

GFR Estimation: From Physiology to Public Health

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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 GFRs than equations developed in chronic kidney disease (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 CKD-EPI (CKD Epidemiology Collaboration) 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 MDRD (Modification of Diet in Renal Disease) 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 GFR, 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 serum creatinine-based eGFR. Further improvement in GFR estimating equations will require 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.” *Am J Kidney Dis.* 63(5):820-834. © 2014 by the National Kidney Foundation, Inc.

INDEX WORDS: Estimated glomerular filtration rate (eGFR); kidney function; GFR estimating equation; filtration marker; renal insufficiency; chronic kidney disease; public health.

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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 criterion for CKD and is

associated with a greater risk of fatal and nonfatal outcomes. More than 60 years ago, Homer Smith² 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 textbook:

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 in only major medical centers. In routine clinical practice, GFR is estimated from serum concentrations of endogenous filtration markers. Serum creatinine is measured more than 280 million times per year in the United States, and $>85\%$ of clinical laboratories now report an

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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 level. In recent years, a number of new equations have been developed for use with standardized serum creatinine assays and have 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 level. 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

Glomerular Filtration Rate

Glomerular filtration is the physiologic process of creating an ultrafiltrate of blood as it flows through the glomerular capillaries. In principle, GFR is the product of the number of nephrons times the average single-nephron GFR. Determinants of 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 ensured by the large number of glomeruli (1 million per kidney), rich renal blood flow (20% of cardiac output, higher than in other capillary beds), extensive total glomerular capillary surface area (1 m²), 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, mean GFR in healthy young adult white individuals is ~125 mL/min/1.73 m², with a wide range.¹⁷ Indexing GFR to body surface area 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 physiologic and pathologic conditions and varies with 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 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. 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.

Accurate measurement of filtration markers is central to the measurement and estimation of GFR. Inulin is difficult to measure, and alternative exogenous markers have been developed to facilitate clearance measurements. 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

GFR is measured indirectly as the clearance of exogenous filtration markers that are eliminated by the kidney only by glomerular filtration. Clearance can be measured as either plasma or urinary clearance (Fig 1A and B).^{22,23} For a marker that is eliminated from 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

Table 1. GFR Estimating Equations Developed by the MDRD Study Group and CKD-EPI

Endogenous Filtration Marker; Notation	Development Population				Equation	Advantages	Study Reference
	Group; Year	Characteristics	GFR Measurement Method	Endogenous Filtration Marker Assay			
Creatinine; eGFR _{cr}	MDRD Study; 1999	N = 1,628 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)
	<i>CKD-EPI; 2009</i>	<i>Diverse population, N = 8,254; mean mGFR = 68</i>	<i>Urinary clearance of iothalamate</i>	<i>Standardized</i>	<i>2009 CKD-EPI creatinine equation^a</i>	<i>Lesser bias at eGFR > 60; recommended by 2012 KDIGO⁸; useful for reporting eGFR throughout the range</i>	<i>Levey et al¹² (Annals, 2009)</i>
Cystatin C; eGFR _{cys}	CKD-EPI; 2008	N = 2,980 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)
	<i>CKD-EPI; 2012</i>	<i>Diverse population, N = 5,352; mean mGFR = 68</i>	<i>Urinary clearance of iothalamate</i>	<i>Standardized</i>	<i>2012 CKD-EPI cystatin C equation^a</i>	<i>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</i>	<i>Inker et al¹⁵ (NEJM, 2012)</i>
Creatinine and Cystatin C; eGFR _{cr-cys}	CKD-EPI; 2008	N = 2,980 with CKD; mean mGFR = 48	Urinary clearance of iothalamate	Standardized creatinine; nonstandardized cystatin C	2008 CKD-EPI creatinine–cystatin C equation	eGFR _{cr-cys} more precise than eGFR _{cr} or eGFR _{cys}	Stevens et al ¹³ (<i>AJKD</i> , 2008)
	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)
	<i>CKD-EPI; 2012</i>	<i>Diverse population, N = 5,352; mean mGFR = 68</i>	<i>Urinary clearance of iothalamate</i>	<i>Standardized creatinine and cystatin C</i>	<i>2012 CKD-EPI creatinine–cystatin C equation^a</i>	<i>Recommended by 2012 KDIGO⁸ as a confirmatory test</i>	<i>Inker et al¹⁵ (NEJM, 2012)</i>

Note: GFRs given in mL/min/1.73 m².

