

# A Comparison of Prediction Equations for Estimating Glomerular Filtration Rate in Adults without Kidney Disease

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**Abstract.** The ability of the Modification of Renal Disease (MDRD) equation to predict GFR when compared with multiple other prediction equations in healthy subjects without known kidney disease was analyzed. Between May 1995 and December 2001, a total of 117 healthy individuals underwent  $^{125}\text{I}$ -iothalamate or  $^{99\text{m}}\text{Tc}$ -diethylenetriamine-pentaacetic acid (DTPA) renal studies as part of a routine kidney donor evaluation at either Brigham and Women's Hospital or Boston Children's Hospital. On chart review, 100 individuals had sufficient data for analysis. The MDRD 1, MDRD 2 (simplified MDRD equation), Cockcroft-Gault (CG), Cockcroft-Gault corrected for GFR (CG-GFR), and other equations were tested. The median absolute difference in ml/min per  $1.73\text{ m}^2$  between calculated and measured GFR was 28.7 for MDRD 1, 18.5 for MDRD 2, 33.1 for CG, and 28.6 for CG-GFR in the  $^{125}\text{I}$ -iothalamate group and was 31.1 for MDRD 1, 38.2 for MDRD 2, 22.0 for CG, and 31.1 for CG-GFR in the  $^{99\text{m}}\text{Tc}$ -DTPA group. Bias was  $-0.5$ ,  $-3.3$ ,  $25.6$ , and  $5.0$  for MDRD 1, MDRD 2, CG, and CG-GFR, respectively, in subjects who received  $^{125}\text{I}$ -iothalamate and  $-33.2$ ,  $-36.5$ ,  $6.0$ , and  $-15.0$

for MDRD 1, MDRD 2, CG, and CG-GFR, respectively, in those who received  $^{99\text{m}}\text{Tc}$ -DTPA studies. Precision testing, as measured by linear regression, yielded  $R^2$  values of 0.04 for CG, 0.05 for CG-GFR, 0.15 for MDRD 1, and 0.14 for MDRD in those who underwent  $^{125}\text{I}$ -iothalamate studies and 0.18 for CG, 0.21 for CG-GFR, 0.40 for MDRD 1, and 0.38 for MDRD 2 for those who underwent  $^{99\text{m}}\text{Tc}$ -DTPA studies. The MDRD equations were more accurate within 30 and 50% of the measured GFR compared with the CG and CG-GFR equations. When compared with the CG equation, the MDRD equations are more precise and more accurate for predicting GFR in healthy adults. The MDRD equations, however, consistently underestimate GFR, whereas the CG equations consistently overestimate measured GFR in people with normal renal function. In potential kidney donors, prediction equations may not be sufficient for estimating GFR; radioisotope studies may be needed for a better assessment of GFR. Further studies are needed to derive and assess GFR prediction equations in people with normal or mildly impaired renal function.

A noninvasive and accurate estimation of GFR is one of the holy grails of nephrology. Not only are prediction equations crucial for estimating GFR or creatinine clearance (CrCl) in the clinical research setting where only a single blood test is available, but also the new K/DOQI guidelines recommend estimating GFR by the Modification of Renal Disease (MDRD) or Cockcroft-Gault (CG) equations (1). Because GFR determinations by inulin or radioisotope studies on large numbers of patients are impractical, cumbersome, and expensive, clinicians also rely on GFR prediction equations on a daily basis.

In 1999, a new prediction equation derived from 1628 subjects with renal insufficiency enrolled in the MDRD study was published (2). This equation has been subsequently evaluated in (1) blacks with chronic kidney disease (CKD) (3), (2) scleroderma patients (4), (3) potential renal transplant donors

with CrCl  $<80$  ml/min by two 24-h urine collections (5), (4) patients with kidney disease and normal serum creatinine (SCr) levels ( $\leq 1.5$  mg/dl) (6), and (5) 46 normal and 46 individuals with type 1 diabetes without evidence of nephropathy (7). In 2000, a simplified MDRD equation (MDRD 2) was published in abstract form that used SCr as the only serum assay (8). To our knowledge, this is the only published study that tests the MDRD 2 equation in people without renal disease compared with actual GFR measurements.

