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A New Equation to Estimate Glomerular Filtration Rate

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Background: Equations to estimate glomerular filtration rate (GFR) are routinely used to assess kidney function. Current equations have limited precision and systematically underestimate measured GFR at higher values.

Objective: To develop a new estimating equation for GFR: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Design: Cross-sectional analysis with separate pooled data sets for equation development and validation and a representative sample of the U.S. population for prevalence estimates.

Setting: Research studies and clinical populations ("studies") with measured GFR and NHANES (National Health and Nutrition Examination Survey), 1999 to 2006.

Participants: 8254 participants in 10 studies (equation development data set) and 3896 participants in 16 studies (validation data set). Prevalence estimates were based on 16 032 participants in NHANES.

Measurements: GFR, measured as the clearance of exogenous filtration markers (iothalamate in the development data set; iothalamate and other markers in the validation data set), and linear regression to estimate the logarithm of measured GFR from standardized creatinine levels, sex, race, and age.

Results: In the validation data set, the CKD-EPI equation performed better than the Modification of Diet in Renal Disease Study equation, especially at higher GFR ($P < 0.001$ for all subsequent comparisons), with less bias (median difference between measured and estimated GFR, 2.5 vs. 5.5 mL/min per 1.73 m^2), improved precision (interquartile range [IQR] of the differences, 16.6 vs. 18.3 mL/min per 1.73 m^2), and greater accuracy (percentage of estimated GFR within 30% of measured GFR, 84.1% vs. 80.6%). In NHANES, the median estimated GFR was 94.5 mL/min per 1.73 m^2 (IQR, 79.7 to 108.1) vs. 85.0 (IQR, 72.9 to 98.5) mL/min per 1.73 m^2, and the prevalence of chronic kidney disease was 11.5% (95% CI, 10.6% to 12.4%) versus 13.1% (CI, 12.1% to 14.0%).

Limitation: The sample contained a limited number of elderly people and racial and ethnic minorities with measured GFR.

Conclusion: The CKD-EPI creatinine equation is more accurate than the Modification of Diet in Renal Disease Study equation and could replace it for routine clinical use.

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*For a list of other CKD-EPI staff and collaborators, see the **Appendix** (available at www.annals.org).

Clinical assessment of kidney function is part of routine medical practice for adults and is essential for assessing overall health; interpreting signs and symptoms; selecting the correct dosage for drugs that are excreted by the kidneys; preparing for invasive diagnostic or therapeutic procedures; and detecting, evaluating, and monitoring acute and chronic kidney diseases. The glomerular filtration rate (GFR) is considered the best overall index of kidney function in health and disease. The GFR cannot be measured easily in clinical practice; instead, it is estimated from equations by using serum creatinine level, age, race, sex, and body size (1, 2). One such equation, the MDRD (Modification of Diet in Renal Disease) Study equation, has gained widespread acceptance (3, 4), and most clinical laboratories estimate GFR by using this equation when serum creatinine measurement is ordered (5). The MDRD Study equation is also used to assess the burden of chronic kidney disease in epidemiologic studies and public health (6). The prevalence of chronic kidney disease in the United States has increased from approximately 10% in 1988 to 1994 to 13% in 1999 to 2004, which corresponds to approximately 26.3 million people in 2000 (6, 7).

The MDRD Study equation was developed by studying people with chronic kidney disease, and as such, its major limitations are imprecision and systematic underestimation of measured GFR (bias) at higher values (8). We sought to develop and validate a new estimating equation based on the serum creatinine level that would be as accurate as the MDRD Study equation at a GFR less than 60 mL/min per 1.73 m^2 and more accurate at a higher GFR. We report development and validation of a new equation and compare it with the MDRD Study equation for estimating measured GFR and U.S. prevalence of chronic kidney disease.

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METHODS

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) is a research group established by the National Institute of Diabetes and Digestive and Kidney

Diseases. The institutional review boards of all participating institutions approved the study. The **Appendix** (available at www.annals.org) provides details about study selection and analytical methods.

Data Sources

Investigators collaborating with CKD-EPI provided data from research studies and clinical populations (hereafter referred to as "studies"). In brief, we identified studies from the MEDLINE database and through investigators' and collaborators' contacts (**Appendix Figure 1**, available at www.annals.org). Key inclusion criteria were measurement of GFR on the basis of exogenous filtration markers and ability to calibrate serum creatinine assay. We restricted ourselves to studies that used urinary clearance of iothalamate for development and internal validation of equations, but included studies that used iothalamate and other filtration markers for external validation. We randomly divided 10 studies (6 research studies and 4 clinical populations) (3, 9–15), comprising 8254 participants, into separate data sets for development (5504 participants) and internal validation (2750 participants) (**Appendix Table 1,** available at www.annals.org). We used 16 other studies (6 research studies and 10 clinical populations) (13, 16–28), comprising 3896 participants, for external validation (**Appendix Table 2,** available at www.annals.org).