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

^aItalics indicate preferred equations as discussed in.⁸

Box 1. Filtration Markers

- Substances that are filtered by glomeruli that 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 (5,200 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 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 radioisotope tracer.

Abbreviations: ⁵¹Cr-EDTA, chromium 51 ethylenediaminetetraacetic acid; ^{99m}Tc-DTPA, technetium 99m diethylenetriamine pentaacetic acid; ¹²⁵I, iodine 125; B2M, β_2 -microglobulin; BTP, β -trace protein; GFR, glomerular filtration rate.

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

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 extrarenal elimination (Fig 1C).^{1,24} GFR is related to the reciprocal of the plasma concentration of the marker, but it also is 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 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 urine. A comparison of the properties, physiologic determinants of serum level, applications in GFR estimation, and 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 determinants.¹ By definition, an estimating equation provides a more accurate estimate of mGFR than 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

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 populations 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 generally is greater at higher than lower GFRs. Considering the various sources of error, the 2002 KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines concluded that an eGFR within 30% of an mGFR was satisfactory for clinical interpretation, and as a performance metric for accuracy, the guidelines recommended that >90% of participants in the validation population have 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 eGFRs 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 noncorrelated non-GFR determinants can improve precision by reducing errors due to variation in non-GFR determinants of

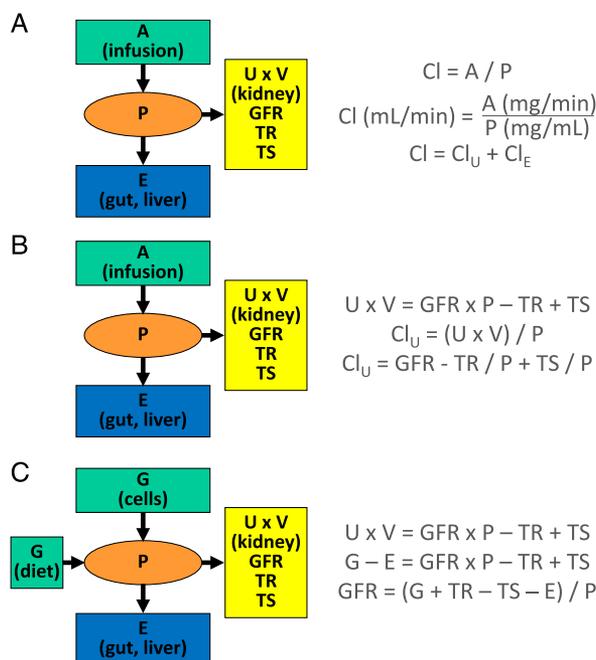


Figure 1. Clearance (Cl) and glomerular filtration rate (GFR). **(A) Definition of Clearance.** Cl (mL/min) is defined as the amount (denoted A) of solute removed from plasma per unit of time (mg/min) divided by average plasma concentration (P; mg/mL) during the interval of observation and can be conceptualized as the virtual volume of plasma “cleared” of a solute per unit time.²² Plasma Cl (Cl_P ; mL/min) is the sum of Cl by all mechanisms, generally categorized as renal (urinary [Cl_U]; mL/min) and extrarenal (Cl_E ; mL/min) Cl (eg, gut and biliary elimination). Cl_P can be computed from the amount of marker administered (mg) divided by the area under the plasma disappearance curve [(mg/mL) × min], assuming a 2-compartment model,²³ and does not require knowledge of A, U, or E. If Cl_P of the marker exceeds its Cl_U , it can be inferred that the marker undergoes extrarenal elimination. **(B) Relationship of Cl_U of exogenous filtration markers to Cl.** Urinary excretion (UV; mg/min) is the sum of the filtered load (the product of GFR × plasma concentration × sieving coefficient) + tubular secretion (TS; mg/min) – tubular reabsorption (TR; mg/min). Cl_U is measured as the amount of marker excreted in urine ($U \times V$) per unit time divided by plasma concentration (P) of the marker during the urine collection period. For an “ideal” filtration marker, TS and TR are zero, hence Cl_U equals GFR. For a marker with an unknown mechanism of excretion, the comparison of Cl_U to GFR enables inference about its renal handling. For example, if Cl_U 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 Cl_U 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/mL) of the filtration marker is maintained because generation (G; mg/min) is equal to the sum of urinary excretion ($U \times V$; mg/min) and