## Materials and Methods

Between May 1995 and December 2001, a total of 117 healthy adults underwent  $^{125}\text{I}$ -iothalamate or  $^{99\text{m}}\text{Tc}$ -diethylenetriamine-pentaacetic acid (DTPA) renal clearance studies as part of a routine work-up for potential kidney donation at either Brigham and Women's Hospital (BWH) or Boston Children's Hospital (Boston, MA). On chart review, a total of 100 subjects had sufficient clinical and laboratory data to estimate GFR, including age, gender, race, weight, height, and SCr. Those with missing data for blood urea nitrogen (BUN;  $n = 4$ ) and serum albumin ( $n = 10$ ) were given the default values of 15 mg/dl and 4.0 g/dl, respectively; the rationale is that these two variables together contribute  $<1\%$  to the observed variance of the calculations (A.S. Levey, personal communication). Of the 100 subjects included in the study, 55 underwent  $^{125}\text{I}$ -iothalamate studies and 45 underwent  $^{99\text{m}}\text{Tc}$ -DTPA.

Subjects who underwent  $^{125}\text{I}$ -iothalamate studies at BWH were asked to fast for at least 8 h and given a water load of 10 ml/kg and

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5 drops of potassium iodide diluted in 15 ml of water orally (to block thyroid uptake of  $^{125}\text{I}$ -iothalamate) at the initiation of the study. Thirty-five micro-Curies of  $^{125}\text{I}$ -iothalamate was injected subcutaneously into the upper arm. Blood was drawn and urine was sampled at time 0 (before  $^{125}\text{I}$ -iothalamate injection) and at 60, 120, and 180 min. Total urine volume and urinary flow rates were assessed every 60 min. Oral fluid hydration was administered at 500 ml/h as tolerated. GFR measurements for two timed urine collections were averaged and standardized for a body surface area (BSA) of 1.73 m<sup>2</sup>. Intra-assay coefficients of variation (CV) were  $\leq 10\%$  for 40 of the 55 iothalamate subjects and  $\geq 10\%$  for the remaining 15 subjects. Forty-six subjects had CV of  $\leq 15\%$ . For those with CV  $\geq 15\%$ , the recorded minimum urinary flow rates ranged from 1.1 to 2.8 ml/min. The acceptable minimum urinary flow rate in the original protocol was 3 ml/min; if this was not achieved at time 60 min, then urine was collected at time 90 min and urinary flow rate was calculated at this time.

Individuals who underwent  $^{99\text{m}}\text{Tc}$ -DTPA studies were hydrated orally or intravenously at 10 ml/kg per h for 30 min before study initiation.  $^{99\text{m}}\text{Tc}$ -DTPA dosed at 50  $\mu\text{Ci}/\text{kg}$  was injected intravenously, and blood was sampled at 120, 180, and 240 min. Three GFR measurements were averaged and standardized for a BSA of 1.73 m<sup>2</sup>. No information on intra-assay CV was available for  $^{99\text{m}}\text{Tc}$ -DTPA studies.

Forty-one of 45 subjects who had  $^{99\text{m}}\text{Tc}$ -DTPA studies had their SCr levels measured from their primary care provider's office at a wide variety of laboratories; the remaining four patients had SCr assayed at the BWH laboratory. For subjects who underwent  $^{125}\text{I}$ -iothalamate testing, 45 of 55 (82%) SCr levels were assayed at the BWH, and the remainder were obtained through different outside laboratories. The BWH laboratory used alkaline picrate reactions with a DAX96 (Bayer) machine to measure SCr through January 31, 2000, and an Olympus 640/2700 machine from February 1, 2000, to the present. The reference normal values for SCr were 0.8 to 1.6 mg/dl in men and 0.8 to 1.3 mg/dl in women from 1992 through September 1999. This changed to 0.7 to 1.3 mg/dl for both men and women starting in September 1999. The laboratory reports that the CV of the assay is 3% for measurements in the normal range.

The prediction equations that we used are listed as follows:

- Cockcroft-Gault (CG) (9):  $\text{CrCl} \times \text{BSA}/1.73 \text{ m}^2$ 
  - For men:  $\text{CrCl} = [(140 - \text{Age}) \times \text{Weight (kg)}]/\text{SCr} \times 72$
  - For women:  $\text{CrCl} = [(140 - \text{Age}) \times \text{Weight (kg)}]/\text{SCr} \times 72 \times 0.85$
- CG-GFR estimate:  $\text{GFR} = 0.84 \times \text{CrCl}$  by Equation (1)
- MDRD 1 (2):  $\text{GFR} = 170 \times [\text{SCr}]^{-0.999} \times [\text{Age}]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}] \times [\text{BUN}]^{-0.170} \times [\text{Alb}]^{0.318}$
- MDRD 2 (8):  $\text{GFR} = 186 \times [\text{SCr}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.212 \text{ if patient is black}]$
- Jellife 1 ( $\times \text{BSA}/1.73 \text{ m}^2$ ) (10)
  - For men:  $(98 - [0.8 \times (\text{age} - 20)])/\text{SCr}$
  - For women:  $(98 - [0.8 \times (\text{age} - 20)])/\text{SCr} \times 0.90$
- Jellife 2 (11)
  - For men:  $(100/\text{SCr}) - 12$
  - For women:  $(80/\text{SCr}) - 7$
- Mawer (12)
  - For men:  $\text{weight} \times [29.3 - (0.203 \times \text{age})] \times [1 - (0.03 \times \text{SCr})]$   
 $(14.4 \times \text{SCr}) \times (70/\text{weight})$
  - For women:  $\text{weight} \times [25.3 - (0.175 \times \text{age})] \times [1 - (0.03 \times \text{SCr})]$

