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

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Purpose: **We sought to reexpress the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for estimation of glomerular filtration rate (GFR) using serum creatinine (S_{cr}) standardized to reference methods.**

Methods: **Serum specimens included creatinine reference materials prepared by the College of American Pathologists (CAP), traceable to primary reference material at the NIST, with assigned values traceable to isotope dilution mass spectrometry (IDMS), a calibration panel prepared by the Cleveland Clinic Research Laboratory (CCRL), and frozen samples from the MDRD Study. Split specimens were measured at the CCRL using the Roche enzymatic and Beckman CX3 kinetic alkaline picrate assays.**

Results: **Roche enzymatic assay results on CAP samples were comparable to IDMS-assigned values. Beckman CX3 assay results in 2004–2005 were significantly higher than but highly correlated with simultaneous Roche enzymatic assay results (r^2 = 0.9994 on 40 CCRL samples) and showed minimal but significant upward drift from Beckman CX3 assay results during the MDRD Study in 1989–1991 (r^2 = 0.9987 in 253 samples). Combining these factors, standardized S_{cr} = 0.95 × original MDRD Study S_{cr}. The reexpressed 4-variable MDRD Study equation for S_{cr} (mg/dL) is GFR = 175 × standardized $S_{cr}^{-1.154}$ × $age^{-0.203}$ × 1.212 (if black) × 0.742 (if female), and for S_{cr} (μmol/L) is GFR = 30849 × standardized $S_{cr}^{-1.154}$ × $age^{-0.203}$ × 1.212 (if black) × 0.742 (if female) [GFR in mL · min^{-1} · $(1.73\ m^2)^{-1}$].**

Conclusion: **When the calibration of S_{cr} methods is traceable to the S_{cr} reference system, GFR should be estimated using the MDRD Study equation that has been reexpressed for standardized S_{cr}.**

To facilitate detection, evaluation, and management of chronic kidney disease (CKD),[6] guidelines recommend that clinical laboratories compute and report estimated glomerular filtration rate (GFR) using estimating equations such as that derived from the Modification of Diet in Renal Disease (MDRD) Study. Many clinical laboratories have begun this practice *(1–6)*. Proper use of GFR estimating equations requires a known calibration of the serum creatinine (S_{cr}) assays *(7, 8)*. Calibration to a single standardized S_{cr} based on gold standard methods has been widely recommended *(3, 8, 9)*. The College of American Pathologists (CAP) has prepared fresh-frozen S_{cr} reference materials, traceable to a primary reference ma-

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[6] Nonstandard abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; S_{cr}, serum creatinine; CAP, College of American Pathologists; IDMS, isotope dilution mass spectrometry; CCRL, Cleveland Clinic Research Laboratory; LC, liquid chromatography; LN24, Creatinine Accuracy Calibration Verification/Linearity Survey LN24; NKDEP, National Kidney Disease Education Program.

terial at the NIST, with assigned values based on isotope dilution mass spectrometry (IDMS), for use as trueness controls to verify the traceability of results from routine methods *(10, 11)*.

To date, the relationship of the MDRD Study creatinine assay to standardized creatinine was unknown, although results of smaller studies suggested the CX3 rate Jaffe assay had a small positive bias compared with an IDMS reference method *(10, 11)*. The purposes of this report are to describe procedures for calibrating the S_{cr} assay at the Cleveland Clinic Research Laboratory (CCRL) where the MDRD Study samples were measured and to reexpress the 4-variable (modified) MDRD Study equation *(6)* for use with standardized S_{cr}.

Materials and Methods

STUDY DESIGN

Chronic Kidney Disease Epidemiology Collaboration is a research group sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases to develop and validate improved estimating equations for GFR by pooling data from research studies and clinical populations. Pooling data requires calibration of S_{cr} assays of collaborating laboratories to creatinine assays currently used at the CCRL. The reference standard method for measurement of S_{cr}, IDMS, is extremely labor intensive, allowing assay of only very few samples. Therefore, we followed recommendations to establish a calibration hierarchy *(12)*. The hierarchy starts with a primary calibrator that materializes the SI units used for expression of creatinine measurements, i.e., the NIST SRM 914a. This primary calibrator is used to directly calibrate the gas chromatography and liquid chromatography (LC) IDMS reference methods. From that point on, all subsequent calibrations or validations of the calibration status of lower-order methods are done via split-sample comparisons at CCRL (Fig. 1). First, CAP Creatinine Accuracy Calibration Verification/Linearity Survey LN24 (LN24) samples were used as trueness controls to verify that the calibration of the Roche enzymatic method was traceable to LC-IDMS and correctly implemented in the CCRL. Second, values measured with the Roche enzymatic assay on a calibration panel of 40 native pooled sera prepared by the CCRL were compared with values assigned using the Beckman CX3 assay, the assay that was used during the MDRD Study and is currently in use in the CCRL. Third, with frozen samples from the MDRD Study, the Beckman CX3 assay was adjusted for drift over the past decade. The study was approved by the institutional review boards of all participating institutions.