extrarenal elimination (E; mg/min). Thus GFR is related to the reciprocal of the plasma concentration of the marker (P), but also is influenced by its non-GFR determinants (generation [G], TS, TR, and extrarenal elimination [E]). If the non-GFR determinants are known, GFR can be estimated from the plasma concentration. In the nonsteady state, the rate and direction of change in level of the filtration marker and estimated GFR (eGFR) also are affected by the magnitude of change in GFR and the volume of distribution of the filtration marker. Hence, eGFR reflects the magnitude and direction of the change in GFR but does not accurately reflect the level of GFR. After a decrease in GFR, the decline in eGFR is less than the decline in GFR and eGFR thus exceeds GFR. Conversely, after an increase in GFR, the increase in eGFR is less than the increase in GFR, and eGFR is thus less than GFR. As the plasma level approaches the new steady state, eGFR approaches GFR, allowing more accurate estimation of GFR. For more information, see Stevens and Levey.²⁴

each marker. New equations that use both creatinine and cystatin C can achieve $P_{30} > 90\%$.

Performance of GFR estimating equations also can 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. However, few population studies have included mGFR, so the accuracy of equations for these purposes 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 also are affected by differences among 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

Table 2. Comparison of Properties of Creatinine and Cystatin C as Endogenous Filtration Markers

Variable	Creatinine	Cystatin C
<u>Molecular Properties</u>		
Weight	113 Da	13,300 Da
Structure	Amino acid derivative	Nonglycosylated basic protein
<u>Physiologic Determinants of Serum Level</u>		
Generation	Varies according to muscle mass and dietary protein; lower in elderly persons, women, and whites	Made by all nucleated cells; thought to be mostly constant; increases in hyperthyroid states and with steroid use; lower in elderly persons and women
Handling by the kidney	Filtered, secreted, and excreted in urine	Filtered, reabsorbed, and catabolized
Extrarenal elimination	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR
<u>Use in GFR Estimating Equations</u>		
Demographic and clinical variables as surrogates for physiologic 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
<u>Assay</u>		
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 autoanalyzers; becoming standardized
Standardized reference materials	SRM 967	ERM-DA471/IFCC
Reference assay	IDMS	PENIA, PETIA, enzyme-amplified single radial immunodiffusion

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

only one class of prognostic markers in kidney disease. Other markers may be associated with prognosis without being correlated strongly with mGFR, indicating a non-GFR mechanism for the association, such as markers of kidney damage (eg, urinary albumin). 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; Fig 2),³⁰ and risk associations in studies by the CKD Prognosis Consortium (CKD-PC; Figs 3-5).^{31,32} For comparisons in estimating the mGFR, we focus on

bias and accuracy (P₃₀). 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 because 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 individuals within the eGFR category of 45-59 mL/min/1.73 m² because reclassification to higher eGFRs 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 GFR was measured

Box 2. Development and Validation of GFR Estimating Equations

- Separate data sets for development and validation populations
 - ◊ But similar methods for all other considerations below
- Study populations with a wide range of clinical characteristics and GFRs, 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”

Abbreviations: GFR, glomerular filtration rate; mGFR, measured glomerular filtration rate.