- $(14.4 \times \text{SCr}) \times (70/\text{weight})$
- Bjornsson (13)
    - For men:  $[27 - (0.173 \times \text{age})] \times \text{weight} \times 0/\text{SCr}$
    - For women:  $[25 - (0.175 \times \text{age})] \times \text{weight} \times 0.07/\text{SCr}$
  - Gates (14)
    - For men:  $(89.4 \times \text{SCr}^{-1.2}) + (55 - \text{age}) \times (0.447 \times \text{SCr}^{-1.1})$
    - For women:  $(89.4 \times \text{SCr}^{-1.2}) + (55 - \text{age}) \times (0.447 \times \text{SCr}^{-1.1})$
  - Salazar-Corcoran (15)
    - For men:  $[137 - \text{age}] \times [(0.285 \times \text{weight}) + (12.1 \times \text{height}^2)]/(51 \times \text{SCr})$
    - For women:  $[146 - \text{age}] \times [(0.287 \times \text{weight}) + (9.74 \times \text{height}^2)]/(60 \times \text{SCr})$

Fisher's exact test was used for proportions and *t* test for comparison of means. A Pearson correlation coefficient was also calculated for the normally distributed GFR data (Shapiro-Wilk test for normality, *P* = 0.98).

The mean and median absolute differences were calculated from absolute difference = predicted value – measured value. The % absolute difference was calculated as % absolute difference = predicted value – measured value  $\times 100$  measured value.

Bias, a measure of systematic error, was defined by the mean prediction error (ME):

$$\text{ME} = \frac{\sum (\text{pe}_i)/N}{i = 1}$$

where  $\text{pe}_i$  = predicted value – true value and *n* = sample size.

The *R*<sup>2</sup> statistic was derived by simple linear regression (PROC GLM) and reflects the predictive ability of the model. *P* = 0.05 was considered significant.

Refitting of the log-linear MDRD equation to our data set was performed with the following code using PROC REG in SAS:

For MDRD 1: Model  $\ln(\text{GFR}) = \ln(\text{SCr}) + \ln(\text{AGE}) + \ln(\text{BUN}) + \ln(\text{albumin}) + \text{race} + \text{gender}$

For MDRD 2: Model  $\ln(\text{GFR}) = \ln(\text{SCr}) + \ln(\text{AGE}) + \text{race} + \text{gender}$

SAS for Windows version 8.0 (Cary, NC) was used for all statistical calculations. Data collection by chart review was approved by the BWH Institutional Review Board.

## Results

Clinical and laboratory characteristics of this study population are summarized in Table 1. The mean measured GFR was 112.8 ml/min per 1.73 m<sup>2</sup> (range, 70.0 to 169.0 ml/min). When data from subjects who received  $^{125}\text{I}$ -iothalamate were compared with those who received  $^{99\text{m}}\text{Tc}$ -DTPA, statistically significant differences were found in distribution of black race, mean weight, albumin, and measured GFR (Table 1).

Performance assessment for several CrCl and GFR equations are presented in Table 2. Mean absolute difference ranged from 26.0 to 49.6, bias from –18.4 to 28.7, median absolute difference from 19.0 to 35.4, median % absolute difference from 17 to 30%, precision from 0.01 to 0.08, and Pearson correlations from 0.14 to 0.28. The percentage of calculated

