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GFR Estimation: From Physiology to Public Health

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Abstract

Estimating glomerular filtration rate (GFR) is essential for clinical practice, research, and public health. Appropriate interpretation of estimated GFR (eGFR) requires understanding the principles of physiology, laboratory medicine, epidemiology and biostatistics used in the development and validation of GFR estimating equations. Equations developed in diverse populations are less biased at higher GFR than equations developed in CKD populations and are more appropriate for general use. Equations that include multiple endogenous filtration markers are more precise than equations including a single filtration marker. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are the most accurate GFR estimating equations that have been evaluated in large, diverse populations and are applicable for general clinical use. The 2009 CKD-EPI creatinine equation is more accurate in estimating GFR and prognosis than the 2006 Modification of Diet in Renal Disease (MDRD) Study equation and provides lower estimates of prevalence of decreased eGFR. It is useful as a “first” test for decreased eGFR and should replace the MDRD Study equation for routine reporting of serum creatinine–based eGFR by clinical laboratories. The 2012 CKD-EPI cystatin C equation is as accurate as the 2009 CKD-EPI creatinine equation in estimating eGFR, does not require specification of race, and may be more accurate in patients with decreased muscle mass. The 2012 CKD-EPI creatinine–cystatin C equation is more accurate than the 2009 CKD-EPI creatinine and 2012 CKD-EPI cystatin C equations and is useful as a confirmatory test for decreased eGFR as determined by an equation based on serum creatinine. Further improvement in GFR estimating equations will require

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development in more broadly representative populations, including diverse racial and ethnic groups, use of multiple filtration markers, and evaluation using statistical techniques to compare eGFR to “true GFR”.

INDEX WORDS

estimated glomerular filtration rate (eGFR); kidney function; eGFR estimating equation; filtration marker; renal insufficiency; chronic kidney disease; public health

Introduction and Current Applications

Assessment of glomerular filtration rate (GFR) is essential for clinical practice; it is crucial for deciphering the symptoms, signs, and laboratory abnormalities that might signify kidney disease, for drug dosing, and for detecting, managing and estimating the prognosis of chronic kidney disease (CKD).¹ A decrease in GFR to <60 ml/min/1.73 m² for 3 or more months is a diagnostic factor for CKD and is associated with a greater risk of adverse outcomes (eg, death). More than 60 years ago Homer Smith summarized his pioneering work on the use of urinary inulin clearance for GFR measurement and wrote of the importance of accurate assessment of GFR in the forward to his now famous textbook²:

Current methods of study of renal function may be too elaborate for general clinical application, but no method is to be disdained if it can aid significantly in deciding the issue between life and death.

Despite advances in GFR measurement since then, it remains a specialized diagnostic test, available only in major medical centers. In routine clinical practice, GFR is estimated from the serum concentrations of endogenous filtration markers. Serum creatinine is measured more than 280 million times per year in the United States, and more than 85% of clinical laboratories now report an estimated GFR (eGFR) when serum creatinine is measured.^{3–5} Thus, improving the accuracy of GFR estimates could affect the health of millions of people.

The first widely used GFR estimating equations were developed in the 1970s to estimate creatinine clearance in adults from serum creatinine. In recent years, a number of new equations have been developed for use with standardized serum creatinine assays and gained worldwide acceptance for implementation into clinical practice as a “first test” for assessing GFR in adults. Recently, equations using standardized cystatin C assays have been proposed as a “confirmatory test” for decreased eGFR from creatinine. The goal of this article is to review the principles of physiology, laboratory medicine, epidemiology and biostatistics necessary for the appropriate use and interpretation of GFR estimates in clinical practice and public health. We focus on the Modification of Diet in Renal Disease (MDRD) Study and CKD Epidemiology Collaboration (CKD-EPI) equations because they were developed using rigorous methods and are recommended by clinical practice guidelines (Table 1).^{6–15}

Physiology

GFR

Glomerular filtration is the physiological process of creating an ultrafiltrate of blood as it flows through the glomerular capillaries. In principle, the GFR is the product of the number of nephrons times the average single-nephron GFR. Determinants of the single-nephron GFR include hemodynamic factors within the glomerular capillary network and the hydraulic properties of the capillary wall. In humans, a high GFR (180 L/d) is assured by the large number of glomeruli (1 million per kidney), the rich renal blood flow (20% of cardiac output, higher than in other capillary beds), the extensive total glomerular capillary surface area (1 square meter), and high glomerular capillary pressure and hydraulic permeability of the glomerular capillary wall (far greater than those of other capillaries).¹⁶

Based on a large body of evidence, the mean GFR in healthy, young adult Caucasians is approximately 125 ml/min/1.73 m², with a wide range.¹⁷ Indexing GFR to body surface area (BSA) reduces variation among healthy individuals and allows comparisons to normative values. There is some evidence that the normal level of GFR varies among ethnic groups.¹⁸ GFR is affected by numerous physiological and pathological conditions and varies with the time of day, dietary protein intake, exercise, age, pregnancy, obesity, hyperglycemia, use of antihypertensive drugs, surfeit or deficit of extracellular fluid, and acute and chronic kidney disease.

It is not possible to directly measure the GFR in humans, thus the “true” GFR cannot be known with certainty. It can be measured indirectly as the clearance of exogenous filtration markers or estimated from serum levels of endogenous filtration markers, but both measured (mGFR) and eGFR are associated with error in their determination. In principle, “true GFR” could be estimated from repeated determinations of mGFR or eGFR and appropriate statistical techniques for incorporating measurement error. We suggest an operational definition of “true GFR” as the average level of GFR over a representative 1- to 2-day period.

Filtration Markers

Filtration markers are low molecular weight substances that are eliminated largely by glomerular filtration (Box 1). Exogenous filtration markers are substances that are administered into the body for the purpose of performing clearance measurements. Inulin fulfills the criteria proposed by Smith for an “ideal” exogenous filtration marker. Endogenous filtration markers are substances generated in the body at a relatively constant rate, the plasma levels of which can be used to estimate GFR. The plasma concentrations of all endogenous filtration markers are affected by factors other than GFR (non-GFR determinants). After accounting for their non-GFR determinants, their plasma concentrations closely approximate mGFR.

Box 1**Filtration Markers and Molecular Weights**

-
- Substances that are filtered by the glomeruli which can be used to measure or estimate the GFR
 - Ideal properties
 - Inert
 - Freely filtered
 - ◆ Molecular weight <20,000 Da
 - ◆ not protein bound
 - Not reabsorbed or secreted by the tubule
 - Not metabolized by the kidney
 - Easy to measure
 - Exogenous filtration markers, for clearance measurements (urinary or plasma)
 - Inulin (5200 Da)
 - Iothalamate (usually with ¹²⁵I) (640 Da)
 - Iohexol (821 Da)
 - ⁵¹Cr-EDTA (372 Da)
 - ^{99m}Tc-DTPA (938 Da)
 - Endogenous filtration markers, for GFR estimation
 - Metabolites (if excreted in the urine, may also be used for clearance measurements)
 - ◆ urea (60 Da)
 - ◆ creatinine (113 Da)
 - Low molecular weight serum proteins
 - ◆ cystatin C (13,300 Da)
 - ◆ B2M (11,700 Da)
 - ◆ BTP (23,000–29,000 Da)
-

Note: Numbers in parentheses are molecular weights, not including the radio-isotope tracer.