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 level, 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 isotope-dilution mass spectrometry-traceable 4-variable MDRD Study equation¹¹; Tables 1 and 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 data sets from diverse studies including individuals with and without

kidney disease and with diabetes, organ transplant recipients, and potential donors. 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 to the Cockcroft-Gault equation²⁸ (P_{30} of 83% vs 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 2 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 above the knots, for women, for whites and other races, and for age younger than approximately 70 years. Evaluation in the validation population showed 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%; Table 4) and drug dosage adjustment (concordance with mGFR, 80% vs 78%; 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 individuals in North America, Europe, and Australia, P_{30} ranged from 59%-95%. P_{30} was higher for the CKD-EPI equation than for 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 for the MDRD Study equation at higher eGFRs, but larger at lower eGFRs; differences on the raw scale were larger at higher eGFRs and smaller and not clinically meaningful at lower eGFRs. The performance of both equations was not as good in regions outside North America, Europe, and Australia, presumably reflecting differences in creatinine generation due to racial, ethnic, and regional variations in muscle mass and

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
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 2-slope spline with sex-specific knots; SCysC is modeled as a 2-slope spline with the same knot for both sexes. The slopes are more 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 creatinine-cystatin C equations are not comparable to MDRD Study and CKD-EPI cystatin C equations. The corresponding sex coefficients for the CKD-EPI creatinine and creatinine-cystatin C 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.

Abbreviations: 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.

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 performance of the CKD-EPI equation appears

Table 4. Comparisons of Equation Performance

Validation Population						
Study Reference	Characteristics	GFR Measurement Method	Endogenous Filtration Marker Assays	Equation	Bias ^a (mL/min/1.73 m ²)	P ₃₀ (%)
Stevens et al ²⁷ (JASN, 2007)	Diverse population, N = 5,504; mean mGFR = 68	Urinary clearance of iothalamate	Standardized	eCiCr by Cockcroft-Gault 1976 ^{28,b} eGFR _{cr} by 2006 MDRD Study	11.4 5.8 ^c	69 83 ^c
Levey et al ¹² (Annals, 2009)	Diverse population; N = 3,771; mean mGFR = 68	Urinary clearance of iothalamate or EDTA, plasma clearance of iohexol	Standardized	eGFR _{cr} by 2006 MDRD Study ^b eGFR _{cr} by 2009 CKD-EPI	5.5 2.5 ^c	80.6 84.1 ^c
Inker et al ¹⁵ (NEJM, 2012)	Diverse population; N = 1,119; mean mGFR = 70	Urinary clearance of EDTA, plasma clearance of iohexol	Standardized	eGFR _{cr} by 2009 CKD-EPI ^b eGFR _{cys} by 2012 CKD-EPI eGFR _{cr-cys} by 2012 CKD-EPI Average of eGFR _{cr} and eGFR _{cys} by 2012 CKD-EPI	3.7 3.4 3.9 3.5	87.2 85.9 91.5 ^c 91.8 ^c

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eCiCr, estimated creatinine clearance; EDTA, ethylenediaminetetraacetic acid; eGFR, estimated GFR; eGFR_{cr}, serum creatinine-based eGFR; eGFR_{cr-cys}, serum creatinine and cystatin C-based eGFR; eGFR_{cys}, cystatin C-based eGFR; GFR, glomerular filtration rate (given in mL/min/1.73 m²); MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR; P₃₀, percent of eGFR within ±30% of mGFR.

^amGFR-eGFR.

^bReference equation for the study.

^cP < 0.05 compared to reference equation.

Table 5. Comparison of Concordance of Drug Dosing Recommendations Between eGFR and mGFR

Equation	Concordant (%) ^a	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-Gault	73	12	16
Cockcroft-Gault (IBW)	66	29	5

Note: Data from Stevens et al.²⁹ 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).