Table 1. Patient characteristics<sup>a</sup>

	Combined	<sup>125</sup> I-iothalamate	<sup>99m</sup> Tc-DTPA
Sample size	100	55	45
Age (yr)	41 ± 10 (18–62)	42 ± 10 (21–62)	40 ± 10 (18–61)
Male gender	42 (42%)	21 (38%)	21 (47%)
Black race <sup>b</sup>	10 (10%)	9 (16%)	1 (2%)
Weight (kg) <sup>b</sup>	78.1 ± 15.7 (44.1–113.0)	75.3 ± 15.7 (44.1–107.3)	81.5 ± 15.3 (46–113)
Height (cm)	168.5 ± 9.4 (142.5–193.0)	168.8 ± 9.2 (154.9–193.0)	168.1 ± 9.8 (142.5–190)
Body surface area (m <sup>2</sup> )	1.9 ± 0.2 (1.4–2.4)	1.9 ± 0.2 (1.4–2.4)	1.9 ± 0.2 (1.4–2.3)
Serum creatinine (mg/dl)	0.9 ± 0.2 (0.5–1.3)	0.8 ± 0.2 (0.5–1.2)	0.9 ± 0.2 (0.5–1.3)
Serum urea nitrogen (mg/dl)	13 ± 4 (5–31)	13 ± 4 (6–31)	13 ± 4 (5–26)
Albumin (gm/dl) <sup>b</sup>	4.5 ± 0.5 (3.3–5.4)	4.5 ± 0.4 (3.7–5.4)	4.3 ± 0.5 (3.3–5.4)
Measured GFR (ml/min per 1.73 m <sup>2</sup> ) <sup>b</sup>	112.8 ± 21.0 (70.0–169.0)	102.8 ± 15.8 (70.0–151.9)	125.1 ± 20.3 (77.–169.0)

<sup>a</sup> Results expressed as mean ± SD (range) or *n* (%).

<sup>b</sup> *P* < 0.05 for iothalamate versus <sup>99m</sup>Tc-DTPA group.

values within 30% of the measured value ranged from 50 to 76%, whereas the percentage within 50% of measured values ranged from 72 to 96%. Results of CG compared with CG-GFR and MDRD 1 compared with MDRD 2 were very similar.

When the predicted values were compared with measured values stratified by the type of study (<sup>125</sup>I-iothalamate or <sup>99m</sup>Tc-DTPA), there was marked improvement in the MDRD predictions (Table 3). For those who received <sup>125</sup>I-iothalamate studies, the mean, median, and median % absolute differences did not change greatly, but the bias, precision, Pearson correlation, and accuracy improved with both MDRD equations. For those who received <sup>99m</sup>Tc-DTPA studies, the mean, median, and median % absolute differences were increased in the MDRD 2 equation, whereas bias, precision, and Pearson correlation increased for both MDRD 1 and 2 equations and accuracy remained approximately the same (Table 3) when compared with the results for the combined <sup>125</sup>I-iothalamate and <sup>99m</sup>Tc-DTPA studies (Table 2).

Because there were many overweight people who might have had a supraphysiologic calculated CrCl by CG, we also restricted the analyses to those with body mass index ≤30 (*n* = 73). No improvements were noted in any of the parameters examined in any of the equations (data not shown).

Refitting of the MDRD equation parameter estimates to our data set resulted in the following prediction equations:

$$\text{MDRD 1: GFR} = 278 \times [\text{SCr}]^{-0.107} \times [\text{Age}]^{-0.169} \times [0.94 \text{ if patient is female}] \times [0.91 \text{ if patient is black}] \times [\text{BUN}]^{-0.089} \times [\text{Alb}]^{-0.028} \quad (R^2 = 0.11)$$

$$\text{MDRD 2: GFR} = 214 \times [\text{SCr}]^{-0.113} \times [\text{Age}]^{-0.174} \times [0.96 \text{ if patient is female}] \times [0.92 \text{ if patient is black}] \quad (R^2 = 0.08)$$

## Discussion

The MDRD and CG equations are the most widely recommended and used formulas for assessment of renal clearance; therefore, this discussion focuses primarily on these two equations. On the basis of a comparison of these findings to those in the published literature (Table 4), our first observation is that the MDRD equations perform much more poorly in subjects

without kidney disease than in those with chronic kidney disease. This is not surprising since the MDRD equation was derived in MDRD study participants who were selected as having moderate to severe renal failure (measured <sup>125</sup>I-iothalamate GFR mean was 39.8 ml/min per 1.73 m<sup>2</sup>) (2).

Second, the MDRD prediction equations seem to systematically underestimate GFR, as indicated by the high negative bias (Table 3), especially as measured by the <sup>99m</sup>Tc-DTPA method. Although the <sup>99m</sup>Tc-DTPA group had a significantly higher mean weight, they also had significantly higher GFR measurements; therefore, these differences between the two groups are unlikely to explain the greater negative bias.