REFERENCE SAMPLES FROM CAP

CAP 2004 LN24 samples 01 through 07 were prepared from a female-only donor pool, so the creatinine value would be slightly lower than a mixed-sex pool *(10, 11, 13)*. Sample 02 is the base female serum pool. Sample 07 had reagent-grade creatinine added to bring the creatinine to ~352 μmol/L (4 mg/dL). Samples 03 through 06 were prepared by gravimetric admixing of samples 02 and 07. Sample 01 was prepared from sample 02 by gravimetric dilution with 0.01 mol/L phosphate buffered saline [prepared by adding one packet of Sigma P-3813 phosphate-buffered saline, pH 7.4, to 1 L of deionized water (personal communication, Mary Zimmer, January 22, 2007)].

Creatinine concentrations in samples LN24-02 and LN24-07 were value-assigned by the NIST using an LC-IDMS method. NIST-assigned values for samples 02 and 07 were 65.032 and 353.32 μmol/L (0.7390 and 4.0150 mg/dL), respectively. The creatinine values in the other pools were computed based on the known admixtures.

CALIBRATION PANEL

We developed a calibration panel of pooled human sera to establish the calibration relationship between the CX3 (2004) and Roche enzymatic methods across the range of S_{cr} for use in patient samples. The calibration panel was developed at the CCRL from pooled patient sera from the Cleveland Clinic. The calibration panel included 40 reference sera (20 aliquots of 1.0 mL each frozen at −70 °C) pooled from at least 10 mixed-sex donors known to have S_{cr} values covering the full range of 177 to 442 μmol/L (0.5 to 5.0 mg/dL).

Briefly, serum pools were constructed by combining within 2 h of collection excess clear serum obtained from apparently healthy patients and patients with CKD as soon as routine testing was completed. Sera were refrigerated and combined according to the creatinine concentration to achieve a final pool volume of ≥25 mL. The

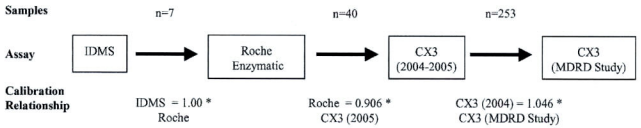

Fig. 1. Steps and results of calibration of the MDRD Study samples to creatinine reference materials.

Stepwise progression by which the Beckman Synchron CX3 (CX3) instrument used at the time of the MDRD Study (CX3 in 1989–1991) was compared with creatinine reference standards measured using IDMS technology. CAP samples with IDMS-assigned values were measured on the Roche enzymatic method and showed equivalence. The CCRL calibration panel was then measured on the Roche instrument and the CX3 machine in 2005. This showed a regression slope of 0.906. Frozen samples from the MDRD study (n = 253) were reassayed in 2004 on the CX3 instrument. This showed a regression slope of 1.046. Multiplication of slopes (1.00 · 0.906 · 1.046) yielded a calibration factor relationship of the original MDRD Study creatinine values to IDMS-traceable reference material of 0.95.

serum pools were mixed by gentle inversion and filtered; their combined creatinine concentrations were measured, and then serum was apportioned into separate 1.0 mL aliquots and frozen at −70 °C. A set of 20 aliquots was thawed and analyzed in triplicate in 3 separate runs on the same day. This process was repeated on a 2nd set of 20 aliquots on a subsequent day. Each sample was analyzed with the Roche enzymatic and CX3 assays after verification that the methods were and remained within internal quality control limits. The runs also included a CAP sample C-02 from the 2003 C mailing *(11)* prepared according to Clinical and Laboratory Standards Institute 37A *(14)* as a validated reference material for each 20 pooled specimens. Runs were deemed acceptable if the concentration value for this material remained within 1 SD of the peer method mean.