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

^aP < 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.

comparable in older individuals to that previously reported in younger individuals 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 right 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%; Fig 2).³⁰ In CKD-PC, there are substantial differences in multivariable-adjusted risk associations, with higher eGFR risk thresholds using the CKD-EPI creatinine versus the MDRD Study equation (Fig 3).³¹ Reclassification among eGFR categories shows more substantial differences between equations (Fig 4).³¹ For example, in individuals 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 0.80, 0.73, and 0.49 lower adjusted risks for mortality, cardiovascular disease mortality, and kidney failure, respectively, than those not reclassified, whereas individuals reclassified to a lower eGFR category had 1.15, 1.25, and 2.67 higher risks, respectively. Overall net reclassification improvement favored the CKD-EPI creatinine equation over the MDRD Study equation for the 3 outcomes. Results generally were 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 level on GFR estimation in CKD populations prior to standardization of the cystatin C assay (Table 1).¹³ The results showed similar accuracy of eGFR values based either on cystatin C or creatinine (P₃₀ of 79% and 84% 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} versus eGFR_{cr} or eGFR_{cys}. The 2008 CKD-EPI cystatin C equations were

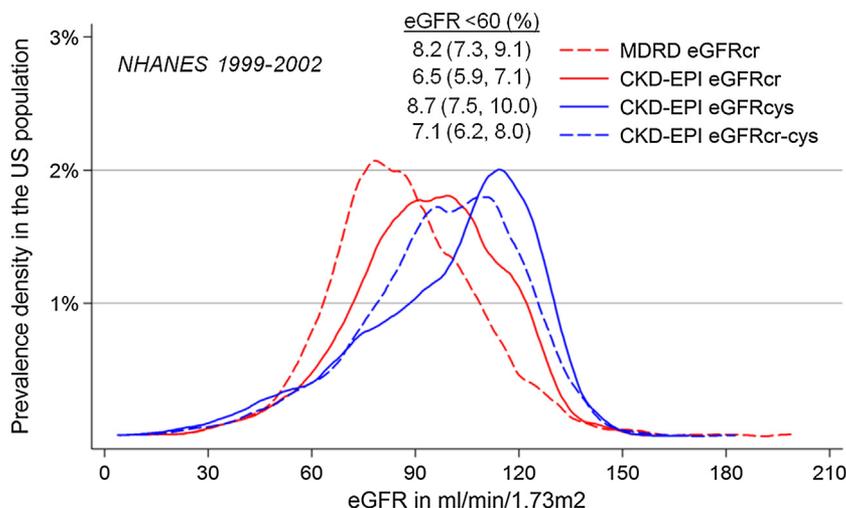


Figure 2. Distribution of estimated glomerular filtration rate (eGFR) and prevalence of eGFR < 60 mL/min/1.73 m² in NHANES (National Health and Nutrition Examination Survey) 1999-2002. Data comprise 8,238 adults in whom serum creatinine and cystatin C were assayed. eGFR computed using the 2006 MDRD (Modification of Diet in Renal Disease) Study equation, 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine (eGFR_{cr}) equation, 2012 CKD-EPI cystatin C (eGFR_{cys}) equation, and 2012 CKD-EPI creatinine–cystatin C (eGFR_{cr-cys}) equation. Prevalence estimates include 95% confidence intervals. Data from Grams et al.³⁰