Third, we have confirmed that the simplified MDRD 2 equation loses very little predictive ability when compared with MDRD 1. Because serum albumin and BUN measurements may not be readily available, especially in the research setting, MDRD 2 is the prediction equation of choice over MDRD 1 in these situations. Likewise, estimating GFR from the CG CrCl calculation does not appreciably improve the predictive ability of the CG equation.

Last, <sup>125</sup>I-iothalamate and <sup>99m</sup>Tc-DTPA techniques do not seem to be highly correlated with each other because the degree of bias, precision, linear correlation, and accuracy varied notably when the results were pooled (Table 2) rather than stratified by type of GFR testing (Table 3). The decreased precision observed when all 100 subjects were pooled for analysis may reflect the interassay variability that was conferred by using two different measurements of GFR for reference. However, high correlations of both <sup>125</sup>I-iothalamate and <sup>99m</sup>Tc-DTPA to simultaneous measures of inulin clearance have been reported (*r* > 0.90) (16), although <sup>125</sup>I-iothalamate measurements exceeded inulin measurements by 14.6 to 25.9 ml/min per 1.73 m<sup>2</sup> (16) and <sup>99m</sup>Tc-DTPA overestimated inulin clearance by 3.5 to 13.5 ml/min per 1.73 m<sup>2</sup> for (16,17). Therefore, analyses of prediction equations must take into account the type of GFR measurement, and caution should be used when comparing results of such investigations using diverse GFR measurement techniques. In this study, other

Table 2. Mean calculated CrCl or GFR, mean absolute difference, bias, precision, and accuracy of GFR prediction equations compared with measured GFR<sup>a</sup>

	Mean CrCl/ GFR <sup>b</sup> (Range)	Mean Absolute Difference	Median Absolute Difference	Median % Absolute Difference	Bias <sup>c</sup>	R <sup>2</sup> <sup>d</sup> (Precision)	Pearson Correlation	Accuracy % within	
								30%	50%
CG <sup>e</sup>	129.6 ± 48.8 (50.1–288.5)	37.9	26.7	23%	16.8	0.06	0.24	58%	79%
CG-GFR <sup>e</sup>	108.9 ± 41 (42.1–242.3)	32.9	30.5	25%	−4.0	0.06	0.25	59%	83%
MDRD 1 <sup>f</sup>	97.6 ± 25 (55.8–201.1)	32.9	30.6	25%	−15.2	0.03	0.17	69%	96%
MDRD 2 <sup>f</sup>	94.5 ± 25.0 (50.3–184.9)	28.7	23.5	22%	−18.3	0.02	0.15	65%	95%
Jelliffe 1 <sup>e</sup>	92.3 ± 22.1 (55.3–176.0)	26.0	26.5	23%	−13.2	0.05	0.23	67%	96%
Jelliffe 2	96.8 ± 22.2 (59.7–188.0)	26.0	19.0	17%	−16.0	0.01	0.25	67%	95%
Mawer	141.6 ± 66.0 (40.9–396.7)	49.6	35.4	30%	28.7	0.07	0.26	50%	72%
Bjornsson	122.5 ± 37.3 (58.2–290.5)	29.5	24.8	23%	9.7	0.08	0.28	66%	86%
Gates	94.4 ± 24.9 (50.3–207.3)	28.8	25.4	25%	−18.4	0.02	0.14	66%	95%
Corcoran-Salazar	114.5 ± 29.1 (56.7–199.4)	26.1	20.9	19%	1.7	0.04	0.21	76%	92%

<sup>a</sup> CrCl, creatinine clearance; CG, Cockcroft-Gault; MDRD, Modification of Renal Disease.

<sup>b</sup> Mean calculated CrCl or GFR expressed as mean ± SD (range).

<sup>c</sup> Bias is the mean prediction error:

$$ME = \frac{\sum_{i=1}^N (pe_i)}{N}$$

where  $pe_i$  = predicted value - true value and N = sample size.

<sup>d</sup> R<sup>2</sup> statistic was derived by simple linear regression and reflects the predictive ability of the model.

<sup>e</sup> Adjusted for BSA of 1.73 m<sup>2</sup>.

<sup>f</sup> Expressed as ml/min per 1.73 m<sup>2</sup>.

factors that may have influenced the different correlations between <sup>125</sup>I-iothalamate and <sup>99m</sup>Tc-DTPA include the higher numbers of blacks and lower mean weights in the <sup>125</sup>I-iothalamate group.