Assigned values for the calibration panel were based on the Roche enzymatic assay. This method was selected because it is free from most interferences and its calibration is traceable to IDMS *(15)*. In addition, as shown later, this method was verified to recover values assigned by NIST to the CAP trueness controls.

STORED SAMPLES FROM THE MDRD STUDY

Samples from the MDRD Study were fresh frozen at −70 °C without thawing until 2004. The MDRD Study equation was derived using samples from the 1st baseline visit (B0) during 1989–1991. The 253 samples used in the current study were from the 3rd baseline visit (B3, ~3 months later) and selected sequentially from the serum repository.

CREATININE ASSAYS AT THE CLEVELAND CLINIC FOUNDATION RESEARCH LABORATORY

The Roche enzymatic assays were performed on a Roche/Hitachi P module automated analyzer with Creatinine Plus enzymatic assay reagents. The enzymatic method is based on the determination of sarcosine after conversion of creatinine with creatininase, creatinase, and sarcosine oxidase. This assay demonstrated CVs of 1.8% and 2.0% at creatinine values of 518 and 78.7 μmol/L (5.86 and 0.89 mg/dL), respectively, in 2004 (n = 194) and 1.1% and 1.6% at creatinine values of 340 and 88.4 μmol/L (3.84 and 1.00 mg/dL), respectively, in 2005 (n = 409).

The Beckman modified kinetic rate alkaline picrate (Jaffe) reaction was performed with the Beckman Synchron CX3 method during the MDRD Study and in 2004. Measurement of the picrate-creatinine complex formation was taken at 520 and 560 nm at 25.6 s after sample introduction. The Beckman CX3 demonstrated CVs of 2.6% and 5.6% at creatinine values of 571 and 78.7 μmol/L (6.46 and 0.89 mg/dL), respectively, in 2004 (n = 390) and 2.4% and 3.8% at creatinine values of 359 and 93.7 μmol/L (4.06 and 1.06 mg/dL), respectively, in 2005 (n = 165).

CAP proficiency test results (n = 25, 2004 C01 to 2005 C10) for these 2 methods at the CCRL demonstrated a mean percentage bias to the peer method target mean of 1.01% (range, 3.46%–5.11%) and 1.79% (range, 2.09%–9.49%) for the Modular P and CX3, respectively. All results were within acceptance criteria. The range of creatinine values for these challenges was 61.9 to 663 μmol/L (0.7 to 7.5 mg/dL).

COMPUTATIONS

The mean values of repeated measurements were used for all computations. Linear regression slopes and intercepts were obtained for each comparison of assays. Intercepts that were very small and nonsignificant ($P > 0.05$) were dropped from the regression. The final calibration relationship was obtained by combining point estimates for slopes and intercepts into a single new equation. The final creatinine calibration factor was rounded to 2 significant digits. The SE for the final calibration factor was computed with the delta method *(16)*. Ordinary least-squares regressions were used instead of errors-in-variables regressions because correlations were >0.993. These extremely high correlations indicated the measurement error variance was a very small fraction of the total variance in this calibration setting, at which samples spanned a wide range of creatinine values and assays were averaged across repeated measurements. The final creatinine calibration factor was then incorporated into the constant in the MDRD Study GFR estimating equation.

Results

STANDARDIZATION OF S_{CR} ASSAYS

Use of CAP sample for verification of traceability of Roche enzymatic assay to IDMS. Results of assays of the LN24

Table 1. S_{cr} concentration in LN24 survey samples measured by Roche enzymatic assay.[a]

	LN24 survey sample						
	01	02	03	04	05	06	07
NIST-assigned value, μmol/L	44	65	123	181	239	297	354
2004 (LN24 pilot), mean of 8 samples, μmol/L	45	71	125	186	244	301	358
2005 (LN24A), mean of 4 samples, μmol/L	45	69	124	184	239	299	354
Mean of all samples, μmol/L	45	70	125	185	241	300	356
Difference between NIST-assigned value and mean of all samples, μmol/L	2	5	2	4	3	3	2

[a] Results are rounded to nearest 1 μmol/L.