Laboratory Methods

For all studies, we recalibrated serum creatinine values to standardized creatinine measurements by using the Roche enzymatic method (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Basel, Switzerland) at the Cleveland Clinic Research Laboratory (Cleveland, Ohio) as described elsewhere (29, 30). We compared new equations with the MDRD Study equation (estimated GFR = $175 \times$ standardized $S_{cr}^{-1.154} \times age^{-0.203} \times 1.212$ [if black] $\times 0.742$ [if female]), in which GFR is expressed as mL/min per 1.73 m^2 of body surface area and S_{cr} is expressed in mg/dL (4).

Analyses in the Development Data Set

We prespecified a process for developing equations that uses transformations of continuous variables and the inclusion of additional variables and interactions to develop a large number of candidate equations. We used least-squares linear regression to relate measured GFR to serum creatinine and clinical characteristics available in all databases. Predictor variables included serum creatinine, age, race (black vs. white and other), and sex in all models, as in the MDRD Study equation, and additional variables in some models (diabetes [yes/no], previous organ transplantation [yes/no], and weight, as assigned by the individual studies). We fit regression models to all patients in the pooled development data set without accounting for study in the models. We transformed GFR and serum creatinine to natural logarithms to reflect their multiplicative (inverse) relationship and to stabilize variance across the range of GFR.

Context

The MDRD (Modification of Diet in Renal Disease) Study equation is commonly used to estimate glomerular filtration rate (GFR), but it is imprecise and underestimates GFR at higher values.

Contribution

These researchers pooled data from studies to develop and validate a new equation, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, to predict GFR. The CKD-EPI equation was somewhat more precise and accurate than the MDRD Study equation, especially at higher GFRs. Using the new equation could decrease false-positive results—the mislabeling of people with high GFR as having poor kidney function.

Caution

The sample used to develop the CKD-EPI equation included few elderly and nonwhite persons. Evaluation of the equation in these populations is needed.

—The Editors

We determined appropriate transformations of log serum creatinine and age by first fitting nonparametric smoothing splines to characterize the shape of the relationship of these factors with mean log measured GFR and then creating piecewise linear splines to correspond to observed nonlinearity (**Appendix Table 3,** available at www.annals.org) (31). We included additional variables and pairwise interactions between them if they were significant ($P < 0.010$ for additional variables and $P < 0.001$ for interactions) and improved model performance (relative reduction in root mean square error $\geq$2%) (**Appendix Table 4,** available at www.annals.org).

Analyses in the Internal Validation Data Set

We verified the statistical significance of predictor variables and interactions for all models and the relative ranking of performance among models. We derived final coefficients for each model by combining the development and internal validation data sets.

Analyses in the External Validation Data Set

We compared performance of the multiple models developed in the development data set with each other as well as with the MDRD Study equation by using a prespecified process. We performed comparisons in the overall data set and in subgroups defined by estimated GFR, clinical characteristics, and type of filtration marker (iothalamate vs. noniothalamate). We ranked equations on performance and ease of application. We performed sensitivity analyses for all steps to evaluate the robustness of results across studies. We selected a single model as the best equation for general use, referred to here as the "CKD-EPI equation."

Metrics for Equation Performance

We compared measured and estimated GFR for each patient graphically by plotting measured GFR and

Table 1. **Patient Characteristics**

Characteristic	Development Data Set (n = 5504)	Internal Validation Data Set (n = 2750)	External Validation Data Set (n = 3896)	*P* Value*
Mean age (SD), *y*	47 (15)	47 (15)	50 (15)	<0.001
Age, *n (%)*				<0.001
<40 y	2058 (37)	1018 (37)	1136 (29)	
41–65 y	2751 (50)	1403 (51)	2192 (56)	
>65 y	695 (13)	329 (12)	568 (15)	
66–70 y	476 (9)	220 (8)	254 (7)	
71–75 y	150 (3)	66 (2)	185 (5)	
76–80 y	41 (0)	30 (1)	92 (2)	
>80 y	28 (0)	13 (0)	37 (0)	
Women, *n (%)*	2391 (43)	1215 (44)	1767 (45)	0.084
Race, *n (%)*				0.001
Black	1728 (32)	857 (31)	384 (10)	
Hispanic	247 (5)	106 (4)	67 (2)	
Asian	62 (1)	38 (1)	67 (2)	
White or other	3467 (63)	1749 (64)	3378 (87)	
Kidney donor, *n (%)*	694 (13)	336 (12)	608 (16)	<0.001
Transplant recipient, *n (%)*	241 (4)	119 (4)	1134 (29)	<0.001
Diabetes, *n (%)*	1581 (29)	825 (30)	1089 (28)	0.173
Mean height (SD), *cm*	170 (10)	170 (10)	170 (10)†	0.90
Mean weight (SD), *kg*	82 (20)	82 (20)	79 (18)	<0.001
Mean body mass index (SD), kg/m^2	28 (6)	28 (6)	27 (6)†	<0.001
Mean body surface area (SD), m^2	1.93 (0.20)	1.93 (0.20)	1.90 (0.23)†	<0.001
Mean GFR (SD), *mL/min per 1.73* m^2‡	68 (40)	67 (40)	68 (36)	0.70
Mean serum creatinine level (SD)				<0.001
μmol/L	146 (106)	148 (106)	134 (88)	
mg/dL	1.65 (1.20)	1.67 (1.20)	1.52 (1.00)	

GFR = glomerular filtration rate.
* For comparison of the combined development and internal validation data sets vs. the external validation data set.
† The sample size is 3875 because of missing data.
‡ To convert GFR from mL/min per 1.73 m^2 to mL/s per m^2, multiply by 0.0167.

the difference (measured GFR − estimated GFR) against estimated GFR. We assessed bias as the median difference, with positive values indicating an underestimation of measured GFR. We assessed precision as interquartile range (IQR) for the differences. We assessed accuracy as root mean square error, relative to measured GFR and the percentage of estimates within 30% of the measured GFR (P_{30}), which takes into account greater errors at higher values and the absolute values of the difference between measured and estimated GFR. We calculated CIs by bootstrap methods (2000 bootstraps) (32) for median differences and IQR of the differences and by the binomial method for P_{30}. We computed receiver-operating characteristic (ROC) curves for measured GFR less than 90, 75, 60, 45, 30, and 15 mL/min per 1.73 m^2. We defined GFR stages as greater than 90, 60 to 89, 30 to 59, 15 to 29, and less than 15 mL/min per 1.73 m^2 (1). We compared sensitivity, specificity, and concordance between estimated and measured GFR among equations by using the McNemar test. We compared concordance of estimated GFR stages among equations by using the sign test.

We used R, version 2 (Free Software Foundation, Boston, Massachusetts), and SAS, version 9.1 (SAS Institute, Cary, North Carolina), to compute all analyses.

Estimation of U.S. Prevalence

The NHANES (National Health and Nutrition Examination Survey) is a cross-sectional, multistage, stratified, clustered probability sample of the civilian, noninstitutionalized population of the United States conducted by the National Center of Health Statistics and appropriate for estimates of prevalence of chronic conditions in the United States. We analyzed data from the 1999 to 2000, 2001 to 2002, 2003 to 2004, and 2005 to 2006 surveys. We limited our study population to 16 032 participants (3754 from 1999 to 2000, 4297 from 2001 to 2002, 4017 from 2003 to 2004, and 3964 from 2005 to 2006) who were 20 years or older, had completed the examination in the mobile examination center, were not pregnant or menstruating, were not missing serum creatinine measurements, and did not have an estimated GFR less than 15 mL/min per 1.73 m^2. Our methods are similar to those used in previous studies (7).

The NHANES did not measure GFR. We measured serum creatinine by using a kinetic-rate Jaffe method and recalibrated results to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (33). We estimated GFR by using the MDRD Study equation and the newly developed CKD-EPI equation. We truncated estimates that exceeded 200 mL/min per 1.73 m^2 at that level. Methods for collection, analysis, and reporting for albuminuria are described elsewhere (7, 34).

We defined albuminuria as an albumin-to-creatinine ratio greater than 30 mg/g. We used repeated measurements, obtained approximately 2 weeks after the original examination in a subset of 1241 participants in NHANES from 1988 to 1994, to estimate the persistence of albuminuria (34). The NHANES data do not include accurate diagnoses of the causes of kidney disease. We defined chronic kidney disease as persistent albuminuria or estimated GFR less than 60 mL/min per 1.73 m^2 (1). We classified chronic kidney disease according to our previously defined estimated GFR stages. We compared distributions of estimated GFR, estimated GFR stages, and prevalence of chronic kidney disease for both equations.