The MDRD equations had the least bias and highest accuracy when compared with <sup>125</sup>I-iothalamate measurements. This is not surprising considering that these equations were derived using <sup>125</sup>I-iothalamate GFR measurements. The CG equation is understandably poorer, because it was derived by CrCl calculated by 24-h urinary creatinine collections as the “gold standard” in 249 adults ages 18 to 92 with mean SCr 0.99 to 1.78 mg/dl (9). In this original study, 96% of study subjects were male, and no information on race was given; this raises the issue of the generalizability of the CG prediction equations. The use of 24-h urine collection as the “gold standard” was also suboptimal because multiple investigations have reported the inaccuracies of using 24-h urine collections to measure CrCl, usually from under- or overcollection by the subject (5,18,19). In fact, Coresh *et al.* (20) concluded that there was no advantage in 24-h urine collection over the CG

estimations when compared with GFR determined by <sup>125</sup>I-iothalamate clearance.

Hsu *et al.* (21) reported finding systematic differences in SCr levels measured at BWH among those measured during 1997 and during 1998 when compared with values measured before 1997; therefore, the investigators adjusted their analysis by adding 0.1 mg/dl to SCr values measured in 1997 and 0.3 mg/dl to values measured in 1998. In our data set, 35 of the 45 SCr assayed at BWH in the <sup>125</sup>I-iothalamate group were performed in 1998 or later, whereas all four of the SCr assayed at BWH in the <sup>99m</sup>Tc-DTPA group were performed after 1998. Because the vast majority of <sup>125</sup>I-iothalamate patients were assayed between 1998 and 2000 and because there is no information (either published or provided by the BWH laboratory) of how SCr assays after 1998 are related to those performed before 1998, we did not attempt to adjust SCr and recalculate the prediction equations, although this is another likely source of measurement error.

The issue of calibration of SCr laboratory measurement is

Table 3. Analysis of CG versus MDRD prediction equations stratified by type of GFR study (<sup>125</sup>I-iothalamate or <sup>99m</sup>Tc-DTPA)

	Mean CrCl/ GFR <sup>a</sup> (Range)	Mean Absolute Difference	Median Absolute Difference	Median % Absolute Difference	Bias <sup>b</sup>	R <sup>2</sup> <sup>c</sup> (Precision)	Pearson Correlation	Accuracy % within	
								30%	50%
<sup>125</sup> I-iothalamate									
Measured	102.8 ± 15.7 (70–151.9)	–	–	–	–	–	–	–	–
CG <sup>d</sup>	108.3 ± 25.1 (57.8–169.4)	42.7	33.1	33%	25.6	0.04	0.13	45%	73%
CG-GFR <sup>d</sup>	107.8 ± 42.1 (42.1–225.2)	33.8	28.6	25%	5.0	0.05	0.13	56%	78%
MDRD 1 <sup>e</sup>	102.3 ± 25.9 (55.8–201.2)	33.8	28.7	25%	–0.5	0.15	0.27	78%	96%
MDRD 2 <sup>e</sup>	99.4 ± 25.5 (50.3–184.9)	20.5	18.5	17%	–3.3	0.14	0.22	78%	95%
<sup>99m</sup> Tc-DTPA									
Measured	125.0 ± 20.3 (77–169)	–	–	–	–	–	–	–	–
CG <sup>d</sup>	106.5 ± 33.0 (63.8–259.2)	31.6	22.0	19%	6.0	0.18	0.41	73%	87%
CG-GFR <sup>d</sup>	110.1 ± 40.0 (48.0–242.3)	31.7	31.1	25%	–15.0	0.21	0.42	62%	89%
MDRD 1 <sup>e</sup>	91.9 ± 22.8 (60.1–172.2)	31.8	31.1	25%	–33.2	0.40	0.45	58%	96%
MDRD 2 <sup>e</sup>	88.5 ± 23.2 (52.9–167.2)	38.8	38.2	32%	–36.5	0.38	0.43	49%	96%

<sup>a</sup> Mean calculated CrCl or GFR expressed as mean ± SD (range).

<sup>b</sup> Bias is the mean prediction error:

$$ME = \sum_{i=1}^N (pe_i)/N$$

where pe<sub>i</sub> = predicted value - true value and N = sample size.

<sup>c</sup> R<sup>2</sup> statistic was derived by simple linear regression and reflects the predictive ability of the model.

<sup>d</sup> Adjusted for BSA of 1.73 m<sup>2</sup>.