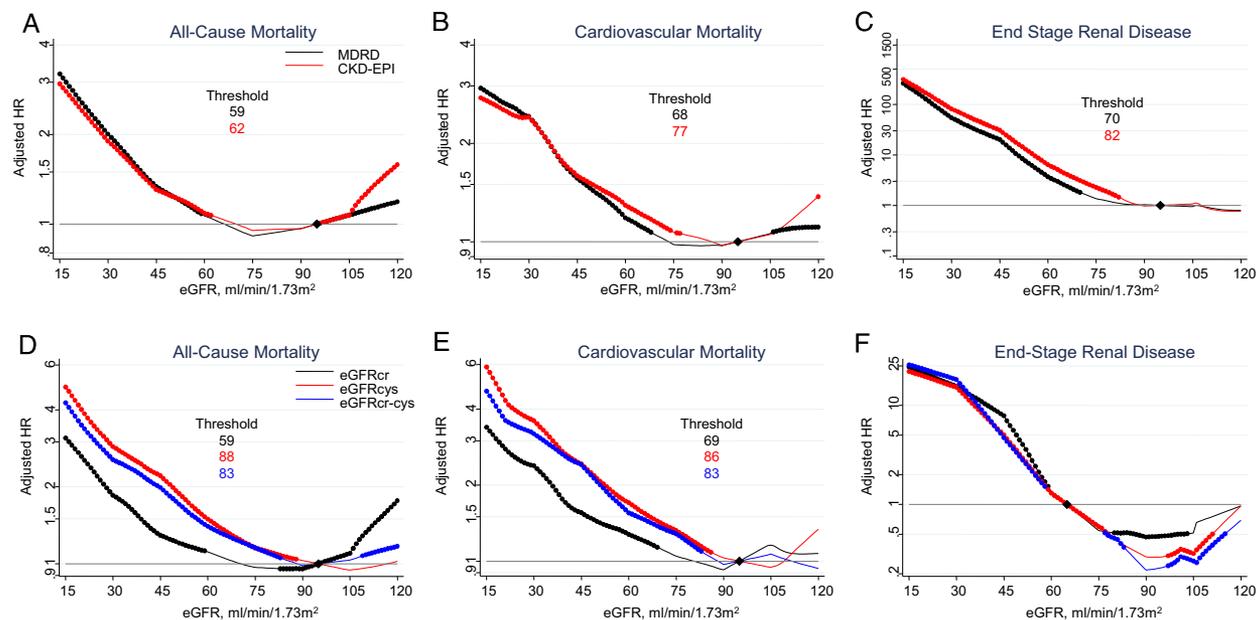


Figure 3. Prognosis of estimated glomerular filtration rate (eGFR) as a continuous variable using the (A-C) 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation and 2006 MDRD (Modification of Diet in Renal Disease) Study equation and (D-F) the 2009 CKD-EPI creatinine equation, 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). HRs were calculated using eGFR splines and adjusted for age, sex, race, body mass index, systolic blood pressure, total cholesterol level, presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes (A-F), and level of albuminuria (D-F). In each panel, solid circles indicate that the adjusted HR at the indicated eGFR level was significant compared with the reference point ($P < 0.05$). (F) Statistical significance could not be computed for the threshold because the threshold was contained within the spline segment including the reference point. (A-C) Adapted and reproduced from Matsushita et al³¹ with permission of the American Medical Association; (D-F) adapted and reproduced with permission from the Massachusetts Medical Society from Shlipak et al³² (©2013 Massachusetts Medical Society).

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 data set 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 between the 2009 CKD-EPI creatinine equation and the 2012 CKD-EPI cystatin C equation, including 2 coefficients for serum creatinine and cystatin C, respectively (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 toward higher accuracy of eGFR_{cys} over eGFR_{cr} for subgroups with lower body mass index. 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

