft–Gault equation, with adjustment for body surface area and correction for bias§‖						
Overall	1628	0.2	10.0 (9.4 to 10.6)	0.5	30.2 (28.2 to 31.8)	83 (81 to 85)
>90 mL/min per 1.73 m^2	12	6.7	41.6 (19.9 to 64.7)	5.7	37.4 (16.1 to 68.1)	83 (51 to 98)
60 to 89 mL/min per 1.73 m^2	165	1.9	21.0 (17.1 to 26.3)	3.0	29.0 (22.9 to 37.8)	84 (78 to 90)
30 to 59 mL/min per 1.73 m^2	871	1.0	12.5 (11.4 to 13.6)	2.1	27.5 (25.2 to 30.6)	83 (81 to 85)
15 to 29 mL/min per 1.73 m^2	487	−0.6	6.5 (6.0 to 7.3)	−2.9	31.3 (28.4 to 36.2)	81 (78 to 84)
<15 mL/min per 1.73 m^2	93	−0.4	3.3 (2.6 to 4.6)	−4.1	29.4 (22.5 to 40.1)	82 (74 to 90)

* Median and median percentage $GFR_{meas} - GFR_{est}$ are expected to be close to 0 for the 4-variable and 6-variable MDRD Study equations and for the bias-corrected Cockcroft–Gault equation because coefficients in these equations were fitted to the MDRD Study data set. est = estimated; GFR = glomerular filtration rate; IQR = interquartile range; MDRD = Modification of Diet in Renal Disease; meas = measured.
† These analyses were performed in the total cohort. In the original report (11), analyses were performed in the validation subgroup only.
§ Cockcroft–Gault equation was adjusted to 1.73 m^2 body surface area.
‖ The correction factor was 0.80 (see text).

Figure 2. **Receiver-operating characteristic curves for 4 estimating equations.**



For each curve, the sensitivity and specificity were computed for varying cutoff values for estimated glomerular filtration rate (GFR) to detect a measured GFR of less than 60 mL/min per 1.73 m^2. AUC = area under the curve; MDRD = Modification of Diet in Renal Disease; NPV = negative predictive value; PPV = positive predictive value.* $P < 0.001$ for the comparison of the AUCs with the 4-variable MDRD Study equation. The AUCs for the Cockcroft–Gault equation with and without adjustment for bias are identical because these equations are equivalent except for a constant multiplier.

mance. Finally, patients may have chronic kidney disease with GFR levels of 60 mL/min per 1.73 m^2 or greater if they have a marker of kidney damage, such as albuminuria. Indeed, all patients enrolled in the baseline period of the MDRD Study were judged by the investigators to have chronic kidney disease. It is possible that the sensitivity and specificity of the MDRD Study and Cockcroft–Gault equations in other samples will differ from those reported here, even when standardized serum creatinine assays are used.

The 4-variable equation is simpler to use than the 6-variable equation because it does not require inclusion of serum urea nitrogen level and serum albumin concentration, which would also require calibration among laboratories for optimal use. Exclusion of these variables may also make the equation less susceptible to error in conditions in which serum urea nitrogen or albumin is strongly influenced by factors other than GFR.

The 4-variable MDRD Study equation seems to perform better than the Cockcroft–Gault equation, even when the Cockcroft–Gault equation is adjusted for body surface area. The Cockcroft–Gault equation was developed in a different sample, and one would expect some reduction in performance when any equation is applied to a different sample. Thus, better performance of the MDRD Study equation is explained in part by development of the MDRD Study equation in this data set. However, improvement in precision was maintained even after the Cockcroft–Gault equation was corrected for bias with respect to the MDRD Study sample. In addition, studies in different samples have compared the MDRD Study and the Cockcroft–Gault equations. These studies show better (14–16, 18, 42) or similar (17, 27, 43, 44) performance of the MDRD Study equation compared with the Cockcroft–Gault equation. A few studies have also shown in particular that the age correction in the Cockcroft–Gault equation is too steep (18, 42, 43).

In addition, several practical details limit GFR estimation using the Cockcroft–Gault equation. First, it is more difficult to use than the MDRD Study equation because it requires measurement of weight and measurement of height for computation of body surface area to compare estimated creatinine clearance with normative values. Second, it estimates creatinine clearance rather than GFR.

Third, the clinical laboratory creatinine assay cannot easily be calibrated to the laboratory that performed the assays on samples used to derive the Cockcroft–Gault equation. Despite these limitations, the Cockcroft–Gault equation has been widely used in pharmacokinetic studies, and until there are more data based on the MDRD Study equation, physicians and pharmacists may choose to continue to use the Cockcroft–Gault equation for adjustment of drug dosages in patients with decreased GFR.

In the MDRD Study sample, the 6-variable and 4-variable equations were also more accurate than measured creatinine clearance, even after the latter was corrected for systematic overestimation of GFR (correction factor of 0.81 using nonstandardized serum creatinine [11]). In clinical practice, there will probably be greater inaccuracy of measured creatinine clearance because of the well-known difficulties in timed urine collections. In principle, this limitation might be overcome by obtaining repeated timed urine collections, but this may not be practical in many settings. In addition, differences in calibration of the urine creatinine assays among clinical laboratories may also limit the accuracy of creatinine clearance measurements. Currently, urine creatinine has not been incorporated into NKDEP's standardization program.