<sup>e</sup> Expressed as mL/min per 1.73 m<sup>2</sup>.

especially critical when estimating GFR in subjects with normal or mildly impaired renal function because small changes in SCr result in large changes in calculated CrCl and GFR. For example, a 40-yr-old black woman who weighs 70 kg and has a SCr of 1.0 mg/dl in steady state has a calculated CrCl of 82.6 ml/min and a calculated GFR of 78.3 ml/min per 1.73 m<sup>2</sup>; an increase of SCr by 0.1 mg/dl to 1.1 mg/dl results in a calculated CrCl of 75.1 ml/min and a calculated GFR of 71.2 ml/min per 1.73 m<sup>2</sup>. In contrast, the same patient with a SCr of 3.1 mg/dl in steady state would have an estimated CrCl of 27.5 ml/min and an estimated GFR of 26.1 ml/min per 1.73 m<sup>2</sup>; an increase in SCr to 3.2 mg/d results in very small changes in estimates to 26.7 ml/min and 25.3 ml/min per 1.73 m<sup>2</sup> for CrCl and GFR, respectively. There is no standard calibration for SCr measurements for laboratories in the United States (22), and investigators have reported that SCr on the same stored serum samples were 0.23 mg/dl higher when assayed by the laboratory used by Third National Health and Nutrition Examination

Survey study when compared with the values obtained by the laboratory used by the MDRD study, a magnitude of difference that was common across different laboratories (18).

Other potential sources of measurement error include (1) intraindividual variability in SCr; (2) intraindividual variability in other clinical or laboratory measurements; (3) intraindividual variability in GFR; and (4) intra-assay variability in GFR measurement. Despite the <sup>125</sup>I-iothalamate protocol requirements for minimum urinary flow rates of 3 ml/min, this was not achieved in all nine subjects who had CV ≥15%. Intra-assay GFR measurement errors are likely minimized in those who underwent <sup>125</sup>I-iothalamate testing with CV ≤10%; however, in those with high CV and those who underwent <sup>99m</sup>Tc-DTPA studies without reported intra-assay CV, we acknowledge that the questionable quality of some of the GFR measurements may not make it a true and reliable “gold standard.”

In refitting the MDRD coefficients to our data, we found that

Table 4. Comparison of CG and MDRD equations in previously published and current studies<sup>a</sup>

	Levey 1999	Lewis 2001	Bertolius 2001	Bostom 2002	Vervoot 2002	Kingdon 2003	Current Study
Sample size	1628	1703	22	109	92	26	100
Subjects	Patients with CKD in MDRD study	Blacks with CKD from hypertension	Potential renal donors with CrCl <80 ml/min by two 24-h urines	CKD cohort	46 healthy adults/46 type 1 diabetics without nephropathy	Patients with scleroderma	Potential kidney donors
Mean age (yr)	51	54	40	43	28/27	58	41
% male	60%	69%	27%	77%	46%	23%	42%
% black	12%	100%	9%	0%	0%	4%	10%
Weight (kg)	79.6 ± 16.8	90.2	71.4 ± 16.5	76 (range 66–85)	69.9/71.5	NR	78.1 ± 15.7 (range 44.1–113)
BSA (m <sup>2</sup> )	1.91 ± 0.23	2.02	1.80 ± 0.21	NR	1.85/1.87	NR	1.9 ± 0.2
Mean SCr (mg/dl)	2.3	1.85	1.1	1.2	0.9/0.8	NR	0.9
Measured GFR (ml/min per 1.73 m <sup>2</sup> )	48.6	56.9	99.3	109 (18–205)	107/122	NR	112 (70–169)
Type of GFR study	<sup>125</sup> I-iothalamate	<sup>125</sup> I-iothalamate	<sup>99m</sup> Tc-DTPA	Iohexol	Inulin	<sup>51</sup> Cr-EDTA	<sup>55</sup> I-iothalamate/45 <sup>99m</sup> Tc-DTPA
R or R <sup>2</sup> for MDRD 1	R <sup>2</sup> = 0.90 (log transformed)	R = 0.90 (log transformed)	R <sup>2</sup> = 0.005	R <sup>2</sup> = 0.31	NR	R = 0.79	R <sup>2</sup> = 0.15/0.40
R or R <sup>2</sup> for CG-GFR	R <sup>2</sup> = 0.80 (log transformed)	NR	NR	NR	NR	R = 0.71	R <sup>2</sup> = 0.05/0.21
R or R <sup>2</sup> for CG	NR	R = 0.85 (log transformed)	R <sup>2</sup> = 0.14	R <sup>2</sup> = 0.17	NR	NR	R <sup>2</sup> = 0.04/0.18
Absolute difference for MDRD 1 (ml/min per 1.73 m <sup>2</sup> )	NR	6.27	NR	NR	9.0/11.8	NR	33.8/31.8
Absolute difference for CG (ml/min per 1.73 m <sup>2</sup> )	NR	(median) 8.34	NR	NR	(mean) 10.7/18.8	NR	(mean) 33.8/31.7
		(median)	(median)	(mean)	(mean)		(mean)