B2M, β 2-microglobulin; BTP, β -trace protein; GFR, glomerular filtration rate; Cr-EDTA, chromium 51; ¹²⁵I, iodine 125; ^{99m}Tc-DTPA, technetium 99m diethylenetriamine pentaacetic acid; EDTA, ethylenediaminetetraacetic acid;

Accurate measurement of filtration markers is central to measurement and estimation of GFR. Inulin is difficult to measure, and alternative exogenous markers have been developed to facilitate measurement. Endogenous markers vary substantially in their ease of measurement, and numerous assays are available for creatinine and cystatin C. The US National Kidney Disease Education Program (NKDEP) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have launched international efforts to improve standardization and harmonization of serum assays for creatinine and cystatin C in clinical laboratories. Standard reference materials for creatinine and for cystatin C were released in 2006 and 2010, respectively.^{14,19–21} Cystatin C assays are more costly than creatinine assays, but the cost is declining with greater use.

Measuring GFR

The GFR is measured indirectly as the clearance of exogenous filtration markers that are excreted by the kidney only by glomerular filtration. Clearance can be measured as either plasma or urinary clearance (Figures 1A and 1B).^{22,23} For a marker that is eliminated from the plasma solely by urinary excretion, plasma and urinary clearance are equal, enabling GFR measurement without urine collection, which minimizes inconvenience and errors due to incomplete bladder emptying. Urinary and plasma clearance of exogenous filtration markers can be assessed when kidney function is stable or changing.

The classic method of Smith for urinary inulin clearance includes a continuous intravenous infusion to achieve a constant plasma level, repeated blood sampling for plasma measurements, and bladder catheterization for urinary collection. Alternative clearance methods, including bolus infusion of the marker and plasma clearance or spontaneous bladder emptying for urinary clearance, are now used far more commonly than the classic method. Measurement error in GFR includes differences from the classic method as well as differences from “true GFR.”

Estimating GFR

The GFR can be estimated from serum levels of endogenous filtration markers without requiring calculation of clearance. Non-GFR determinants of plasma concentrations of endogenous filtration markers include generation, tubular reabsorption or secretion and extra-renal elimination (Figure 1C).^{1,24} The GFR is related to the reciprocal of the plasma concentration of the marker, but it is also influenced by its non-GFR determinants. Endogenous filtration markers in current use include low molecular weight metabolites, such as creatinine, and serum proteins, such as cystatin C (Box 1). Filtered metabolites may be excreted in the urine and may be used to measure urinary clearance. By contrast, filtered serum proteins are reabsorbed and degraded within the tubule with little appearance in the urine. A comparison of the properties, physiologic determinants of the serum level, applications in GFR estimation, and the assays for creatinine and cystatin C is shown in Table 2.

Development and Evaluation of Estimating Equations

Estimating equations for GFR are regression equations that estimate mGFR from plasma levels of endogenous filtration markers and demographic and clinical variables as observed surrogates for the unmeasured non-GFR determinants¹. By definition, an estimating equation provides a more accurate estimate of mGFR than the plasma concentration alone. Estimating equations for GFR are derived in the steady state; therefore, GFR estimates are more accurate in the steady state than in the nonsteady state. Development and validation of GFR estimating equations should be undertaken with appropriate attention to epidemiologic and statistical techniques (Box 2).²⁵

Box 2**Development and Validation of GFR Estimating Equations**

- Separate datasets for development and validation populations
 - But similar methods for all other considerations below
- Study populations with a wide range of clinical characteristics and GFR, representative of the clinical populations in which equations are to be applied
 - Representative samples of general population
 - Patients with kidney disease
- Reference methods for mGFR and serum concentrations
 - Plasma or urinary clearance of an exogenous filtration marker for mGFR
 - Serum assays traceable to reference method for standardized reference material for endogenous filtration markers
- Surrogates with *a priori* relationship to non-GFR determinants
 - For example: age, sex and race for creatinine generation by muscle
- Linear regression of the logarithm of mGFR (log mGFR) on the logarithm of the plasma concentration of the endogenous filtration marker (log P)
 - Logarithmic transformation reflects the multiplicative relationship between GFR and serum creatinine
 - Logarithmic transformation satisfies the stable variance assumption of linear regression
- Standard metrics for evaluation compared to mGFR
 - Bias
 - Precision
 - Accuracy
 - Classification
 - Reclassification
- Novel metrics for evaluation compared to “true GFR”

GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate;

Assessment of performance of GFR estimating equations in estimating mGFR requires evaluation in a different population than the one in which the equation was developed (validation population). Accuracy of GFR estimates requires “trueness” (absence of bias) and precision. Bias reflects a systematic difference between mGFR and eGFR, generally due to differences between the development and validation population in measurement methods for GFR, assays for filtration markers, or the relationship of the surrogates to the non-GFR determinants of the filtration marker. Imprecision reflects random error due to variation in non-GFR determinants and GFR measurement error; imprecision is generally greater at higher than lower GFRs. Considering the various sources of error, the 2002 KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines considered that an eGFR within 30% of an mGFR was satisfactory for clinical interpretation, and as a performance metric for accuracy, the guidelines recommended that more than 90% of subjects in the validation population have an eGFR within 30% of the measured GFR ($P_{30} > 90\%$).⁶ As shown later, GFR estimating equations developed in diverse populations have lesser bias at higher eGFR than equations developed in CKD populations. However, even in the absence of bias, imprecision remains a barrier to exceeding this criterion for equations using only one filtration marker

(either creatinine or cystatin C). In principle, the use of multiple filtration markers with non-correlated non-GFR determinants can improve precision by reducing errors due to variation in non-GFR determinants of each marker. Indeed, new equations that use both creatinine and cystatin C can achieve $P_{30} > 90\%$.

Performance of GFR estimating equations can also be evaluated in large populations by implications for drug dosing, prevalence estimates for reduced eGFR and the strength of associations of reduced eGFR with kidney disease prognosis, for example, risk of mortality, cardiovascular disease, or kidney failure. Understanding the potential sources of the error is important for the interpretation of GFR estimates. In principle, bias in eGFR would lead to errors in drug dosing, prevalence estimates and risk associations. Imprecision in eGFR would lead to errors in drug dosing but not prevalence estimates, and would weaken risk associations. Few population studies have included mGFR, however, so accuracy of equations cannot be evaluated. In general, differences among equations using the same filtration markers reflect differences in the variables included in the equations and the forms and coefficients of the variables. Differences among equations using different filtration markers are also affected by differences among the filtration markers in non-GFR mechanisms, such as direct effects of the filtration markers on outcomes, confounding by factors that are associated with the non-GFR determinants of the filtration markers, or biological variation and measurement error. Of note, filtration markers represent only one class of prognostic markers in kidney disease. Other markers may be associated with prognosis without being strongly correlated with mGFR, indicating a non-GFR mechanism for the association, such as markers of kidney damage (eg, urinary albumin). Indeed, the combination of eGFR and albuminuria is more accurate in predicting CKD prognosis than eGFR alone.²⁶

Description and Performance of Estimating Equations

In this section, we describe the MDRD Study and CKD-EPI equations (Table 3)^{10–12,15} and compare their performance in estimating the mGFR and implications for drug dosing in studies by CKD-EPI (Tables 4 and 5),^{12,15,27–29} the prevalence of decreased eGFR in the US population in the NHANES (National Health and Examination Surveys) (Figure 2)³⁰, and risk associations in studies by the CKD Prognosis Consortium (CKD-PC) (Figures 3–5).^{31,32} For comparisons in estimating the mGFR, we focus on bias and accuracy (P_{30}). For implications for drug dosing, we focus on concordance with mGFR. For comparisons of prevalence estimates, we focus on a CKD detection threshold of eGFR < 60 ml/min/1.73 m², since this is a diagnostic criterion for CKD. For comparisons of risk associations, we focus on eGFR risk thresholds below which the risk for adverse outcomes is higher than the reference eGFR. We also compare risk categories using reclassification of subjects within the eGFR category of 45–59 ml/min/1.73 m², since reclassification to higher eGFR would not fulfill the criteria for CKD in patients who do not have markers of kidney damage.