survey materials on the Roche enzymatic assay are shown in Table 1. The Roche assay recovered the NIST-assigned values for the LN24 trueness controls, confirming that the Roche method was calibrated to be traceable to IDMS. Assays of the LN24 survey materials in 2004 and 2005 showed nearly identical regression parameters (Fig. 2). For all samples combined, the intercept (SE) was −3.01 (0.88) μmol/L [−0.035 (0.01) mg/dL; P = 0.02], and the slope was 1.00 (0.004), r^2 = 0.9999. Assay results for samples 01 to 07 were all within 6% of the LN24 survey assigned values [with all values >88 μmol/L (1.0 mg/dL) assaying within 2%]; Statistically, the data suggest that 3.01 μmol/L (0.035 mg/dL) could be subtracted from the Roche enzymatic assay to get the best comparability to NIST-assigned values. Because this difference is small and its inclusion would complicate calculations and the final equation, however, this difference was omitted, and the Roche enzymatic values were used without correction to assign reference values.

Standardization of Beckman Synchron CX3 method to Roche enzymatic assay using the CCRL calibration panel. The Beckman Synchron CX3 and Roche enzymatic methods were highly correlated (Fig. 3). The regression of the Roche enzymatic on the Beckman Synchron CX3 method showed a slope (SE) of 0.915 (0.009) and intercept of −2.30 (2.21) μmol/L [−0.026 (0.025) mg/dL]. The P value for the intercept was 0.31. After the small and nonsignificant intercept was dropped, the slope (SE) was 0.906 (0.004; r^2 = 0.996).

Adjustment of Beckman Synchron CX3 for drift over time by re-assay of MDRD Study samples. Analysis of 253 frozen MDRD Study samples in 2004 revealed a change over the past decade (Fig. 4). The regression showed a slope of 1.037 (0.008) and intercept of 2.53 (2.12) μmol/L [0.029 (0.024) mg/dL], with an intercept P value of 0.23. After the small and nonsignificant intercept value was dropped, slope was 1.046 (0.0024), r^2 = 0.9986.

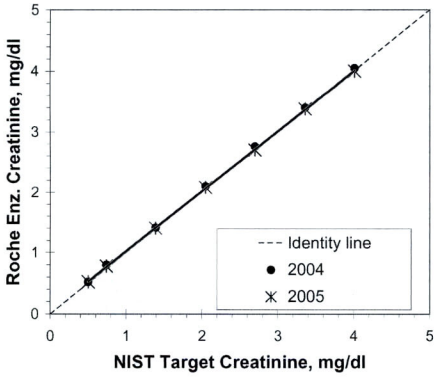

Fig. 2. Roche enzymatic (*enz.*) assay vs NIST-assigned creatinine values using LC-IDMS on CAP LN24 survey samples.

Linear regression intercept −3.01 μmol/L (−0.035 mg/dL), SE 0.88 μmol/L (0.01 mg/dL); slope 1.00, SE 0.004; r^2 = 0.9999).

COMPUTATION OF THE IDMS-TRACEABLE CALIBRATION FACTORS AND REEXPRESSION OF THE MDRD STUDY EQUATION

The general method for calibrating the CCRL assays to the IDMS assay at NIST is given in Table 2, equation 1. For all 3 comparisons, intercepts for the regression were taken to be zero, so the final calibration was derived by multiplication of regression slopes (1.0 · 0.906 · 1.046 = 0.95; Fig. 1). The SE of this correction factor, calculated with the delta method and assuming the Roche enzymatic method to be equivalent to the gold standard method, was 0.005. The published MDRD Study equation (Table 2, equation 2) was reexpressed by substitution of equation 1 for the term S_{cr} (Table 2, equation 3). Sensitivity analyses retaining intercepts and retaining additional significant digits to the final calibration factors to compute estimated GFR did not show clinically meaningful differences (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol53/issue4).

Discussion

Variability among clinical laboratories in calibration of S_{cr} assays is an important limitation in the use of GFR estimating equations. Variation in calibration introduces error in GFR estimates, especially at high GFRs *(17)*, and may account in part for the recent reports of widely varying performance of the MDRD Study equation in populations with higher GFRs *(18–38)*. In particular, the bias at high GFR levels appears greater among studies in which the S_{cr} assay was not calibrated *(18)*. This source of error can be overcome by recalibration of the clinical laboratory creatinine assay to the creatinine assay values of the research laboratory in which the estimating equation was developed. Calibration of clinical laboratory assay values obtained at a specific research laboratory is not practical for widespread implementation of reporting GFR estimates, however.