<sup>a</sup> BSA, body surface area; SCr, serum creatinine; NR, not reported.

the intercept terms are different for both MDRD 1 and MDRD 2, suggesting that, as expected, our study population varies considerably from the original cohort in which these equations were derived. Furthermore, the regression coefficients for all laboratory assays (Scr, BUN, and alb) are also considerably different, likely reflecting lack of calibration in a central laboratory and measurement error, whereas the regression coefficients for age and gender are similar. The coefficient for black race is in the opposite direction of those in the MDRD equations but are based on only 10 blacks. Using the MDRD predictors of GFR resulted in models that explain only 8 to 10% of the variance in our data set of normal subjects, which is not surprising in light of the relatively small sample size of 100 subjects and the various sources of measurement error as previously discussed, especially those involving SCr calibration.

Our results are consistent with other published investigations in the literature (Table 4). A study by Bostom *et al.* (6) of 109 patients with known kidney disease and SCr  $\leq 1.5$  mg/dl reported an  $R^2$  of 0.31 for MDRD1, 0.29 for MDRD 2, and 0.17 for CG (Table 4). The Bostom study differed from this current study on several points: it included patients with renal disease, there was a narrower range of weights among the subjects, the majority of subjects had some degree of proteinuria, and iothexol was used to determine GFR (Table 4). Despite the “normal serum creatinine levels” (range, 1.0 to 1.3 mg/dl), measured GFR by iothexol was as low as 18 ml/min per 1.73 m<sup>2</sup> (25th to 75th percentile range was 88 to 138 ml/min per 1.73 m<sup>2</sup>). In addition, 25% had iothexol GFR  $< 80$  ml/min per 1.73 m<sup>2</sup>, and 59% had glomerular disease, whereas our cohort were healthy, normal adults.

Another recent study of 46 healthy adults and 46 individuals who had type 1 diabetes without evidence of nephropathy and underwent inulin clearance studies found median absolute differences of 10.7 *versus* 9.0, respectively, when comparing MDRD 1 and CG equations in healthy subjects; the CG equation was corrected to reflect GFR by either a multiplication factor of 0.9 and the formula  $Y = -0.004 + 1.54$  (Table 4) (7). No analyses of bias, precision, or accuracy were presented (7). On the basis of the higher median absolute differences in the MDRD 1 equation compared with the CG equation for all subjects, the authors concluded that the MDRD 1 equation underestimated GFR, especially in women with diabetes, and that the MDRD 1 equation was less “accurate” than the CG equation. Whereas we also found that the MDRD 1 equation consistently underestimated GFR measurements (most notably in those who underwent <sup>99m</sup>Tc-DTPA), we observed that the MDRD equations were less biased, more precise, and more accurate than the CG equation.

Several limitations of this study should be noted. First, very few black individuals were included, so the findings may not be generalizable to this group. Second, these analyses were performed on a relatively small sample size with wide variability in clinical and laboratory parameters. Our study participants, however, are likely representative of the general population with normal or mildly decreased kidney function. Third, SCr measurements were not performed at the same time in the same laboratory and were not calibrated with a standardized

measurement, although the vast majority (82%) of those who underwent <sup>125</sup>I-iothalamate studies had SCr measured in the same BWH laboratory with a low reported CV. Despite these limitations, however, this is the first study to evaluate rigorously these GFR formulas in healthy individuals without chronic kidney disease. Moreover, the lack of calibration of SCr across different laboratories continues to be a reality that physicians face daily in clinical practice.

In addition to the inaccuracies of the formulas themselves, this study underscores how multiple sources of measurement error (including intra-assay SCr variability, intraindividual Scr variability, lack of calibration of Scr assays across different laboratories, intra-assay GFR variability, intraindividual GFR variability, and measurement error of other variables in the prediction equations) can affect the precision and accuracy of renal clearance prediction equations. In the future, researchers and clinicians would greatly benefit from a study of a large and racially diverse cohort of people with normal or mildly impaired kidney function that would allow investigators to derive an improved prediction equation for estimating GFR.

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