Creatinine Equations

The 1999 MDRD Study equation was developed from participants in the baseline period of the MDRD Study, a randomized trial studying the effects of dietary protein restriction and lower blood pressure on CKD progression (Table 1).⁹ The GFR was measured as the urinary

clearance of iothalamate. Serum creatinine was measured prior to the development of the standard reference material for creatinine and reference methods for its assay. Performance in an external validation population was not reported. The original equation included 6 variables: serum creatinine, age, sex, race (African American vs. white and other), and serum urea nitrogen and albumin concentrations. In 2000, it was simplified to a 4-variable equation,¹⁰ and in 2006, it was re-expressed for use with standardized serum creatinine assays (ie, the IDMS [isotope-dilution mass spectrometry]-traceable 4-variable MDRD Study equation¹¹; Tables 1, 3). Serum creatinine values in the MDRD Study laboratory were 5% lower after standardization; the 2006 MDRD Study equation has an adjustment in the intercept term without a change to the creatinine coefficient.³³

The CKD-EPI was formed in 2003 by the National Institute of Diabetes and Digestive and Kidney Diseases to evaluate and improve GFR estimating equations. The CKD-EPI assembled pooled datasets from diverse studies including individuals with and without kidney disease, people with diabetes, organ transplant recipients, and potential donors. The GFR was measured by clearances of exogenous filtration markers, and serum samples were available for calibration to reference materials and methods in all studies. The 2006 MDRD Study equation was found to be more accurate compared with the Cockcroft-Gault equation²⁸ (P_{30} of 83% versus 69%, respectively) because of lesser bias and greater precision (Table 4) and more accurate for adjusting drug doses (concordance with mGFR, 78% vs. 73%) (Table 5).^{27,29} The main limitations to the MDRD Study equation were a systematic bias to underestimate mGFR at higher levels and imprecision throughout the range.

The 2009 CKD-EPI creatinine equation was developed to overcome the shortcomings of the 2006 MDRD Study equation (Table 1).¹² Variables included in the final equation are the same as those in the MDRD Study equation, but the forms of the variables and the coefficients differ (Table 3). Of particular importance is the use of two coefficients for serum creatinine, with larger negative values for creatinine values above the knots (-1.209) and smaller negative values below the knots. Diabetes status, organ transplant status and weight were considered for inclusion but did not enhance equation performance.³⁴ In comparison to the 2006 MDRD Study equation, the CKD-EPI creatinine equation yields higher eGFR values for serum creatinine concentrations below the knots, for women, for whites and other races, and for age less than approximately 70 years. Evaluation in the validation population showed a lesser bias of the CKD-EPI than the MDRD Study equation, especially at eGFR >60 ml/min/1.73 m², but only moderate improvement in overall accuracy (P_{30} of 84.1% vs. 80.6%, respectively) (Table 4) and in drug dosage adjustment (concordance with mGFR, 80% vs. 78%, respectively) (Table 5).^{27,29}

A recent systematic review compared the performance of the 2009 CKD-EPI creatinine equation versus the 2006 MDRD Study equation in studies using standardized creatinine assays.³⁵ Among 12 studies including 12,898 subjects in North America, Europe and Australia, the P_{30} ranged from 59%–95%. The P_{30} was higher for the CKD-EPI equation than the MDRD Study equation in 10 studies and less accurate in 2 studies. Bias varied according to level of eGFR. Bias was smaller for the CKD-EPI creatinine equation than the MDRD Study equation at higher eGFR but larger at lower eGFR; the differences on the raw

scale were larger at higher eGFR and smaller and not clinically meaningful at lower eGFR. The performance of both equations was not as good in regions outside of North America, Europe and Australia, presumably reflecting differences in creatinine generation due to racial, ethnic and regional variations in muscle mass and diet that are not captured by the race coefficients. Other equations and modifications using a local coefficient generally improved performance, but did not generalize to other studies. In general, the CKD-EPI creatinine equation with local modifications performed better than the MDRD Study equation with local modifications. Recent data indicate that the performance of the CKD-EPI equation appears comparable in older subjects to that previously reported in younger subjects and that an equation developed in an elderly population does not perform substantially better than the CKD-EPI creatinine equation in validation studies.^{36–38}

Multiple studies have demonstrated the differences between the 2009 CKD-EPI creatinine equation versus the 2006 MDRD Study equation for prevalence and risk associations.^{12,31,39–49} In NHANES, there is a marked shift to the left in the distribution of eGFR values using the CKD-EPI creatinine versus the MDRD Study equation, with a correspondingly lower prevalence of eGFR <60 ml/min/1.73 m² (6.5% vs. 8.2%, respectively) (Figure 2).³⁰ In CKD-PC, there are substantial differences in multivariable-adjusted risk associations, with higher eGFR risk thresholds using the CKD-EPI creatinine vs. the MDRD Study equation (Figure 3).³¹ Reclassification among eGFR categories shows more substantial differences between equations (Figure 4).³¹ For example, among subjects with eGFR of 45–59 ml/min/1.73 m² using the MDRD Study equation, the CKD-EPI creatinine equation reclassifies 34.7% to eGFR of 60–89 ml/min/1.73 m² and 1.2% to eGFR of 30–44 ml/min/1.73 m². Individuals reclassified to a higher eGFR category had a 0.80, 0.73 and 0.49 lower adjusted risk for mortality, CVD mortality and kidney failure, respectively, than those not reclassified, whereas subjects reclassified to a lower eGFR category had a 1.15, 1.25 and 2.67 higher risk, respectively. Overall net reclassification improvement (NRI) favored the CKD-EPI creatinine equation over the MDRD Study equation for the three outcomes. Results were generally similar among African Americans, whites and Asians.