The 4-variable MDRD Study equation has now been validated extensively in multiple samples with and without chronic kidney disease. In general, these studies show good performance in patients with chronic kidney disease, including those with diabetes or kidney transplants, those who are elderly, and those who are African American (15, 17, 18). Other reports have indicated that the MDRD Study equations underestimate measured GFR in patients without chronic kidney disease and a GFR less than 90 mL/min per 1.73 m^2 (14, 16, 27). Differences in creatinine calibration may account for this finding in some studies, but other sources of error in the equations probably also contribute (45). Underestimation of measured GFR in samples consisting primarily of persons with normal GFR is an important limitation of current estimating equations, especially when using GFR estimates to screen for chronic kidney disease or to determine the prevalence of chronic kidney disease in the general population. Future studies should assess the tradeoff between improving early detection of chronic kidney disease and mislabeling persons because of falsely low estimated GFR.

All creatinine-based GFR estimating equations are inaccurate in patients with low creatinine generation, including those with muscle wasting or reduced meat intake. Some studies suggest that cystatin C may be a more accurate filtration marker in patients with low creatinine generation and could be incorporated into estimating equations (46, 47). Future equations should be expressed in terms of NIST-traceable values for serum creatinine or cystatin C and should be accompanied by an assessment of the error and uncertainty of GFR estimates at various levels.

Current guidelines recommend that clinical laboratories report estimated GFR whenever serum creatinine is measured (1–3, 5–10). With the availability of appropriate calibrator materials from NIST (SRM 967) and trueness control materials from the College of American Pathologists (LN24 Linearity Survey), clinical laboratories can establish and maintain standardized serum creatinine assays and use reexpressed estimating equations, such as the 4-variable MDRD Study equation, to report GFR estimates.

Clinicians should measure serum creatinine levels to estimate GFR in persons with chronic kidney disease or in those at increased risk for this disease (1, 2). Clinicians should be aware of limitations of the MDRD Study equation and other GFR estimating equations in apparently healthy persons with low GFR estimates and in patients with low creatinine generation. If greater accuracy is needed in such individuals, then a clearance measurement can be performed by using exogenous filtration markers or creatinine clearance.

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References

1. **Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al.** National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137-47. [PMID: 12859163]

2. **Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al.** Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089-100. [PMID: 15882252]

3. **National Kidney Foundation.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis. 2002;(2 Suppl 1):S1-266. [PMID: 11904577]

4. **Wesson L.** Physiology of the Human Kidney. New York: Grune & Stratton; 1969.

5. **Siegel N.** Renal Express. Accessed at www.asn-online.org/newsletter/renal_express/2003/03-10_Rxpress.aspx on 23 June 2006.

6. National Kidney Disease Education Program. Information of Health Professionals. Creatinine Standardization Program. Accessed at www.nkdep.nih.gov/labprofessionals/index.htm on 9 February 2006.