The National Kidney Disease Education Program (NKDEP) has initiated a creatinine standardization program to improve and normalize S_{cr} results used in estimating equations *(8)*. After creatinine reference materials that are traceable to higher order reference standards are developed, a proficiency testing system will be used to enable ongoing monitoring of calibration among clinical laboratories. This process is expected to be completed by 2008. Reexpression of the MDRD Study equation based on standardized assays will enable implementation of reporting estimated GFR in clinical practice using calibrated S_{cr} assays, thereby overcoming this limitation to the current use of GFR estimating equations.

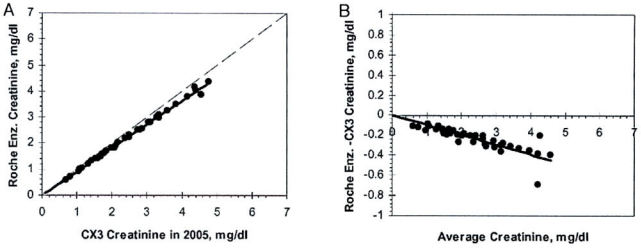

Fig. 3. Roche enzymatic (*enz.*) vs Beckman Synchron CX3 assays using calibration panel.

(*A*), intercept set to zero since it was not significant; slope 0.906, SE 0.004, r^2 = 0.9994. (*B*), Bland–Altman plot.

Using the 2004 CAP LN24-A survey samples, we found the Roche enzymatic assay is comparable to IDMS across a range of S_{cr} values from ~0.5 to 4.0 mg/dL. Note that CAP LN24 survey samples were used as recommended for trueness control, validating the Roche assay, rather than as calibration materials *(8)*. Using the CCRL calibration panel and adjusting the Beckman CX3 assay for drift since the MDRD Study, we calibrated the S_{cr} assay at the MDRD Study laboratory and reexpressed the 4-variable MDRD Study equation for use with creatinine methods traceable to an IDMS reference measurement procedure *(8)*.

Based on the Roche method's performance in the CAP LN24, creatinine results from the Roche enzymatic method were considered to be traceable to IDMS values. These results have consistently showed the Roche enzymatic method to give results in agreement with IDMS target values. The LN24 samples were verified by the NKDEP Laboratory Working Group to have results that were commutable with those for native clinical samples for the Roche enzymatic creatinine method (personal communication, Greg Miller, December 12, 2006). From a practical perspective, the CAP LN24 is the only material currently available for use as a trueness control and is reasonable to use for a clinical laboratory verification.

These methods may not fully account for measurement error. Our study design includes a 2-step approach to IDMS-traceable calibration of the MDRD Study samples, using combined results from 2 regressions based on split samples rather than results of a single regression based on reassay of original MDRD Study specimens on the Roche enzymatic assay. Nonetheless, our approach is robust. First, the CCRL calibration panel was prepared with rigorous techniques, and the MDRD Study stored samples were collected at the same time as the samples used to develop the equation. Second, several factors make multiplication of the regression slopes a maximum likelihood estimator with high efficiency. The 2 regressions have extremely high correlations (r^2 = 0.987 and 0.994), making the loss of efficiency very small. These extremely high correlations over a wide range of creatinine show the linear relationship between the different assays. The SEs for all comparisons performed in this study were minute. Omission of the intercepts is justified by their small magnitude and absence of a statistically or clinically meaningful effect on GFR estimates in sensitivity analyses. The final IDMS-traceable calibration factor of 0.95, relating original MDRD Study S_{cr} measures to standardized creatinine, is our best approximation. Regardless of study design, storage effects on specimens are possible, but the small difference between results on thawed MDRD Study specimens assayed a decade later and CAP samples assayed a year later suggests that any storage effects are small.

The 2003 CAP survey of 5624 clinical laboratories, using a fresh-frozen serum reference material with an assigned value of 79.38 μmol/L (0.902 mg/dL) by IDMS, showed a range of method-dependent bias across laboratories from an underestimate of 5.28 μmol/L (0.06 mg/dL) to an overestimate of 27.28 μmol/L (0.31 mg/dL) *(10)*. This finding suggests that in many laboratories,

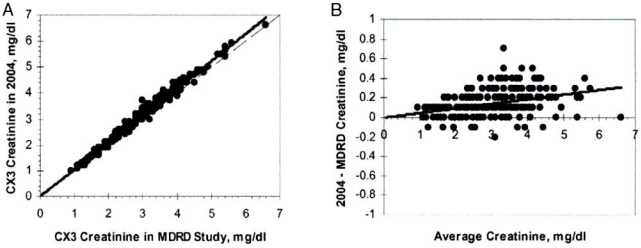

Fig. 4. Results for Beckman Synchron CX3 assays performed at the Cleveland Clinic Research Laboratory with MDRD Study samples during 2004 vs during the MDRD Study.