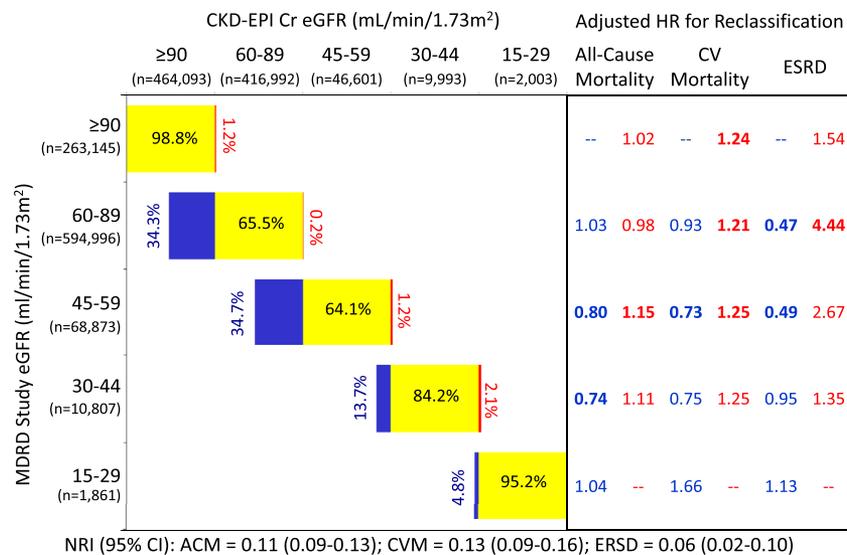


Figure 4. Prognosis of estimated glomerular filtration rate (eGFR) categories using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation versus the 2006 MDRD (Modification of Diet in Renal Disease) Study Equation. (Left panel) Cross-classification by eGFR categories using both equations; (right panel) adjusted hazard ratios (HRs) for reclassification using the CKD-EPI creatinine equation. Data are from general population cohorts (940,366 participants in 25 cohorts). (Left panel) Blue segments indicate the proportion of participants reclassified to a higher eGFR category; red segments, reclassified to a lower eGFR category; yellow segments, not reclassified. (Right panel) HRs for all-cause mortality (ACM), cardiovascular (CV) mortality (CVM), and end-stage renal disease (ESRD) compares participants reclassified to a higher (blue font) and lower eGFR (red font) with those not reclassified (reference). HRs in bold type are statistically significant ($P < 0.05$). HRs adjusted for age, sex, race, body mass index, systolic blood pressure, total cholesterol level, presence or absence of a history of CV disease, smoking status, and presence or absence of diabetes. Net reclassification improvement (NRI) for ACM, CVM, and 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 chronic kidney disease [CKD] cohorts). Data from Matsushita et al.³¹

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 $eGFR_{cr}$. Prevalences of $eGFR < 60$ mL/min/1.73 m² for $eGFR_{cys}$ and $eGFR_{cr-cys}$ are 8.7% and 7.1%, respectively (Fig 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 2, 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 $eGFR_{cr}$ (Fig 4). Reclassification among eGFR categories also showed large differences (Fig 5).³² For example, among individuals with $eGFR_{cr}$ of 45-59 mL/min/1.73 m², 31.8% were reclassified to $eGFR_{cr-cys}$ of 60-89 mL/min/1.73 m², whereas 11.5% were reclassified to $eGFR_{cr-cys}$ of 30-44 mL/min/1.73 m². Individuals reclassified to a higher eGFR category had 0.67, 0.83, and 0.31 lower adjusted risks for mortality, cardiovascular disease mortality, and kidney failure, respectively, than those not reclassified, whereas individuals reclassified to a lower eGFR

category had 1.64, 1.72, and 2.29 higher risks. Overall net reclassification improvement favored $eGFR_{cr-cys}$ over $eGFR_{cr}$ for all-cause and cardiovascular mortality. Results generally were similar among African Americans and whites.