7. New Jersey State Senate, 211th Legislature. S2232 Madden, Bryant; 2005:1-2.

8. **Mathew TH, Australasian Creatinine Consensus Working Group.** Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. Med J Aust. 2005;183:138-41. [PMID: 16053416]
9. La Caisse Nationale d'Assurance Maladie des Professions Indépendantes. Avenant à la convention nationale des directeurs de laboratoire privé d'analyses médicales. Accessed at www.admi.net/jo/20030227/SANS0320604X.html on 8 November 2004.
10. **British Columbia Ministry of Health.** Guidelines and Protocols, Advisory Committee. Accessed at www.healthservices.gov.bc.ca/msp/protoguides/gps/ckd.pdf on 21 October 2005.
11. **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]
12. **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.
13. **Stevens LA, Levey AS.** Clinical implications of estimating equations for glomerular filtration rate [Editorial]. Ann Intern Med. 2004;141:959-61. [PMID: 15611494]
14. **Poggio ED, Wang X, Greene T, Van Lente F, Hall PM.** Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol. 2005;16:459-66. [PMID: 15615823]
15. **Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, et al.** Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. Am J Kidney Dis. 2001;38:744-53. [PMID: 11576877]
16. **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]
17. **Gonwa TA, Jennings L, Mai ML, Stark PC, Levey AS, Klintmalm GB.** Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. Liver Transpl. 2004;10:301-9. [PMID: 14762871]
18. **Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P.** Predictive performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol. 2005;16:763-73. [PMID: 15659562]
19. **Hallan S, Asberg A, Lindberg M, Johnsen H.** Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. Am J Kidney Dis. 2004;44:84-93. [PMID: 15211442]
20. **Lin J, Knight EL, Hogan ML, Singh AK.** A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol. 2003;14:2573-80. [PMID: 14514734]
21. **Bostom AG, Kronenberg F, Ritz E.** Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol. 2002;13:2140-4. [PMID: 12138147]
22. **Zuo L, Ma YC, Zhou YH, Wang M, Xu GB, Wang HY.** Application of GFR-estimating equations in Chinese patients with chronic kidney disease. Am J Kidney Dis. 2005;45:463-72. [PMID: 15754268]
23. **Gaspari F, Ferrari S, Stucchi N, Centemeri E, Carrara F, Pellegrino M, et al.** Performance of different prediction equations for estimating renal function in kidney transplantation. Am J Transplant. 2004;4:1826-35. [PMID: 15476483]
24. **Lamb EJ, Webb MC, Simpson DE, Coakley AJ, Newman DJ, O'Riordan SE.** Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: is the Modification of Diet in Renal Disease formula an improvement? J Am Geriatr Soc. 2003;51:1012-7. [PMID: 12834524]
25. **Vervoort G, Willems HL, Wetzels JF.** Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. Nephrol Dial Transplant. 2002;17:1909-13. [PMID: 12401845]
26. **Skluzacek PA, Szewc RG, Nolan CR 3rd, Riley DJ, Lee S, Pergola PE.** Prediction of GFR in liver transplant candidates. Am J Kidney Dis. 2003;42:1169-76. [PMID: 14655188]
27. **Ibrahim H, Mondress M, Tello A, Fan Y, Koopmeiners J, Thomas W.** An alternative formula to the Cockcroft-Gault and the Modification of Diet in Renal Diseases formulas in predicting GFR in individuals with type 1 diabetes. J Am Soc Nephrol. 2005;16:1051-60. [PMID: 15716336]
28. **Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, et al.** Estimation of glomerular filtration rate in diabetic subjects: Cockcroft formula or Modification of Diet in Renal Disease study equation? Diabetes Care. 2005;28:838-43. [PMID: 15793182]
29. **Pöge U, Gerhardt T, Palmedo H, Klehr HU, Sauerbruch T, Woitas RP.** MDRD equations for estimation of GFR in renal transplant recipients. Am J Transplant. 2005;5:1306-11. [PMID: 15888034]
30. **Grubb A, Björk J, Lindström V, Sterner G, Bondesson P, Nyman U.** A cystatin C-based formula without anthropometric variables estimates glomerular filtration rate better than creatinine clearance using the Cockcroft-Gault formula. Scand J Clin Lab Invest. 2005;65:153-62. [PMID: 16025838]
31. **Fehrman-Ekholm I, Skeppholm L.** Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. Scand J Urol Nephrol. 2004;38:73-7. [PMID: 15204431]
32. **Coresh J, Stevens LA.** Kidney function estimating equations: where do we stand? Curr Opin Nephrol Hypertens. 2006;15:276-84. [PMID: 16609295]
33. **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]
34. **Miller WG, Myers GL, Ashwood ER, Killeen AA, Wang E, Thienpont LM, et al.** Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. Arch Pathol Lab Med. 2005;129:297-304. [PMID: 15737021]
35. **Murthy K, Stevens LA, Stark PC, Levey AS.** Variation in the serum creatinine assay calibration: a practical application to glomerular filtration rate estimation. Kidney Int. 2005;68:1884-7. [PMID: 16164667]
36. **Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al.** 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]
37. **Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek J, et al.** Expressing the MDRD Study equation for estimating GFR with IDMS traceable (gold standard) serum creatinine values [Abstract]. J Am Soc Nephrol. 2005;16:69A.
38. **Cockcroft DW, Gault MH.** Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41. [PMID: 1244564]
39. **Junge W, Wilke B, Halabi A, Klein G.** Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffé method. Clin Chim Acta. 2004;344:137-48. [PMID: 15149882]
40. **Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al.** The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330:877-84. [PMID: 8114857]
41. **DeLong ER, DeLong DM, Clarke-Pearson DL.** Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45. [PMID: 3203132]
42. **Cirillo M, Anastasio P, De Santo NG.** Relationship of gender, age, and body mass index to errors in predicted kidney function. Nephrol Dial Transplant. 2005;20:1791-8. [PMID: 15998649]
43. **Verhave JC, Fesler P, Ribstein J, du Cailar G, Mimran A.** Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. Am J Kidney Dis. 2005;46:233-41. [PMID: 16112041]
44. **Rule AD, Gussak HM, Pond GR, Bergstralh EJ, Stegall MD, Cosio FG, et al.** Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis. 2004;43:112-9. [PMID: 14712434]
45. **Greene T, Li L, Coresh J, Poggio P, Schimd C, Stark P, et al.** A statistical explanation for different relationships of serum creatinine (Scr) vs. GFR across populations: preliminary results [Abstract]. J Am Soc Nephrol. 2005;16:319A.
46. **Stevens LA, Levey AS.** Chronic kidney disease in the elderly—how to assess risk [Editorial]. N Engl J Med. 2005;352:2122-4. [PMID: 15901867]
47. **Coresh J, Stevens LA, Greene T, Eggers O, Kusek J, Van Lente F, et al.** Comparison of GFR estimating equations using serum cystatin and creatinine: a pooled analysis of 1706 individuals [Abstract]. J Am Soc Nephrol. 2005;16:69A.

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