(*A*), intercept set to zero since it was not significant, slope 1.046, SE 0.002, r^2 = 0.9870. (*B*), Bland–Altman Plot.

Table 2. Summary of equations for use of standardized S_{cr} assays.[a]

Equation 1. Calibration to standardized S_{cr} assay

Standardized $S_{cr} = A + B \times$ Original MDRD Study $S_{cr} = 0.95 \times$ Original MDRD Study S_{cr}

Equation 2: Published MDRD Study equation before calibration

GFR = 186 × Original MDRD Study $S_{cr}^{-1.154} \times age^{-0.203} \times$ 1.212 (if black) × 0.742 (if female)

Equation 3: Reexpression of MDRD Study equation after IDMS-traceable calibration[b]

GFR = 186 × (Standardized $S_{cr}/0.95)^{-1.154} \times age^{-0.203} \times$ 1.212 (if black) × 0.742 (if female)

= 175 × Standardized $S_{cr}^{-1.154} \times age^{-0.203} \times$ 1.212 (if black) × 0.742 (if female)

[a] Standardized S_{cr} traceable to isotope dilution mass spectrometry at NIST. Units: GFR, mL · min^{-1} · (1.73 m^2)$^{-1}$; S_{cr}, mg/dL; age, years; race, African American or non–African American. *A* is the intercept and *B* is the slope of the final regression relationship of S_{cr} using the reference assay vs S_{cr} using the original MDRD Study or clinical laboratory assay.

[b] Using standard international units for S_{cr} (μmol/L), equation 3 is as follows: GFR = 30849 × Standardized $S_{cr}^{-1.154} \times age^{-0.203} \times 1.212$ (if black) × 0.742 (if female).

standardization of S_{cr} assays will lead to decreased reported S_{cr} concentrations, requiring redefinition of the reference range. Without reexpression of estimating equations, lower reported values for S_{cr} would increase GFR estimates. Reexpression of the MDRD Study equation according to the standardized assay enables consistent interpretation of estimated GFR by use of this equation. Use of other GFR estimating equations will require reexpression of the equations with standardized S_{cr}. The effect of standardization of S_{cr} assays on urine creatinine results has not been studied. Thus, it is not possible at this time to determine the effect of standardization on measurements and estimates of creatinine clearance.

Creatinine calibration is only 1 limitation of the current estimating equations. Despite calibration, performance of the MDRD Study equation in populations with higher GFRs appears worse than in populations with lower GFRs. Possible reasons for decreased accuracy include reduced creatinine generation attributable to loss of muscle mass or decreased protein intake, especially in elderly and chronically ill persons, greater measurement error and biological variation in GFR at higher GFR levels, and limitations of generalizing equations developed in populations with CKD to populations without CKD *(38)*. The Chronic Kidney Disease Epidemiology Collaboration is addressing these issues by use of pooled analysis of individual patient data and IDMS-traceable calibration of stored specimens by standardized methods.

NKDEP currently suggests that laboratories should report estimated GFR using the original 4-variable MDRD Study equation (Table 2, equation 2), even without IDMS-traceable calibration of S_{cr} assays, recognizing lesser accuracy, especially at levels of GFR >60 mL · min^{-1} · (1.73 m^2)$^{-1}$ *(17)*. With the availability of appropriate IDMS-traceable calibrator materials from NIST (SRM 967) and trueness control materials from the CAP (LN24 Survey), clinical laboratories can establish and maintain IDMS-traceable calibrated S_{cr} assays and use reexpressed estimating equations, such as the 4-variable MDRD Study equation, to report GFR estimates (Table 2, equation 3). Data presented here and in the 2003 CAP survey suggest the Roche enzymatic method meets these criteria. Until improved equations are developed, it may be appropriate to report a specific numeric result only for estimated GFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$, as is recommended by current guidelines *(4)*. Although differentiating higher estimates may be useful in research studies, higher values can be reported as "$>$60 mL · min^{-1} · (1.73 m^2)$^{-1}$" for clinical reports.

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