Cystatin C Equations and Combined Creatinine–Cystatin C Equations

The 2008 CKD-EPI cystatin C and 2008 CKD-EPI creatinine–cystatin C equations were developed in a preliminary study to evaluate the impact of cystatin C on GFR estimation in CKD populations prior to standardization of the cystatin C (Table 1).¹³ The results showed similar accuracy of eGFR values based either on cystatin C or creatinine-based eGFR (P₃₀ values of 85% and 79% for eGFR_{cys} and eGFR_{cr}, respectively), but higher accuracy of eGFR_{cr-cys} (P₃₀ of 90%). The improvement in accuracy was due to improved precision of eGFR_{cr-cys} vs. eGFR_{cr} or eGFR_{cys}. The 2008 CKD-EPI cystatin C equations were re-expressed for use with standardized serum cystatin C assays in 2011 (Table 1).¹⁴

The 2012 CKD-EPI cystatin C equation and the 2012 CKD-EPI creatinine–cystatin C equation were developed and evaluated in a diverse population, consisting of a subset of the 2009 CKD-EPI creatinine equation development and validation dataset in which samples were available for measurement of serum cystatin C (Table 1).¹⁵ Studies that involved

kidney transplant recipients were excluded because preliminary analyses indicated considerable variations among them regarding the relationship between serum cystatin C concentrations and mGFR. There are many similarities to the 2009 CKD-EPI creatinine equation, including two coefficients for both serum creatinine and cystatin C (Table 3). Of importance, the coefficient for cystatin C above the knot (-1.328) is similar to that of creatinine, but the coefficients for age and sex are smaller, and the coefficient for African American race was not significant, so this latter variable was not included. By comparison, in the combined creatinine–cystatin C equation, the coefficients for serum creatinine and cystatin C above the knot are approximately half the magnitude of the corresponding coefficients in the separate creatinine and cystatin C equations (-0.601 and -0.711 , respectively), and the age, sex and race coefficients are intermediate between the values of the separate creatinine and cystatin C equations. Diabetes status and weight were considered for inclusion but did not improve equation performance. Evaluation in the validation population showed lesser bias of the 2012 CKD-EPI equations than the 2011 CKD-EPI equations. The results showed similar accuracy of $eGFR_{cys}$ and $eGFR_{cr}$ (P_{30} of 87.2% and 85.9%, respectively), but higher accuracy of $eGFR_{cr-cys}$ (P_{30} of 91.5%) due to improvement in precision rather than bias (Table 4). Of interest, the average of $eGFR_{cr}$ and $eGFR_{cys}$ had similar accuracy as $eGFR_{cr-cys}$ (P_{30} of 91.8%). There were few African Americans in the validation population, but evaluation in subgroups showed uniform higher accuracy of $eGFR_{cr-cys}$ over $eGFR_{cr}$ and $eGFR_{cys}$, with a trend towards higher accuracy of $eGFR_{cys}$ over $eGFR_{cr}$ for subgroups with lower BMI. Evaluation of the 2012 CKD-EPI cystatin C equation in a Japanese population showed that it has less bias than the 2009 CKD-EPI creatinine equation, and does not require modification by a local coefficient.⁵⁰ Studies using other equations have confirmed the findings that $eGFR_{cr-cys}$ is more precise than $eGFR_{cr}$ or $eGFR_{cys}$ and that $eGFR_{cys}$ may not require a local coefficient for racial or ethnic groups.^{37,51–53}

In NHANES, the distribution of $eGFR_{cys}$ is broader and shifted to the right compared to $eGFR_{cr}$; the distribution of $eGFR_{cr-cys}$ is intermediate but more similar to $eGFR_{cr}$. The prevalence of $eGFR < 60$ ml/min/1.73 m² for $eGFR_{cys}$ and $eGFR_{cr-cys}$ are 8.7% and 7.1%, respectively (Figure 2). In CKD-PC, the differences in risk associations between $eGFR_{cys}$ and $eGFR_{cr}$ are striking, with the multivariable-adjusted risk associations of $eGFR_{cr-cys}$ intermediate between the two, but more similar to $eGFR_{cr}$ than $eGFR_{cys}$. The threshold values for higher risk are much higher for $eGFR_{cys}$ and $eGFR_{cr-cys}$ than for $eGFR_{cr}$ (Figure 4). Reclassification among eGFR categories also showed large differences (Figure 5).³² For example, among individuals with $eGFR_{cr}$ of 45–59 ml/min/1.73 m², 31.8% were reclassified to $eGFR_{cr-cys}$ 60–89 ml/min/1.73 m², whereas 11.5% were reclassified to $eGFR_{cr-cys}$ of 30–44 ml/min/1.73 m². Subjects reclassified to higher eGFR category had a 0.67, 0.83 and 0.31 lower adjusted risk for mortality, CVD mortality and kidney failure, respectively, than those not reclassified, whereas subjects reclassified to a lower eGFR category had a 1.64, 1.72 and 2.29 higher risk. Overall NRI favored $eGFR_{cr-cys}$ over $eGFR_{cr}$ for all-cause and cardiovascular mortality. Results were generally similar among African Americans and whites.

Recommendations

There has been controversy about GFR estimation.^{54–56} In response, the KDIGO 2011 clinical update on drug dosing considerations in patients with acute and chronic kidney disease and the KDIGO 2012 clinical practice guidelines for evaluation and management of chronic kidney disease included several recommendations for the evaluation of GFR in all countries.^{7,8} The new guidelines recommended using eGFR based on serum creatinine for initial assessment and eGFR based on serum cystatin C or mGFR for confirmatory testing in particular situations when eGFR based on serum creatinine is not as accurate. For reporting eGFR_{cr} in adults, the new guidelines recommended using the 2009 CKD-EPI creatinine equation or an alternative creatinine-based equation if it has been shown to improve accuracy of GFR estimates compared to this CKD-EPI creatinine equation. For reporting eGFR_{cys} and eGFR_{cr-cys} in adults, the new guidelines recommended using the 2012 CKD-EPI cystatin C equations or another cystatin C–based GFR estimating equation if it has demonstrated improved accuracy of GFR estimates compared to these CKD-EPI cystatin C equations. Important applications for GFR estimation include drug dosing and detection of CKD. The clinical update recommended GFR as the standard measure for evaluating kidney function for CKD staging and drug dosing purposes rather than creatinine clearance and that clinicians should use the most accurate method/tool to evaluate kidney function for each patient rather than relying on estimated creatinine clearance from the Cockcroft-Gault equation. The guidelines recommend measuring cystatin C in adults with eGFR_{cr} of 45–59 ml/min/1.73 m² without markers of kidney damage if CKD confirmation is required. If eGFR_{cr-cys} is also <60 ml/min/1.73 m², the CKD diagnosis is confirmed. If eGFR_{cr-cys} is ≥60 ml/min/1.73 m², the CKD diagnosis is not confirmed.

The clinical update and new guidelines do not provide a comprehensive set of instructions for clinical practice, leaving many important questions left unanswered. How should clinicians interpret pharmacokinetic studies performed with non-calibrated serum creatinine assays? When should pharmacokinetic studies be repeated using state-of-the-art methods? When should clinicians suspect that eGFR_{cr} is inaccurate? In these circumstances, is eGFR_{cys} or eGFR_{cr-cys} more accurate than eGFR_{cr}? When is it preferable to measure GFR using clearance of an exogenous filtration marker rather than estimate it from serum levels of endogenous filtration markers? Available data are not able to answer these questions at the present time, but we expect that new studies will help refine these recommendations.

Summary and Future Directions

The 1999 and 2006 MDRD Study equations have been successfully implemented for eGFR reporting on a large scale in whites and blacks in North America, Europe and Australia. They can be used for estimating mGFR, detection of CKD, drug dosing and estimating prognosis. The 2009 CKD-EPI creatinine equation is more accurate than the MDRD Study equation for GFR estimation and risk prediction and provides lower prevalence estimates for decreased eGFR. It has replaced the MDRD Study equation for GFR reporting in France and Australia and by the two largest clinical laboratory service providers in the United States, Quest and LabCorp, and should be reported by all clinical laboratories worldwide. It should also be the standard for comparison for new creatinine equations developed for other races

and other regions. Limitations include imprecision, requirement for specification of race, and bias in conditions with low muscle mass.