RECOMMENDATIONS

There has been controversy about GFR estimation.⁵⁴⁻⁵⁶ In response, the KDIGO (Kidney Disease: Improving Global Outcomes) 2011 clinical update on drug dosing considerations in patients with acute and chronic kidney disease and the KDIGO 2012 clinical practice guideline for evaluation and management of chronic kidney disease included several recommendations for the evaluation of GFR in all countries.^{7,8} The new guideline recommended using eGFR based on serum creatinine level for initial assessment and eGFR based on serum cystatin C level or mGFR for confirmatory testing in particular situations for which eGFR based on serum creatinine is not as accurate. For reporting $eGFR_{cr}$ in adults, the new guideline 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 guideline recommended using the 2012 CKD-EPI

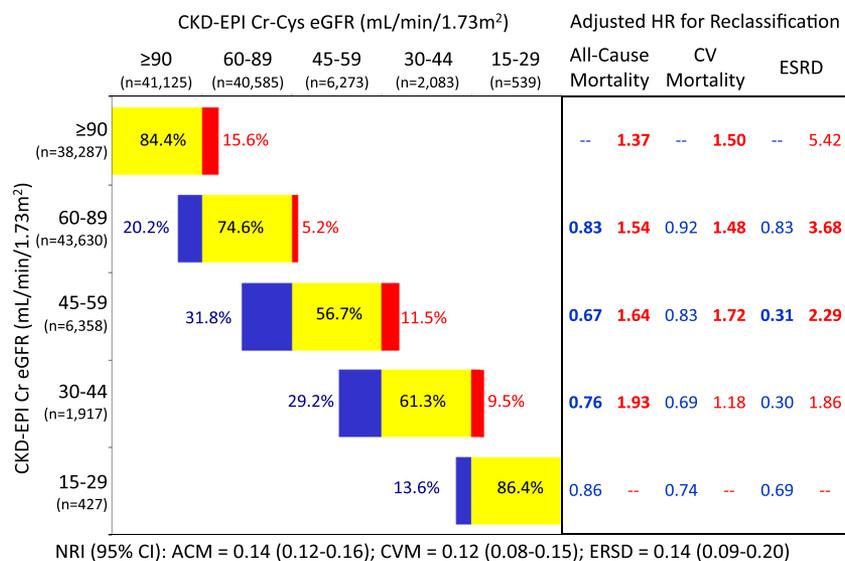


Figure 5. Prognosis of estimated glomerular filtration rate (eGFR) categories using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine (Cr) equation versus the 2012 CKD-EPI creatinine-cystatin C (Cr-Cys) equation. (Left panel) Cross-classification by eGFR categories using both equations; (right panel) adjusted hazard ratios (HRs) for reclassification using the CKD-EPI Cr-Cys equation. Data are from general population cohorts (90,750 participants in 11 cohorts). (Left panel) Blue segments indicate the proportion of participants reclassified to a higher eGFR category; red segments, reclassified to a lower eGFR category; yellow segments, not reclassified. (Right panel) HRs for all-cause mortality (ACM), cardiovascular (CV) mortality (CVM), and end-stage renal disease (ESRD) compare participants reclassified to a higher (blue font) and lower eGFR (red font) with those not reclassified (reference). HRs in bold type are statistically significant ($P < 0.05$). HRs adjusted for age, sex, race, body mass index, systolic blood pressure, total cholesterol level, presence or absence of a history of CV disease, smoking status, presence or absence of diabetes, and level of albuminuria. Net reclassification improvement (NRI) for ACM, CVM, and ESRD from 93,710 participants (90,750 in 11 general population cohorts and 2,960 in 5 CKD cohorts). Data from Shlipak et al.³²

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 guideline recommends 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 $eGFR_{cr-cys}$ also is <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 unanswered. How should clinicians interpret pharmacokinetic studies performed with noncalibrated 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 4-variable MDRD Study equations have been implemented successfully 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 2 largest clinical laboratory service providers in the United States, Quest and LabCorp, and should be reported by all clinical laboratories worldwide. It also should 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 accuracy similar to the 2009 CKD-EPI creatinine equation and does not require specification of race. It also may be more accurate in people with low body mass index 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 level. It may be useful for confirmation of $eGFR_{cr} < 60$ mL/min/1.73 m². 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 GFRs and are more appropriate for general use. Equations that use both creatinine and cystatin C levels 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 downweight 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 the development of strategies for diagnostic testing using “first” and “confirmatory” tests for decreased GFR.

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