We performed the analyses by using Stata, version 10.0 (StataCorp, College Station, Texas), and incorporated the sampling weights from the complex NHANES sampling design to obtain unbiased estimates. We obtained standard errors for all estimates by using the Taylor series (linearization) method and followed NHANES-recommended procedures and weights (35–37). We used bootstrap methods implemented in Stata to derive CIs for the prevalence estimates for chronic kidney disease stages, incorporating persistence data on albuminuria. We applied prevalence estimates to the 2000 U.S. Census data to estimate the number of persons with chronic kidney disease in the United States.

Role of the Funding Source

The study was funded by a cooperative agreement with the National Institute of Diabetes and Digestive and Kidney Diseases, which allows them substantial involvement in the design of the study and in the collection, analysis, and interpretation of the data. The funding source was not required to approve publication of the finished manuscript.

RESULTS

Selection of Studies and Clinical Characteristics

Table 1 shows the clinical characteristics of the participants in each data set. In the development data set, mean measured GFR was 68 mL/min per 1.73 m^2 (SD, 40) and ranged from 2 to 190 mL/min per 1.73 m^2. The external validation data set had similar mean measured GFR, sex, and proportion of diabetes to the development and internal validation data sets but differed in age; body size; and the proportion of ethnic and racial minorities, kidney donors, and organ transplant recipients.

Description of the CKD-EPI Equation

The CKD-EPI equation for estimating log GFR includes log serum creatinine (modeled as a 2-slope linear spline with sex-specific knots at 62 μmol/L [0.7 mg/dL] in women and 80 μmol/L [0.9 mg/dL] in men), sex, race, and age on the natural scale. In comparison, the MDRD Study equation includes log serum creatinine without a spline, sex, race, and age on the log scale (**Appendix Table 5**, available at www.annals.org). The spline for log serum creatinine in the CKD-EPI equation allows steeper and identical slopes of GFR versus serum creatinine for men and women at creatinine levels above the knots and less steep and different slopes for men and women at creatinine levels below the knots. The slope for the CKD-EPI equation is similar to that of the MDRD Study equation above the knots but less steep below the knots, which leads to higher estimated GFR at lower creatinine values. The coefficient for black persons is greater than 1.0 in both equations, which leads to a higher estimated GFR for blacks than white persons at all levels of serum creatinine; however, the CKD-EPI equation yields a smaller difference in estimated GFR between black persons and white persons than does the MDRD Study equation. In the CKD-EPI equation, the relationship between GFR and sex varies by serum creatinine level. For example, the predicted female-to-male ratio for estimated GFR varies from 0.83 to 0.92 when the serum creatinine level is between 44 and 71 μmol/L (0.5 and 0.8 mg/dL) and is 0.75 when the serum creatinine level is greater than 80 μmol/L (>0.9 mg/dL). However, it is constant at 0.74 for all serum creatinine values in the MDRD Study equation. Estimated GFR is inversely related to age in both equations, but at older ages, the age term on the natural scale in the CKD-EPI equation leads to lower estimated GFR for the same creatinine level than does the log age term in the MDRD Study equation. In the external validation data set, models with additional variables for diabetes, organ transplantation, weight, or interactions among variables did not substantially improve per-

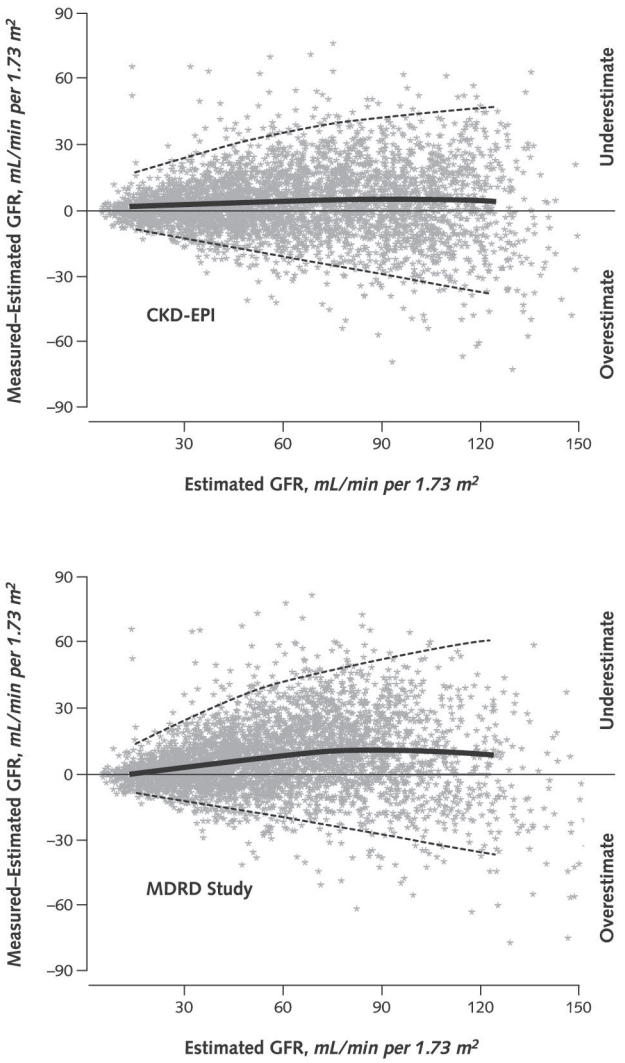
Table 2. **The CKD-EPI Equation for Estimating GFR on the Natural Scale***

Race and Sex	Serum Creatinine Level, μmol/L (mg/dL)	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

* Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min per 1.73 m^2 to mL/s per 1.73 m^2, multiply by 0.0167. We derived equation coefficients from pooled development and internal validation data sets. The CKD-EPI equation, expressed as a single equation, is $GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

Figure. **Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.**



Both panels show the difference between measured and estimated versus estimated GFR. A smoothed regression line is shown with the 95% CI (computed by using the lowest smoothing function in R), using quantile regression, excluding the lowest and highest 2.5% of estimated GFR. To convert GFR from mL/min per 1.73 m^2 to mL/s per m^2, multiply by 0.0167. CKI-EPD = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

formance compared with the simpler models. **Table 2** shows the CKD-EPI equation in a form that could be implemented in clinical laboratories.

Comparison of Performance

The **Figure** and **Table 3** show the performance of both equations in the validation data set. (**Appendix Table 6,** available at www.annals.org, shows performance in the development and internal validation data sets.) The CKD-EPI equation yielded improved median difference (bias), IQR, P_{30}, and root mean square error ($P < 0.001$ for all). The CKD-EPI equation was as accurate as the MDRD Study equation in the subgroup with estimated GFR less than 60 mL/min per 1.73 m^2 and substantially more accurate in the subgroup with estimated GFR greater than 60 mL/min per 1.73 m^2. Results were consistent across studies and subgroups defined by age, sex, race, diabetes, transplant status, and body mass index (data not shown).

The ROC curves to detect GFR less than 90, 75, 60, 45, 30 and 15 mL/min per 1.73 m^2 did not differ between the CKD-EPI and MDRD Study equations. The areas under the ROC curves were 0.95, 0.96, 0.96, 0.97, 0.97, and 0.98, respectively, for both equations. For detection of measured GFR less than 60 mL/min per 1.73 m^2, the estimated GFR value with highest combination of sensitivity and specificity was 59 mL/min per 1.73 m^2 for the CKD-EPI equation and 55 mL/min per 1.73 m^2 for the MDRD Study equation. The sensitivity and specificity of estimated GFR less than 60 mL/min per 1.73 m^2 were 91% and 87% according to the CKD-EPI equation and 95% and 82% according to the MDRD Study equation ($P < 0.001$ for both comparisons). Concordance of estimated and measured GFR stages was 69% for the CKD-EPI equation and 64% for the MDRD Study equation ($P < 0.001$). **Table 4** shows classification of GFR stages estimated by the CKD-EPI and MDRD Study equations, with significant ($P < 0.001$) reclassification to higher values by the CKD-EPI equation at values of 30 to 59 mL/min per 1.73 m^2 and higher. Among those classified differently by the 2 equations, classification by the CKD-EPI equation was correct more often than classification by the MDRD Study equation (63% vs. 34%; $P < 0.001$). Overall, our results indicate better classification by estimated GFR with the CKD-EPI equation, primarily because of reduction in bias.

Comparison of Estimated GFR and Prevalence of Chronic Kidney Disease in NHANES

The transformations and coefficients for variables in the CKD-EPI equation translate into differences in the estimated GFR distribution and prevalence of chronic kidney disease among NHANES participants from 1999 to 2006 compared with the MDRD Study equation. Both equations show a similar distribution at estimated GFR less than 45 mL/min per 1.73 m^2, but the CKD-EPI equation leads to a shift to the right at higher levels of estimated GFR (**Appendix Figure 2**, *top*, available at www.annals.org). Mean estimated GFR (±SE) was 93.2 ± 0.39 using the CKD-EPI equation versus 86.3 ± 0.40 mL/min per 1.73 m^2 using the MDRD Study equation (median, 94.5 mL/min per 1.73 m^2 [IQR, 79.7 to 108.1 mL/min per 1.73 m^2] versus 85.0 mL/min per 1.73 m^2 [IQR, 72.9 to 98.5 mL/min per 1.73 m^2]). Comparison of classification of stages of estimated GFR showed reclassification to higher values with the CKD-EPI equation at values of 30

to 59 mL/min per 1.73 m^2 and higher (**Appendix Table 7**, available at www.annals.org). We observed similar reclassification of estimated GFR distribution among patients with and without albuminuria (**Appendix Table 8**, available at www.annals.org).

The CKD-EPI equation yields a lower estimated prevalence of chronic kidney disease than the MDRD Study equation (11.5% [CI, 10.6% to 12.4%] vs. 13.1% [CI, 12.1% to 14.0%]), primarily because of a lower estimated prevalence of stage 3 disease (6.3% [CI, 5.8% to 6.9%] vs. 7.8% [CI, 7.2% to 8.5%]) (**Appendix Figure 2**, *bottom*, available at www.annals.org). Reclassification to higher estimated GFR leads to a higher prevalence of stage 1 disease and a lower prevalence of stage 2 disease. The CKD-EPI equation leads to a lower prevalence in women and white persons, such that the prevalence of stage 3 or 4 disease is not significantly higher in women versus men or in white persons versus black persons, as it is in the MDRD Study (data not shown). The prevalence of chronic kidney disease increases with age when either equation is used, but among patients older than 70 years, the CKD-EPI equation leads to a similar rather than lower estimated prevalence of chronic kidney disease. On the basis of the 2000 U.S. population of 201 million people older than 20 years, the CKD-EPI equation yields a prevalence of chronic kidney disease of 23.2 million (CI, 21.3 to 25.0 million), approximately 3 million fewer than that yielded by the MDRD Study equation (**Appendix Table 9**, available at www.annals.org).

Discussion

We developed a new equation, the CKD-EPI equation, to estimate GFR in adults from serum creatinine by using a large database pooled from 10 studies. Using data pooled from 16 additional studies, we validated the CKD-EPI equation and showed that it is more accurate than the widely used MDRD Study equation. The CKD-EPI equation has lower bias, especially at an estimated GFR greater than 60 mL/min per 1.73 m^2; however, precision remains limited. The improved accuracy of the CKD-EPI equation overcomes some of the limitations of the MDRD Study equation and has important implications for public health and clinical practice.

The lower bias at higher estimated GFR reflects our use of a spline term for serum creatinine. The spline accounts for a weaker relationship between creatinine and GFR at lower creatinine levels than at higher levels, which is consistent with reports from studies primarily comprising patients with higher measured GFR, such as kidney donors and young people with type 1 diabetes without microalbuminuria (10, 15, 38). Like the MDRD Study equation, the CKD-EPI equation includes age, race, and sex as surrogates for non-GFR determinants of serum creatinine. These variables are associated with muscle mass, the main determinant of creatinine generation (39). The imprecision of GFR estimates suggests that age, race, and sex do not account for all variation in non-GFR determinants of serum creatinine.

The CKD-EPI equation should lead to more accurate estimates of the distribution of estimated GFR and the burden of chronic kidney disease in the U.S. population. Median estimated GFR was 9.5 mL/min per 1.73 m^2 higher, which decreases the prevalence estimate for chronic kidney disease by 1.6% (11.5% vs. 13.1% using the MDRD Study equation). The high prevalence estimates for elderly persons, women, and white persons, compared with the low incidence rates of treated kidney failure in these groups, have raised concern about the use of the

Table 3. **Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set***

Variable and Equation	All Patients	Patients With Estimated GFR <60 mL/min per 1.73 m^2	Patients With Estimated GFR ≥60 mL/min per 1.73 m^2
Median difference (95% CI), *mL/min per 1.73 m^2*†			
CKD-EPI	2.5 (2.1–2.9)	2.1 (1.7–2.4)	3.5 (2.6–4.5)
MDRD Study	5.5 (5.0–5.9)	3.4 (2.9–4.0)	10.6 (9.8–11.3)
Interquartile range for differences (95% CI), *mL/min per 1.73 m^2*‡			
CKD-EPI	16.6 (15.9–17.3)	11.3 (10.7–12.1)	24.2 (22.8–25.3)
MDRD Study	18.3 (17.4–19.3)	12.9 (12.0–13.6)	25.7 (24.4–27.1)
P_{30} (95% CI), %§			
CKD-EPI	84.1 (83.0–85.3)	79.9 (78.1–81.7)	88.3 (86.9–89.7)
MDRD Study	80.6 (79.5–82.0)	77.2 (75.5–79.0)	84.7 (83.0–86.3)
Root mean square error (95% CI)			
CKD-EPI	0.250 (0.241–0.259)	0.284 (0.270–0.298)	0.213 (0.203–0.223)
MDRD Study	0.274 (0.265–0.283)	0.294 (0.280–0.308)	0.248 (0.238–0.258)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
* To convert GFR from mL/min per 1.73 m^2 to mL/s per 1.73 m^2, multiply by 0.0167.
† Median difference refers to measured GFR minus estimated GFR.
‡ Interquartile range refers to the 25–75th percentile.
§ P_{30} refers to percentage of GFR estimates that are within 30% of measured GFR.

Table 4. **Comparison of the CKD-EPI and MDRD Study Equations in Estimating GFR Stage and Comparison With Measured GFR in the Validation Data Set***

CKD-EPI–Estimated GFR and Measured GFR	MDRD Study–Estimated GFR, *n (%)*					Total Patients, *n (%)*
	>90 mL/min per 1.73 m^2	60–89 mL/min per 1.73 m^2	30–59 mL/min per 1.73 m^2	15–29 mL/min per 1.73 m^2	<15 mL/min per 1.73 m^2	
Estimated GFR >90 mL/min per 1.73 m^2	670 (17.2)	319 (8.2)	0	0	0	989 (25.4)
Measured GFR						
>90 mL/min per 1.73 m^2	586 (15.0)	221 (5.7)				
60–89 mL/min per 1.73 m^2	75 (1.9)	93 (2.4)				
30–59 mL/min per 1.73 m^2	9 (0.3)	4 (0.1)				
15–29 mL/min per 1.73 m^2	0	1 (0.0)				
<15 mL/min per 1.73 m^2	0	0				
Estimated GFR 60–89 mL/min per 1.73 m^2	2 (0.0)	803 (20.6)	190 (4.9)	0	0	995 (25.5)
Measured GFR						
>90 mL/min per 1.73 m^2	0	263 (6.8)	11 (0.3)			
60–89 mL/min per 1.73 m^2	1 (0.0)	459 (11.8)	110 (2.8)			
30–59 mL/min per 1.73 m^2	1 (0.0)	77 (2.0)	69 (1.8)			
15–29 mL/min per 1.73 m^2	0	4 (0.1)	0			
<15 mL/min per 1.73 m^2	0	0	0			
Estimated GFR 30–59 mL/min per 1.73 m^2	0	2 (0.0)	1251 (32.1)	42 (1.1)	0	1295 (33.2)
Measured GFR						
>90 mL/min per 1.73 m^2		0	118 (3.0)	0		
60–89 mL/min per 1.73 m^2		2 (0.0)	221 (5.7)	0		
30–59 mL/min per 1.73 m^2		0	903 (23.7)	20 (0.5)		
15–29 mL/min per 1.73 m^2		0	105 (2.7)	21 (0.5)		
<15 mL/min per 1.73 m^2		0	4 (0.1)	0		
Estimated GFR 15–29 mL/min per 1.73 m^2	0	0	9 (0.2)	462 (11.9)	2 (0.0)	473 (12.1)
Measured GFR						
>90 mL/min per 1.73 m^2			0	0	0	
60–89 mL/min per 1.73 m^2			0	0	0	
30–59 mL/min per 1.73 m^2			5 (0.1)	109 (2.8)	1 (0.0)	
15–29 mL/min per 1.73 m^2			4 (0.1)	302 (7.8)	1 (0.0)	
<15 mL/min per 1.73 m^2			0	51 (1.3)	0	
Estimated GFR <15 mL/min per 1.73 m^2	0	0	0	5 (0.1)	139 (3.6)	144 (3.7)
Measured GFR						
>90 mL/min per 1.73 m^2				0	0	
60–89 mL/min per 1.73 m^2				0	2 (0.0)	
30–59 mL/min per 1.73 m^2				0	0	
15–29 mL/min per 1.73 m^2				2 (0.0)	32 (0.8)	
<15 mL/min per 1.73 m^2				3 (0.1)	105 (2.7)	
Total	672 (17.3)	1124 (28.9)	1450 (37.2)	509 (13.1)	141 (3.6)	3896 (100)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
* Cell percentages may not total to margin percents because of rounding. Shaded cells represent agreement. Cells above the shaded diagonal cells represent disagreements in which estimated GFR category was higher with the CKD-EPI equation than with the MDRD Study equation; cells below the shaded diagonal cells represent disagreements in which estimated GFR category was lower. To convert GFR from mL/min per 1.73 m^2 to mL/s per 1.73 m^2, multiply by 0.0167.

MDRD Study equation (7, 40, 41). When the CKD-EPI equation is used, the prevalence is reduced in women and white persons but remains high in elderly persons. Possible explanations for the remaining disparities between prevalence and incidence include competing risk from fatal cardiovascular disease in elderly persons and faster progression of kidney disease in men and black persons (42, 43).

The greater accuracy of the CKD-EPI equation should improve clinical decision making in patients with decreased kidney function. In particular, lower bias should reduce the rate of false-positive diagnoses of stage 3 chronic kidney disease (estimated GFR <60 mL/min per 1.73 m^2) in patients without chronic kidney disease (measured GFR >60 mL/min per 1.73 m^2 and no markers of kidney damage). Patients with chronic kidney disease are at higher risk for various complications (44–50), and guidelines and recommendations call for reducing the dosage of drugs excreted by the kidney, avoiding contrast media for imaging procedures and phosphate-based enemas in preparation for colonoscopy, and setting lower targets for cardiovascular risk factors in patients with decreased GFR. Falsely low estimated GFRs could therefore lead to insufficient drug dosing, withholding of important diagnostic tests, and overaggressive cardiovascular risk factor reduction in patients without chronic kidney disease. The effect of more accurate estimates at higher GFRs on clinical decision making should be evaluated.

The strengths of our study include its design, with separate large data sets for development and validation of the new equation, and a prespecified rigorous statistical analytical plan for introduction and testing of all variables in the development data set. The pooled development and validation data sets include participants with diverse clinical characteristics, with and without kidney disease, and across a wide range of measured GFR, which allows more

general applicability than does the MDRD Study equation. Comparison of equations in a separate validation data set overcomes limitations of differences among studies in patient characteristics and methods for measurement of GFR and serum creatinine.

Our study also has limitations. First, a single equation is unlikely to work equally well in all populations. Second, we have pooled studies of different populations to develop and validate the CKD-EPI equation. We performed extensive analyses to examine possible study effects but cannot rule out that some of our findings may reflect the specific studies we included in our database. Third, our study sample is not representative of the general population because few participants had a higher GFR and relatively few participants were older than 70 years or of racial minorities other than black (who are at increased risk for chronic kidney disease). Fourth, we had incomplete data on diabetes type, immunosuppressive agents for transplantation, measures of muscle mass, and other clinical conditions and medications that might affect serum creatinine independent of GFR; however, the variables that we evaluated are the most readily available and easy to ascertain for widespread clinical application. Fifth, the CKD-EPI equation is more complex than the MDRD Study equation, but it can readily be implemented into clinical laboratory information systems by using the same input variables required for the MDRD Study equation. Finally, our equation does not overcome the limitations of serum creatinine as an endogenous filtration marker. All creatinine-based equations should be used with caution in people with abnormally high or low muscle mass. Nevertheless, serum creatinine is currently central for clinical assessment of kidney function, and GFR estimates based on serum creatinine will continue to be used in clinical practice for the foreseeable future.

Further research is needed to improve GFR estimation. Imprecision in GFR estimates may be secondary to non-GFR determinants of creatinine. Measurement errors in GFR may also inflate measures of imprecision. Research should be directed toward improving GFR measurement and evaluating cystatin C and novel filtration markers for GFR estimation, either alone or in combination with serum creatinine (51). Studies of representative samples, especially elderly persons and racial and ethnic minorities, are necessary.

In summary, the CKD-EPI creatinine equation is more accurate than the MDRD Study equation across various study populations and clinical conditions. Bias is improved, especially at higher estimated GFRs, although precision remains suboptimal. Improved accuracy of the CKD-EPI equation could have important implications for public health and clinical practice. We suggest that the CKD-EPI equation could replace the MDRD Study equation in general clinical use to estimate GFR.

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