The 2012 CKD-EPI cystatin C equation has similar accuracy as the 2009 CKD-EPI creatinine equation and does not require specification of race. It may also be more accurate in people with low BMI and should be evaluated in conditions associated with low muscle mass. The 2012 CKD-EPI creatinine–cystatin C equation is more precise than equations using only creatinine or cystatin C. It may be useful for confirmation of $\text{eGFR}_{\text{Cr}} < 60 \text{ ml/min/1.73 m}^2$. Both equations are more accurate for risk prediction than the 2009 CKD-EPI creatinine equation. They should be evaluated in African Americans and outside North America and Europe, and should be the standards for comparison to new equations using cystatin C. Limitations include poor understanding of non-GFR determinants of cystatin C, lesser accuracy in transplant recipients, and incomplete study of strategies for diagnostic testing.

In conclusion, the development and validation of GFR estimating equations is based on principles of physiology, laboratory medicine, epidemiology and biostatistics. They are useful in clinical practice, research and public health. No single equation will be optimal for all populations. Equations developed in diverse populations are less biased than equations developed in CKD populations at higher GFR and are more appropriate for general use. Equations that use both creatinine and cystatin C are more precise than equations that use either marker alone, and it is likely that equations using multiple endogenous filtration markers can be even more precise. The CKD-EPI equations are the most accurate GFR estimating equations that have been evaluated in large, diverse populations at this time. They can be reported routinely by clinical laboratories, and they are applicable for general clinical use worldwide. Improvement in GFR estimation in special populations will require better understanding of non-GFR determinants of endogenous filtration markers and use of alternative endogenous filtration markers without systematic bias in the population. Improvement in GFR estimating equations for general use will require development in more broadly representative populations including diverse racial and ethnic groups, use of multiple filtration markers, analytic methods to down-weight the contribution of deviant markers, and evaluation using statistical techniques to compare eGFR to “true GFR”. Improvement in application of GFR estimates in clinical practice will require better understanding of usual levels of GFR in representative populations and non-GFR determinants of endogenous filtration markers, as well as development of strategies for diagnostic testing using “first” and “confirmatory” tests for decreased GFR.

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References

1. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med*. 2006; 354(23):2473–2483. [PubMed: 16760447]
2. Smith, HW. *The Kidney: Structure and Function in Health and Disease*. New York, NY: Oxford University Press; 1951. p. viiForeword
3. Steindel SJ, Rauch WJ, Simon MK, Handsfield J. National Inventory of Clinical Laboratory Testing Services (NICLTS). Development and test distribution for 1996. *Arch Pathol Lab Med*. 2000; 124(8):1201–1208. [PubMed: 10923084]
4. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis*. 2010; 55(4):622–627. [PubMed: 20338463]
5. College of American Pathologists. [Accessed October 8, 2013.] Current Status Of Reporting Estimated Glomerular Filtration Rate (eGFR). 2012. http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtl_t&cntvwrPtl_t%7BactionForm.contentReference%7D=committees%2Fchemistry%2Fchemistry_resources.html&_state=maximized&_pageLabel=cntvwr
6. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39(2 Suppl 1):S1–266. [PubMed: 11904577]
7. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011; 80(11):1122–1137. [PubMed: 21918498]
8. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter, Suppl*. 2013; 3(1):1–150.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999; 130(6):461–470. [PubMed: 10075613]
10. Levey AS, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract A0828]. *J Am Soc Nephrol*. 2000; 11:155A.
11. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006; 145(4):247–254. [PubMed: 16908915]
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150(9):604–612. [PubMed: 19414839]
13. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008; 51(3):395–406. [PubMed: 18295055]
14. Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Cystatin C Equations for Estimating GFR With Standardized Serum Cystatin C Values. *Am J Kidney Dis*. 2011; 58(4):682–684. [PubMed: 21855190]
15. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012; 367(1):20–29. [PubMed: 22762315]
16. Hall, JE.; Guyton, AC. *Guyton and Hall textbook of medical physiology*. 12. Philadelphia, PA: Saunders/Elsevier; 2011. p. 303-322.
17. Wesson, L. *Physiology of the Human Kidney*. New York: Grune & Stratton; 1969. p. 96-108.
18. Jafar TH, Islam M, Jessani S, et al. Level and Determinants of Kidney Function in a South Asian Population in Pakistan. *Am J Kidney Dis*. 2011; 58(5):764–772. [PubMed: 21840098]
19. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem*. 2006; 52(1):5–18. [PubMed: 16332993]

20. Grubb A, Blirup-Jensen S, Lindstrom V, Schmidt C, Althaus H, Zegers I. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010; 48(11): 1619–1621. [PubMed: 21034257]
21. Blirup-Jensen S, Grubb A, Lindstrom V, Schmidt C, Althaus H. Standardization of Cystatin C: development of primary and secondary reference preparations. *Scand J Clin Lab Invest Suppl*. 2008; 241:67–70. [PubMed: 18569968]
22. Smith, HW. *The Kidney: Structure and Function in Health and Disease*. New York, NY: Oxford University Press; 1951. Measurement of the Filtration Rate; p. 39-62.
23. Sapirstein LA, Vidt DG, Mandel MJ, Hanusek G. Volumes of distribution and clearances of intravenously injected creatinine in the dog. *Am J Physiol*. 1955; 181(2):330–336. [PubMed: 14376619]
24. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol*. 2009; 20(11):2305–2313. [PubMed: 19833901]
25. Stevens LA, Zhang Y, Schmid CH. Evaluating the performance of equations for estimating glomerular filtration rate. *J Nephrol*. 2008; 21(6):797–807. [PubMed: 19034863]
26. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011; 80(1):17–28. [PubMed: 21150873]
27. Stevens LA, Coresh J, Feldman HI, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol*. 2007; 18(10):2749–2757. [PubMed: 17855641]
28. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16(1):31–41. [PubMed: 1244564]
29. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kidney Dis*. 2009; 54(1):33–42. [PubMed: 19446939]
30. Grams ME, Juraschek SP, Selvin E, et al. Trends in the prevalence of reduced GFR in the United States: a comparison of creatinine- and cystatin C-based estimates. *Am J Kidney Dis*. 2013; 62(2): 253–260. [PubMed: 23619125]
31. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012; 307(18):1941–1951. [PubMed: 22570462]
32. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013; 369(10):932–943. [PubMed: 24004120]
33. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007; 53(4):766–772. [PubMed: 17332152]
34. Stevens LA, Schmid CH, Zhang YL, et al. Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant*. 2010; 25(2):449–457. [PubMed: 19793928]
35. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med*. 2012; 156(11): 785–795. [PubMed: 22312131]
36. Kilbride HS, Stevens PE, Eaglestone G, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. *Am J Kidney Dis*. 2013; 61(1):57–66. [PubMed: 22889713]
37. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med*. 2012; 157(7):471–481. [PubMed: 23027318]
38. Inker L, Fan L, Okparavero A, et al. Comparing Cystatin C and Creatinine for Estimating Measured GFR and CKD Prevalence in a Community-Based Sample of the Elderly [Abstract TH-PO267]. *J Am Soc Nephrol*. 2013; 24:164A.
39. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for

- estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis.* 2010; 55(4):648–659. [PubMed: 20189275]
40. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis.* 2010; 55(4):660–670. [PubMed: 20138414]
 41. Stevens LA, Li S, Kurella Tamura M, et al. Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study Equations: Risk Factors for and Complications of CKD and Mortality in the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis.* 2011; 57(3):S9–S16. [PubMed: 21338849]
 42. Kitiyakara C, Yamwong S, Vathesatogkit P, et al. The impact of different GFR estimating equations on the prevalence of CKD and risk groups in a Southeast Asian cohort using the new KDIGO guidelines. *BMC Nephrol.* 2012; 13:1. [PubMed: 22226403]
 43. Arora P, Rajagopalan S, Patel N, Nainani N, Venuto RC, Lohr JW. The MDRD equation underestimates the prevalence of CKD among blacks and overestimates the prevalence of CKD among whites compared to the CKD-EPI equation: a retrospective cohort study. *BMC Nephrol.* 2012; 13:4. [PubMed: 22264268]
 44. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. *Am Heart J.* 2011; 162(3):548–554. [PubMed: 21884875]
 45. Corsonello A, Pedone C, Lattanzio F, et al. Agreement between equations estimating glomerular filtration rate in elderly nursing home residents and in hospitalised patients: implications for drug dosing. *Age and ageing.* 2011; 40(5):583–589. [PubMed: 21398293]
 46. Pugliese G, Solini A, Bonora E, et al. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provides a better definition of cardiovascular burden associated with CKD than the Modification of Diet in Renal Disease (MDRD) Study formula in subjects with type 2 diabetes. *Atherosclerosis.* 2011; 218(1):194–199. [PubMed: 21612781]
 47. Shafi T, Matsushita K, Selvin E, et al. Comparing the association of GFR estimated by the CKD-EPI and MDRD study equations and mortality: the third national health and nutrition examination survey (NHANES III). *BMC Nephrol.* 2012; 13:42. [PubMed: 22702805]
 48. Tomaszuk-Kazberuk A, Kozuch M, Malyszko J, Bachorzewska-Gajewska H, Dobrzycki S, Musial WJ. Which method of GFR estimation has the best prognostic value in patients treated with primary PCI: Cockcroft-Gault formula, MDRD, or CKD-EPI equation?--A 6-year follow-up. *Ren Fail.* 2011; 33(10):983–989. [PubMed: 22013931]
 49. AlFaleh HF, Alsuwaida AO, Ullah A, et al. Glomerular filtration rate estimated by the CKD-EPI formula is a powerful predictor of in-hospital adverse clinical outcomes after an acute coronary syndrome. *Angiology.* 2012; 63(2):119–126. [PubMed: 21602255]
 50. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. GFR estimation using standardized serum cystatin C in Japan. *Am J Kidney Dis.* 2013; 61(2):197–203. [PubMed: 22892396]
 51. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. *Kidney Int.* 2006; 69(2):399–405. [PubMed: 16408133]
 52. Ma YC, Zuo L, Chen JH, et al. Improved GFR estimation by combined creatinine and cystatin C measurements. *Kidney Int.* 2007; 72(12):1535–1542. [PubMed: 17898698]
 53. Teo BW, Xu H, Koh YY, et al. Estimating kidney function in a multiethnic Asian population with multiple filtration markers. *Am J Kidney Dis.* 2012; 60(3):500–502. [PubMed: 22721932]
 54. Rainey PM. Automatic reporting of estimated glomerular filtration rate--jumping the gun? *Clin Chem.* 2006; 52(12):2184–2187. [PubMed: 17068169]
 55. Glasscock RJ. Estimated glomerular filtration rate: time for a performance review? *Kidney Int.* 2009; 75(10):1001–1003. [PubMed: 19404279]
 56. Rule AD. The CKD-EPI equation for estimating GFR from serum creatinine: real improvement or more of the same? *Clin J Am Soc Nephrol.* 2010; 5(6):951–953. [PubMed: 20448068]

Figure 1. Clearance and GFR

A. Clearance (Cl, ml/min) is defined as the amount (A) of solute removed from the plasma per unit of time (mg/min) divided by the average plasma concentration (P, mg/ml) during the interval of observation and can be conceptualized as the virtual volume of plasma “cleared” of a solute per unit time.²² Plasma clearance (Cl_P , ml/min) is the sum of clearance by all mechanisms, generally categorized as renal (urinary, Cl_U , ml/min) and extra-renal (Cl_E , ml/min) clearance (for example, gut and biliary elimination). Plasma clearance can be computed from the amount of the marker administered (mg) divided by the area under the plasma disappearance curve [(mg/ml)*min], assuming a two-compartment model²³, and does not require knowledge of A, U or E. If plasma clearance of the marker exceeds its urinary clearance, it can be inferred that the marker undergoes extra-renal elimination. **B.** Relationship of Urinary Clearance of Exogenous Filtration Markers to Clearance. Urinary excretion (UV, mg/min) is the sum of the filtered load (the product of GFR times the plasma concentration times the sieving coefficient) plus tubular secretion (TS, mg/min) minus tubular reabsorption (TR, mg/min). Urinary clearance (Cl_U) is measured as the amount of the marker excreted in the urine (UV) per unit time divided by the plasma concentration (P) of the marker during the urine collection period. For an “ideal” filtration marker, tubular secretion and tubular reabsorption are zero, hence urinary clearance

equals GFR. For a marker whose mechanism of excretion is unknown, the comparison of urinary clearance to GFR enables inference about its renal handling. For example, if urinary clearance of the marker is less than GFR, it can be inferred that the marker is not freely filtered or is reabsorbed by the tubule. Conversely, if urinary clearance of the marker is greater than GFR, it can be inferred that the marker is secreted by the tubule. **C. Relationship of Plasma Level of Endogenous Filtration Markers to GFR.** In the steady state, a constant plasma concentration (P , mg/min) of the filtration marker is maintained because generation (G , mg/min) is equal to the sum of urinary excretion (UV , mg/min) and extrarenal elimination (E , mg/min). Thus GFR is related to the reciprocal of the plasma concentration of the marker (P), but it is also influenced by its non-GFR determinants [generation (G), tubular secretion (TS), tubular reabsorption (TR) and extra-renal elimination (E)]. If the non-GFR determinants are known, the GFR can be estimated from the plasma concentration. In the nonsteady state, the rate and direction of change in the level of the filtration marker and estimated GFR (eGFR) are also affected by the magnitude of change in GFR and the volume of distribution of the filtration marker. Hence, the eGFR reflects the magnitude and direction of the change in GFR but does not accurately reflect the level of GFR. After a fall in GFR, the decline in eGFR is less than the decline in GFR, and eGFR thus exceeds GFR. Conversely, after a rise in GFR, the rise in eGFR is less than the rise in GFR, and eGFR is thus less than GFR. As the plasma level approaches the new steady state, the eGFR approaches the GFR, allowing more accurate estimation of GFR.

For more information, see Stevens and Levey.²⁴

Figure 2. Distribution of eGFR and Prevalence of eGFR <60 ml/min/1.73 m² in NHANES 1999–2002

Data comprise 8238 adults in whom serum creatinine and cystatin C were assayed. eGFR computed using 2006 MDRD Study equation, 2009 CKD-EPI creatinine equation, 2012 CKD-EPI cystatin C equation; and 2012 CKD-EPI creatinine–cystatin C equation. Prevalence estimates include 95% confidence intervals. Abbreviations: MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Survey. Data from Grams et al.³⁰

Figure 3. Prognosis of eGFR as a Continuous Variable using the (A–C) 2009 CKD-EPI Creatinine Equation and the 2006 MDRD Study Equation and (D–F) the 2009 CKD-EPI Creatinine Equation, 2012 CKD-EPI Cystatin C Equation and 2012 CKD-EPI Creatinine–Cystatin C Equation in General Population Cohorts

The graphs show associations by plotting the adjusted hazard ratio (HR) versus the reference points, which are indicated by black diamonds (at 95 ml/min/1.73 m² for death from any cause and death from cardiovascular causes and at 65 ml/min/1.73 m² for end-stage renal disease). The hazard ratios were calculated using eGFR splines and adjusted for age, sex, race, body-mass index, systolic blood pressure, total cholesterol, presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes (all panels), and level of albuminuria (panel D–F only). In each panel, solid circles indicate that the adjusted hazard ratio at the indicated eGFR level was significant, as compared with the reference point. Thresholds indicate the eGFR below which the risk is significantly higher than the reference point ($p < 0.05$). Statistical significance could not be computed for the threshold for Panel F because the threshold was contained within the spline segment including the reference point. Panels A–C adapted and reproduced from Matsushita et al.³¹ with permission of the American Medical Association; panels D–F adapted and reproduced with permission from the Massachusetts Medical Society from Shlipak et al.³² (©2013 Massachusetts Medical Society)..

Figure 4. Prognosis of eGFR Categories using the 2009 CKD-EPI Creatinine Equation vs. the 2006 MDRD Study Equation

Left panel: cross-classification by eGFR categories using both equations; right panel: adjusted hazard ratios (HR) for reclassification using the CKD-EPI creatinine equation. Data are from general population cohorts (940,366 participants in 25 cohorts). In left panel, blue segments indicate the proportion of participants reclassified to a higher eGFR category; red segments indicate the proportion reclassification to a lower eGFR category; yellow segments indicate the proportion not reclassified. In the right panel, HR for all-cause mortality, cardiovascular (CV) mortality, and end-stage renal disease (ESRD) compares participants reclassified to a higher eGFR (blue font) and lower eGFR (red font) to participants not reclassified (reference). HR in bold are statistically significant ($p < 0.05$). HR adjusted for age, sex, race, body-mass index, systolic blood pressure, total cholesterol, presence or absence of a history of cardiovascular disease, smoking status, and presence or absence of diabetes. Net reclassification improvement (NRI) for all-cause mortality (ACM), CV mortality (CVM) and end-stage renal disease (ESRD) from 1.1 million participants (940 366 from 25 general population cohorts, 151 494 from 7 high-risk cohorts, and 38 612 from 13 CKD cohorts). Data from Matsushita et al.³¹

Figure 5. Prognosis of eGFR Categories using the 2009 CKD-EPI Creatinine Equation vs. the 2012 CKD-EPI Creatinine-Cystatin C Equation

Left panel: cross-classification by eGFR categories using both equations; right panel: adjusted hazard ratios (HR) for reclassification using the CKD-EPI creatinine-cystatin C (Cr-Cys) equation. Data are from general population cohorts (90,750 participants in 11 cohorts). In left panel, blue segments indicate the proportion of participants reclassified to a higher eGFR category; red segments indicate the proportion reclassification to a lower eGFR category; yellow segments indicate the proportion not reclassified. In the right panel, HR for all-cause mortality, cardiovascular (CV) mortality, and end-stage renal disease (ESRD) compares participants reclassified to a higher eGFR (blue font) and lower eGFR (red font) to participants not reclassified (reference). HR in bold are statistically significant ($p < 0.05$). HRs adjusted for age, sex, race, body-mass index, systolic blood pressure, total cholesterol, presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes, and level of albuminuria. Net reclassification improvement (NRI) for all-cause mortality (ACM), cardiovascular mortality (CVM) and end-stage renal disease (ESRD) from 93,710 participants (90,750 in 11 general population cohorts and 2960 in 5 CKD cohorts). Data from Shlipak et al.³²

Table 1

GFR Estimating Equations Developed by the MDRD Study Group and CKD-EPI

Filtration Marker; Notation	Group; Year	Development Population			Equation	Advantages	Study Reference
		Characteristics	GFR Measurement Method	Filtration Marker Assay			
Creatinine; eGFR _{cr}	MDRD Study; 1999	N = 1628 with CKD; mean mGFR = 40	Urinary clearance of iothalamate	Nonstandardized	6-variable MDRD Study equation and 4-variable MDRD Study equation	4-variable recommended by 2002 NKF-KDOQI ⁶ ; Useful for reporting eGFR <60	6-variable: Levey et al ⁹ (<i>Annals</i> , 1999); 4-variable: Levey et al ¹⁰ (<i>JASN</i> abstract, 2000)
	MDRD Study; 2006	Same as above	Same as above	Standardized	IDMS-traceable 4-variable MDRD Study equation	Re-expressed for use with standardized assays	Levey et al ¹¹ (<i>Annals</i> , 2006)
	CKD-EPI; 2009	Diverse population, N = 8254; mean mGFR = 68	Urinary clearance of iothalamate	Standardized	2009 CKD-EPI creatinine equation*	Lesser bias at eGFR >60; Recommended by 2012 KDIGO ⁸ ; Useful for reporting eGFR throughout the range	Levey et al ¹² (<i>Annals</i> , 2009)
Cystatin C; eGFR _{cys}	CKD-EPI; 2008	N = 2980 with CKD; mean mGFR = 48	Urinary clearance of iothalamate	Nonstandardized	2008 CKD-EPI cystatin C equation	eGFR _{cys} as accurate as eGFR _{cr}	Stevens et al ¹³ (<i>AJKD</i> , 2008)
	CKD-EPI; 2011	Same as above	Same as above	Standardized	2011 CKD-EPI cystatin C equation	Re-expressed for use with standardized assays	Inker et al ¹⁴ (<i>AJKD</i> , 2011)
	CKD-EPI; 2012	Diverse population, N = 5352; mean mGFR = 68	Urinary clearance of iothalamate	Standardized	2012 CKD-EPI cystatin C equation*	Lesser bias at eGFR >60; as accurate as eGFR _{cr} without requiring specification of race and may be more accurate if muscle mass is decreased	Inker et al ¹⁵ (<i>NEJM</i> , 2012)
Creatinine and Cystatin C; eGFR _{cr-cys}	CKD-EPI; 2008	N = 2980 with CKD; mean mGFR = 48	Urinary clearance of iothalamate	Standardized creatinine; nonstandardized cystatin C	2008 CKD-EPI creatinine–	eGFR _{cr-cys} more precise than	Stevens et al ¹³ (<i>AJKD</i> , 2008)

Filtration Marker; Notation	Group; Year	Development Population			Equation	Advantages	Study Reference
		Characteristics	GFR Measurement Method	Filtration Marker Assay			
	CKD-EPI; 2011	Same as above	Same as above	Standardized creatinine and cystatin C	2011 CKD-EPI creatinine-cystatin C equation	Re-expressed for use with standardized assays	Inker et al ¹⁴ (<i>AJKD</i> , 2011)
	CKD-EPI; 2012	Diverse population, N = 5352; mean mGFR = 68	Urinary clearance of iothalamate	Standardized creatinine and cystatin C	2012 CKD-EPI creatinine-cystatin C equation *	Recommended by 2012 KDIGO ⁸ as a confirmatory test	Inker et al ¹⁵ (<i>NEJM</i> , 2012)

* preferred equations as discussed in⁸

Note: GFRs given in mL/min/1.73 m².

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; NKf, National Kidney Foundation; eGFR, estimated glomerular filtration rate; eGFR_{cr}, serum creatinine-based eGFR; eGFR_{cys}, cystatin C-based eGFR; eGFR_{cr-cys}, serum creatinine and cystatin C-based eGFR; IDMS, isotope-dilution mass spectrometry

Table 2
Comparison of properties of creatinine and cystatin C as endogenous filtration markers

Variable	Creatinine	Cystatin C
Molecular Properties		
Weight	113 Da	13,300 Da
Structure	Amino acid derivative	Nonglycosylated basic protein
Physiological Determinants of Serum Level		
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women and whites	Thought to be mostly constant by all nucleated cells; increases in hyperthyroid states and with steroid use; lower in elderly persons and women
Handling by the kidney	Filtered, secreted and excreted in the urine	Filtered, reabsorbed and catabolized
Extrarenal elimination	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR
Use in GFR Estimating Equations		
Demographic and clinical variables as surrogates for physiological determinants	Age, sex, and race; related to muscle mass	Age and sex
Factors associated with inaccurate estimates	Nonsteady state; GFR >60 ml/min/1.73 m ² ; conditions associated with alterations in muscle mass, drugs that inhibit tubular secretion, interferents with serum assays	Nonsteady state; GFR >60 ml/min/1.73 m ² ; conditions associated with alterations in thyroid or steroid hormones, possibly obesity
Assay		
Method	Colorimetric and enzymatic	Immunoassays
Assay precision	Very good except at low range	Precision varies across assays
Clinical laboratory practice	Multiple assays; widely used; widely standardized	Not on most auto-analyzers; becoming standardized
Standardized reference materials	SRM 967	ERM-DA471/IFCC
Reference assay	IDMS	PENIA, PETIA, enzyme-amplified single radial immunodiffusion

Abbreviations: GFR, glomerular filtration rate; SRM, standard reference material; ERM, European Reference Materials; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; IDMS, isotope-dilution mass spectrometry; PENIA, particle-enhanced nephelometric immunoassay; PETIA, particle-enhanced turbidimetric immunoassay

Table 3

Coefficients for Variables in the MDRD Study and CKD-EPI Equations

Variable	MDRD Study Equation ^{10,11}		CKD-EPI Equations			
	SCr	SCr ¹²	SCysC ¹⁵	SCr and SCysC ¹⁵		
Year	2006	2009	2012	2012	2012	
SCr, when >0.9 mg/dl for men and 0.7 mg/dl for women	SCr ^{-1.154}	SCr ^{-1.209}	-	-	SCr ^{-0.601}	
SCr, when ≤0.9 mg/dl for men and 0.7 mg/dl for women	-	SCr ^{-0.329} if female; SCr ^{-0.411} if male	-	-	SCr ^{-0.248} if female; SCr ^{-0.247} if male	
SCysC, when >0.8 mg/dl	-	-	SCysC ^{-1.328}	SCysC ^{-0.711}		
SCysC, when ≤0.8 mg/dl	-	-	SCysC ^{-0.499}	SCysC ^{-0.375}		
Age	Age ^{-0.203}	0.993 ^{Age}	0.996 ^{Age}	0.995 ^{Age}		
Female Sex	0.742	1.018	0.932	0.969		
Black Race	1.212	1.159	-	1.08		

Note: For the MDRD Study, the coefficient of -1.154 for the exponent of SCr indicates that eGFR is 1.154% lower for each 1% higher SCr. For any value of SCr, older age and female sex are associated with lower eGFR_{cr} and African American race is associated with higher eGFR_{cr}. For the CKD-EPI equations, creatinine is modeled as a two-slope spline with sex-specific knots; SCysC is modeled as a two-slope spline with the same knot for both sexes. The slopes are less steep above than below the knots. Because of the sex specific knots for the creatinine coefficients, the sex coefficients in the CKD-EPI creatinine and SCr-SCysC equations are not comparable to MDRD Study and CKD-EPI SCysC equations. The corresponding sex coefficients for the CKD-EPI SCr and SCr-SCysC equations would be 0.75 and 0.83 for SCr values 0.9 mg/dl, respectively. Conversion factor for SCr in mg/dL to μmol/L, ×88.4.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; eGFR_{cr}, serum creatinine-based eGFR; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; SCysC, serum cystatin C;

Table 4

Comparisons of Equation Performance

Study Reference	Validation Population		Equation	Bias [#] (ml/min/1.73 m ²)	P ₃₀ (%)
	Characteristics	GFR Measurement Method			
Stevens et al ²⁷ (<i>JASN</i> , 2007)	Diverse population; N = 5504; mGFR = 68	Urinary clearance of iothalamate	eCCr by Cockcroft-Gault 1976 ^{†28}	11.4	69
			eGFR _{cr} by 2006 MDRD Study	5.8*	83*
Levey et al ¹² (<i>Annals</i> , 2009)	Diverse population; N = 3896; mGFR = 68	Urinary clearance of iothalamate or EDTA, plasma clearance of iothexol	eGFR _{cr} by 2006 MDRD Study [†]	5.5	80.6
			eGFR _{cr} by 2009 CKD-EPI	2.5*	84.1*
Inker et al ¹⁵ (<i>NEJM</i> , 2012)	Diverse population; N = 1119; mGFR = 70	Urinary clearance of EDTA, plasma clearance of iothexol	eGFR _{cr} by 2009 CKD-EPI [†]	3.7	87.2
			eGFR _{cys} by 2012 CKD-EPI	3.4	85.9
			eGFR _{cr-cys} by 2012 CKD-EPI	3.9	91.5*
			Average of eGFR _{cr} and eGFR _{cys} by 2012 CKD-EPI	3.5	91.8*

Abbreviations: GFR, glomerular filtration rate (given in mL/min/1.73 m²); mGFR, measured GFR; eCCr, estimated creatinine clearance; eGFR, estimated GFR; P₃₀, percent of eGFR with $\pm 30\%$ of mGFR.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR_{cr}, serum creatinine-based eGFR; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; SCysC, serum cystatin C; eGFR_{cys}, cystatin C-based eGFR; eGFR_{cr-cys}, serum creatinine and cystatin C-based eGFR; EDTA, ethylenediaminetetraacetic acid

[#] mGFR – eGFR.

[†] reference equation for the study;

* P < 0.05 compared to reference equation

Table 5
Comparison of Concordance of Drug Dosing Recommendations between eGFR and mGFR

Equation	Concordant (%) [*]	Discordant (%)	
		eGFR predicts lower dose than mGFR	eGFR predicts higher dose than mGFR
2009 CKD-EPI	80	9	11
2006 MDRD Study	78	14	8
Cockcroft and Gault	73	12	16
Cockcroft and Gault (IBW)	66	29	5

^{*} p-value <0.001 for the difference in concordance among equations. Concordance defined based on categories suggested by the US Food and Drug Administration for drug dosing adjustment: >80, 50–80, 30–49, or <30 ml/min.

Note: Data from Stevens et al²⁹. Dosing recommendations based on kidney function levels for 15 drugs excreted by the kidney: 2 dosing levels (enoxaparin, eptifibatide, ranitidine); 3 dosing levels (acyclovir, atenolol, cefazolin, digoxin, levofloxacin, tenofovir, tramadol); 4 dosing levels (allopurinol, gabapentin, sotalol); 5 dosing levels (disopyramide, lamivudine).

IBW, computed from ideal body weight. eGFR, estimated glomerular filtration rate; mGFR, measured GFR; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease