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Traditions and innovations in assessment of glomerular filtration rate using creatinine to cystatin C

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Abstract

Purpose of Review—Glomerular filtration rate (GFR) is the best index for kidney function and estimated GFR (eGFR) calculated from endogenous filtration markers like serum creatinine and cystatin C is widely used in clinical practice for chronic kidney disease diagnosis and prognostication. We sought to review the evolution of GFR estimating equations, nuances of eGFR interpretation, and utility of eGFR in drug dosing.

Recent Findings—The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum creatinine eGFR equation was recently updated to exclude the race variable and the CKD-EPI creatinine–cystatin C equation demonstrated the highest reliability. Although calculated creatinine clearance by Cockcroft Gault has been traditionally used for drug dosing, the use of eGFR is slowly being adapted by the Food and Drug Administration for pharmacokinetic studies. However, the individual-level accuracy of eGFR using the CKD-EPI 2021 equations remained low, with the distribution of measured GFR at a given eGFR value spanning several CKD stages.

Summary—Although current methods of estimating GFR have improved in population measures of reliability, all have significant individual-level inaccuracies that can be an issue when clinical decision-making is contingent on the actual level of GFR. Modern methods of GFR measurements should be made widely available to enhance individualized patient decision-making.

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Conflicts of interest

There are no conflicts of interest.

Keywords

cystatin C; drug dosing; estimated glomerular filtration rate; serum creatinine

INTRODUCTION

The assessment of kidney function carries significant diagnostic, prognostic, and treatment implications relevant to clinical medicine, research, and epidemiology. The glomerular filtration rate (GFR) – the rate of plasma ultrafiltrate formation across all glomerular capillaries – is a metric for global kidney function [1]. Although measuring the timed clearance of an exogenous substance (i.e., inulin, iothalamate) is the gold standard for assessing GFR, this is not routinely performed in clinical practice. Instead, clinical decision-making now almost exclusively relies on estimated GFR (eGFR), calculated from endogenous filtration markers such as serum creatinine and serum cystatin C, which can be measured in routine blood tests [2–4,5■■].

The use of eGFR offers clinicians a simple but imperfect method for diagnosing and staging chronic kidney disease (CKD) [6]. Serum creatinine and cystatin C can be conveniently monitored through time to track disease progression. GFR is also used to determine the safety of renally active or renally cleared medications such as sodium-glucose co-transporter 2 inhibitors, metformin, antibiotics, and certain chemotherapeutic agents [7■,8]. Many individual patient-level decision making also relies on GFR cut-offs, from drug eligibility to dialysis preparation and transplant referrals. In clinical practice, eGFR is now routinely used as a direct measured GFR replacement to make these clinical decisions. In this review, we will discuss the evolution of GFR estimating equations, the changing prevalence of CKD in the United States, the application of estimating equations for drug dosing, and the limitations of eGFR in the context of its intra-individual inaccuracies.

A REVIEW OF THE EVOLUTION OF CREATININE-BASED ESTIMATING EQUATIONS USED TO ESTIMATE GLOMERULAR FILTRATION RATE

Metrics for assessing glomerular filtration rate estimating equations

Population-level metrics to assess estimating equations include bias, precision, accuracy (commonly P30). Bias is the median of the individual differences between measured GFR (mGFR) and eGFR. Precision is determined by the interquartile range of the bias. Accuracy is determined by both bias and precision. The most common expression of accuracy for eGFR equations is P30, which is the percentage of the eGFRs that differ by >30% from the mGFR [2]. The P30 has since been adapted by the National Kidney Foundation Disease Outcomes Quality Initiative as the acceptable metric for accuracy [9]. More stringent measures of accuracy, such as P10 or the percentage of eGFRs that differ by >10% from the mGFR, have been suggested by some as an error of 30% for GFR estimation is considered to be large [10]. Moreover, the application of these population-level metrics in individual-level clinical decision making is limited – the P30 metric is uninterpretable on an individual-level as it is interpretable only if mGFR is available.

Serum creatinine

Serum creatinine (molecular weight: 113 Da) is the most common endogenous filtration marker used to estimate GFR. It is mainly produced in skeletal muscles from the continuous nonenzymatic degradation of *creatine,* a nitrogenous organic acid produced by the liver, kidneys, and pancreas that is phosphorylated in skeletal muscles as an accessible source of energy for muscle contraction. Creatinine is primarily eliminated by the kidneys – it is freely filtered through the glomerulus and secreted by the organic anionic and cationic transporters mainly in the proximal tubules [11■,12]. Proximal tubular secretion of creatinine is variable among individuals. It increases in certain conditions, such as sickle cell disease, and as kidney function declines [13]. Thus, creatinine clearance overestimates GFR by about 10–20%, particularly at the lower levels of GFR [14].

Non-glomerular filtration rate determinants of serum creatinine

Serum creatinine is influenced by conditions that affect muscle mass [15]. It has also been shown to be a marker of health status independent of kidney function (Fig. 1) [16]. Chronic conditions that lead to a reduced muscle mass and sarcopenia such as liver cirrhosis can lead to lower levels of creatinine and thus GFR overestimation [17]. Medications such as cimetidine and trimethoprim that competitively inhibit kidney tubular secretion of creatinine lead to a rise in serum creatinine and a lower eGFR without causing true kidney injury [18].

Diet can also affect serum creatinine. Creatine supplementation has been reported to cause an elevated serum creatinine leading to a misdiagnosis of CKD [19]. High protein intake, particularly cooked meat, can increase serum creatinine and thus lead to GFR underestimation [20–23]. Consumption of cooked beef was shown to increase serum creatinine, but not cystatin C, among healthy participants [24]. In another study of healthy volunteers and patients with diabetic kidney disease, intake of protein from a cooked meat meal led to an increase in serum creatinine, and this was not observed in the group that consumed the same amount of protein from a nonmeat meal [25]. Timing of the consumption of animal protein may also affect levels of serum creatinine. In the same study, it was observed that the peak rise of serum creatinine was more delayed among those with more advanced kidney disease compared to those with more preserved kidney function [25].

In another reported case, the daily intake of ‘beef tea’ (boiled beef slurry with high concentrations of protein and creatinine) led to serum creatinine fluctuations from 1 mg/dl to 6.3 mg/dl.

Cessation of the ‘beef tea’ led to a drop in serum creatinine to 1.0 mg/dl 24 h thereafter [26]. The individual-level variation of measured serum creatinine throughout 24 h is substantial particularly among persons without kidney disease, as levels usually increased postprandially [27]. The effects of diet and daily variability of measured serum creatinine are often underappreciated; however, this context is relevant given that modern creatinine-based GFR estimating equations were developed from cohorts with variable timing of sample collection (i.e., fasting samples were obtained in the Modification of Diet in Renal Disease [MDRD] cohort while the fasting status was variable for the blood samples used to

measure creatinine in the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] cohort).

The Cockcroft–Gault equation for estimating creatinine clearance

The first widely used renal function estimating equations was the Cockcroft–Gault (CG) equation. It was developed in 1973 using data from 249 hospitalized adult males with timed urinary creatinine clearance. The mean creatinine clearance per decade of age was reported in the study, ranging from a mean of 114.9 ml/min among those age 18–29 years, to a mean of 37.4 ml/min among those age 80–92 years. The CG equation accounts for non-GFR determinants of creatinine by using age, weight, and sex [28]. As the equation was developed from a cohort with a mean weight of 72 kg, one of its biggest limitations is the resulting bias of creatinine clearance estimation at the extremes of weight, especially for the purpose of drug dosing. Although no consensus exists on the application of the CG equation to patients at the extremes of weight, suggested practices include weight-based adjustments in the equation – using actual body weight for underweight persons (BMI < 18.5 kg/m^2), ideal body weight for persons with normal weight (BMI 18.5–24.9 kg/m^2), and adjusted body weight for obese persons (BMI ≥ 30 kg/m^2; adjusted body weight is 40% of actual body weight) Did we intentionally exclude the overweight population, BMI 25–29.9? [29]. Another practical solution for drug dosing proposed using a functional creatinine clearance range with the ideal body weight and total body weight determining the lower and upper bounds, respectively, as drug dosing recommendations are contingent on ranges of creatinine clearance and its absolute value [30]. Another limitation with creatinine based estimates of GFR is the accuracy among elderly people. The geriatric population can have lower body mass and relatively low creatinine levels (<0.8 mg/dl) [31]. The GFR estimates in elderly patients will vary substantially from small variations in their lower levels of serum creatinine [32].

The modification of diet in renal disease estimated glomerular filtration rate equation

The MDRD equation was developed to estimated glomerular filtration rate (eGFR) using the data from 1628 participants in the MDRD study who had GFRs measured using urinary clearance of ^{125}I-iothalamate. This was derived from 1070/1628 participants and validated using datapoints from the remaining 558 participants. The mGFR of the cohort was 39.8 ml/min/1.73 m^2. Although the MDRD cohort was well balanced in sex and age distribution, its participants were predominantly White. The final MDRD-eGFR equation included serum creatinine and demographic variables including age, sex, and race (Black vs. non-Black). The race coefficient was 1.212, such that a Black person will have a 21% higher eGFR compared to a non-Black person with the same serum creatinine, age, and sex.

At a population level, the MDRD-eGFR equation was shown to perform better than other creatinine clearance estimating equations.

It also performed as well among the subgroup of MDRD participants with higher serum creatinine concentrations (>2.5 mg/dl; more advanced kidney disease) [2]. Since its development in 1999, the MDRD-eGFR equation had been applied broadly in clinical

laboratories nationwide and had been used to determine CKD prevalence in the United States and the global burden of CKD [33–35].

The chronic kidney disease epidemiology collaboration estimated glomerular filtration rate equation

One of the limitations of the MDRD-eGFR equation was a higher bias (population level difference between mGFR and eGFR) and lower reliability in estimating GFR in those with GFR ≥60 ml/min/1.73 m^2 [36]. To address this limitation, the CKD-EPI developed a new estimating equation which is less biased at both higher and lower levels of GFR. Ten different CKD cohorts using urinary iothalamate clearance to measure GFR were used and randomly divided for the derivation and internal validation of the CKD-EPI serum creatinine (CKD-EPIcr) 2009 equation. Sixteen other CKD cohorts were used for external validation. Overall mean mGFR of the cohort was 68 ml/min/1.73 m^2. Although the distribution of sex was balanced, persons <65 years were heavily represented in the cohorts (>80% of the derivation and internal/external validation data sets). Compared to the MDRD population, the proportion of Black participants increased to >30% in the derivation and internal validation cohorts, albeit making up only 10% of the external validation cohort. The final CKD-EPIcr 2009 equation was still determined by serum creatinine and similar demographic variables (age, sex, and dichotomous race variables), with the coefficient for Black race decreasing from 1.212 in MDRD-eGFR to 1.159 in CKD-EPIcr 2009 [3]. Thus, with CKD-EPIcr 2009, a Black person is assigned a 16% higher eGFR compared to a non-Black person with similar age, sex, and serum creatinine. Compared with the performance of MDRD-eGFR, CKD-EPIcr 2009 had reduced bias and improved accuracy and precision for both eGFR <60 ml/min/1.73 m^2 and eGFR ≥60 ml/min/1.73m^2 subgroups in the validation cohort [3].Since the estimating equation is generalizable to its development cohort, it is important to note that the CKD-EPI cohorts did not include patients with acute illnesses, hospitalized patients, decompensated heart failure, cirrhosis, sickle cell disease, and patients with malignancy undergoing cancer chemotherapy. Thus, eGFR may not be reliable for individual level decisions in these patient populations.

In recent years, the use of the race variable in eGFR calculations and other aspects of medicine has faced increasing scrutiny given the risks of inequities that disproportionately affect minority groups, most especially African American patients [37]. Consequently, some institutions responded by removing the race variable from the original CKD-EPIcr 2009 equation. The effects of this policy change were evaluated using the Chronic Renal Insufficiency Cohort, which had >30% self-identified Black participants. This study found that simply omitting the race variable led to larger biases in eGFR underestimation among self-identified Black participants in the study [38].

To address these evolving issues in GFR estimation, the CKD-EPI group reexamined the accuracy of current estimating equations at that time and redeveloped new equations to estimate GFR without the use of the race variable, published in 2021. The derivation dataset used for CKD-EPIcr 2021 was similar to the one used for CKD-EPIcr 2009, whereas a different dataset comprised of 12 studies (14% Black participants) was used for external validation. Consistent with Hsu *et al.* [38] the CKD-EPI group found that omission of

the race coefficient from CKD-EPIcr 2009 led to larger population-level biases with GFR underestimation among Black participants compared to CKD-EPIcr 2009 with the race variable and CKD-EPIcr 2021. The newly developed CKD-EPIcr 2021 equation reduced the overestimation of GFR among Black patients but had increased overestimation among non-Black, patients, compared to CKD-EPIcr 2009. Accuracy of the creatinine-base equations were overall acceptable [5■■].

CYSTATIN C FOR GLOMERULAR FILTRATION RATE ESTIMATION

Cystatin C is an endogenous 13-kDa cysteine proteinase constitutively produced by all nucleated cells, freely filtered through the glomerulus, and completely reabsorbed and catabolized by proximal tubular cells [39]. Extrarenal elimination of cystatin C occurs through the liver and the gut [40].

Non-estimate glomerular filtration rate determinants of cystatin C

Epidemiologic studies of the associations of clinical variables with cystatin C have found age and sex were less associated with cystatin C than creatinine. Black race was not associated with cystatin C [41,42]. Cystatin C has been shown to be unaffected by lean body mass [43], but has been positively associated with weight and BMI, which is postulated to be due to its association with fat mass [41]. Cystatin C has also been shown to be associated with a proinflammatory state, with positive associations seen with the presence of diabetes, surrogates of increased fat mass, white blood cell count, hemoglobin, C-reactive protein, and proteinuria [41]. Although dietary protein intake does not affect serum cystatin C [20], certain conditions such as diabetes [41], steroid administration [44,45], and thyroid dysfunction [46] may affect its levels.

Cystatin C-based estimating equations of kidney function

Equations using cystatin C to estimate GFR were developed in 2012 by the CKD-EPI group. Thirteen studies were included randomly divided into the derivation (n = 3522) and internal validation (n = 1830) datasets. In this pooled cohort, mean age was 47 years with a high proportion of those ≤65 years, 42% were female, and 40% belonged to the Black race. Over 30% of the participants had a BMI >30 kg/m^2. Another five studies with 1119 participants, 3% of which belonged to the Black race, were pooled to comprise the external validation dataset. The CKD-EPI cystatin-C (CKD-EPIcys) 2012 equation was determined by cystatin C, age, sex, and without the race variable, while the CKD-EPI creatinine-cystatin C (CKD-EPIcr-cys) 2012 equation was determined by creatinine, cystatin C, age, sex, and the dichotomous race variable. In terms of performance metrics, bias was generally similar across the CKD-EPIcr 2009, CKD-EPIcys 2012, and CKD-EPIcr-cys 2012 equations. CKD-EPIcr-cys 2012 was found to have better accuracy and improved precision over CKD-EPIcr 2009 and CKD-EPIcys 2012. The CKD-EPIcr-cys 2012 equation improved the reclassification of CKD (eGFR 60 ml/min/1.73 m^2 as cutoff) among those with milder forms of the disease (eGFR range 45–74 ml/min/1.73m^2) [4].

The combined CKD-EPIcr-cys equations were remodeled in 2021 without the race variable. Among all the equations studied, the CKD-EPIcr-cys 2021 equation, compared to CKD-

EPIcr 2009, CKD-EPIcys 2012, and CKD-EPIcr 2021, had the least bias among Black participants and best accuracy overall [5■■].

DIAGNOSIS AND PREVALENCE OF GLOMERULAR FILTRATION RATE

Current guidelines in glomerular filtration rate diagnosis

The 2021 National Kidney Foundation-American Society of Nephrology Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease recommend the following: immediate implementation of the CKD-EPIcr 2021 race-free equation to estimate GFR, and increase in routine use of cystatin C as a confirmatory test for eGFR in clinical decision making [47■■].

The diagnosis of CKD requires assessment of GFR and in routine practice, eGFR is used to make management decisions. Guidelines from Kidney Disease Improving Global Outcomes 2012 state that CKD is diagnosed when the GFR is reduced (<60 ml/min/1.73 m^2) or there are positive markers of kidney damage such as albuminuria (albumin excretion rate ≥30 mg/24h or urine albumin-to-creatinine ratio ≥30 mg/g) for over 3 months [6].

Changing prevalence of glomerular filtration rate in the United States using estimating equations

The advent of GFR estimating equations has allowed their use as a population health metric to estimate the prevalence and burden of CKD in the population. Using MDRD-eGFR, it was estimated that the prevalence of CKD stages 1–4 (persons with eGFR <15 ml/min/1.73 m^2 were excluded in this study) in the United States increased from 10.03% in 1988–1994 to 13.07% in the 1999–2004 National Health and Nutrition Examination Survey (NHANES) periods. The increase in prevalence was consistent across each stage of CKD [34]. Comparing the use of MDRD-eGFR to CKD-EPIcr 2009, the prevalence of CKD in the United States during the 1999–2006 NHANES survey period decreased with the use of the latter (13.1% for MDRD-eGFR vs. 11.5% for CKD-EPIcr 2009) due to the reclassification of a proportion of those with CKD stage 3 to stage 2 when CKD-EPIcr 2009 was used [3]. Prevalence of CKD stages 3 and 4 remained stable at around 6.9% in the following decade from 2011–2012 vs. 2003–2004 [48].

Prevalence estimates of CKD are highly dependent on the equation used. Thus, the prevalence changed with the implementation of the CKD-EPIcr 2021 equation. Among Black persons, CKD prevalence increased from 14.3% using CKD-EPIcr 2009 to 16.3% using CKD-EPIcr 2021. Conversely, non-Black persons had a decrease in estimated CKD prevalence, from 11.7% using CKD-EPIcr 2009 to 10.25% using CKD-EPIcr 2021. CKD prevalence had less changes per subgroup using the CKD-EPIcr-cys 2012 and 2021 equations – from 13.6% to 13.9% among Black persons and 11.9% to 11.0% among non-Black persons, respectively [5■■]. The reclassification of a proportion of Black persons to a more severe CKD stage and of non-Black persons to milder stages using CKD-EPIcr 2021 has been demonstrated in other cohorts and real-world patient data [49■,50,51].

THE USE OF CYSTATIN C ESTIMATED GLOMERULAR FILTRATION RATE IN DRUG DOSING

Historically, the Food and Drug Administration (FDA) recommended the use of the CG equation to determine kidney function and the corresponding drug dose adjustment [52]. These recommendations have evolved overtime to be more inclusive of other assessment of eGFR including the MDRD and CKD-EPI equations [53]. The FDA recommends the use of eGFR pharmacokinetic studies due to the widespread availability and incorporation of eGFR into clinical practice. No recommendations were made regarding preference of eGFR methodology or incorporation of accuracy (P30) for dosing. These recommendations continuously evolve, but the guidance may not always keep up with the most recent advances in determining eGFR such as using cystatin C [4].

Accurately determining kidney function is vital to medication initiation and dose adjustments. There are numerous medications in various classes that require adjustments based on the severity of kidney impairment [54]. Medications requiring dose adjustment based on kidney function and narrow therapeutic indexes (Table 1) would benefit from more precision in estimating GFR. “The presence of kidney impairment can alter the medication choice as well as the safest, most effective dose.”

Despite the lack of data validating the CKD-EPI equations in hospitalized patients, several studies have compared different drug dosing strategies using $eGFR_{Cys}$. Peters *et al.* evaluated the potential dosing implications when $eGFR_{Cys}$ was used in place of the CG creatinine clearance estimations [55]. They found that in most cases the medication dose would have been lower if $eGFR_{Cys}$ were used. Inappropriate medication doses can lead to supra-/sub-therapeutic levels and medication toxicity. Several studies have compared different dosing strategies involving $eGFR_{Cys}$. Predication of vancomycin elimination based on $eGFR_{Cys}$ performed better than CG to estimate eGFR based [56]. In a prospective evaluation comparing two vancomycin dosing strategies based on either CG or $eGFR_{Cys}$, less overall trough concentration variability with fewer supra- and sub-therapeutic concentrations were seen with $eGFR_{Cys}$ compared to CG [57]. Cystatin C was shown to be more predictive than serum creatinine in determining vancomycin concentrations in critically ill patients [58]. Similar results were also seen with carboplatin elimination when cystatin C in combination with creatinine was used to estimate GFR compared to creatinine alone [59,60]. The use of cystatin C also has the potential for detecting medication related toxicity. Iversen *et al.* [61] evaluated various biomarkers to detect vancomycin induced kidney injury. They found that cystatin C was significantly elevated patients with vancomycin induced kidney injury compared to the two control groups (with and without vancomycin therapy). Cystatin C showed strong negative correlation with eGFR and remained a significant factor associated with the development for kidney injury in the multivariable logistic regression model [62].

LIMITATIONS OF ESTIMATING EQUATIONS

Recently, the limitations of estimating equations have been rigorously explored. Although the performances of these equations have been routinely quantified by population-level

metrics such as bias, precision, and accuracy, these benchmarks are usually not as intuitive and applicable in the context of individual-level patient decision-making. In a cross-sectional study of a pooled cohort comprising of persons with and without CKD (N = 3223; mean age 59 years, 32% Black participants), our group employed the 95% prediction interval (PI) as a metric to quantify the range of expected mGFRs (2.5th to 97.5th percentile) for a person with a given eGFR value. Overall, the individual-level differences between mGFR and eGFR were very wide, with the 95% PI ranging from 50 to 55 ml/min/1.73 m^2 depending on which estimating equation was used to calculate the eGFR. The degree of magnitude of the 95% PI was consistent across age, sex, and race groups. In practical terms, at a calculated CKD-EPIcr 2021 eGFR of 60 ml/min/1.73 m^2 in the pooled cohort, 50% of the mGFRs ranged from 52 to 67 ml/min/1.73 m^2, 80% of the mGFRs ranged from 45 to 76 ml/min/1.73 m^2, and 95% of the mGFRs ranged from 36 to 87 ml/min/1.73 m^2 (Fig. 2) [63■■]. As mGFR is the gold standard of quantifying kidney function, the study showed that the range of plausible true kidney function for a given eGFR spans across several stages and severity of kidney disease. Given this individual-level inaccuracy, there is a role for *measuring* GFR as part of clinical care when clinical decision-making is contingent on the actual kidney function, especially since modern methods of GFR measurements are simpler and no longer cumbersome [64,65■■].

SUMMARY/CONCLUSION

Widely used methods to estimate GFR have evolved from the CG creatinine clearance equation, to the MDRD eGFR equation and CKD-EPI creatinine and cystatin C equations. In 2021, the CKD-EPIcr equation was redeveloped to exclude the race variable with the aim of reducing health inequities that disproportionately affect minority groups. Although the newly developed CKD-EPIcr-cys 2021 equation was shown to be more reliable in terms of population-level metrics, individual-level inaccuracies are still significant in all current available methods to estimate GFR. Given the importance of GFR as the most important index of kidney function and use in clinical decision-making, measuring GFR should be considered in situations where clinical management is dependent on the actual level of kidney dysfunction. This is of particular importance in drug dosing where some agents have very narrow therapeutic indices.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Rose BD, Post TW. Clinical physiology of acid-base and electrolyte disorders. 5th ed. McGraw-Hill; 2001.
2. Levey AS, Bosch JP, Lewis JB, et al. 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; 130:461–470. [PubMed: 10075613]
3. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604. [PubMed: 19414839]

4. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367:20–29. [PubMed: 22762315]

5■■. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021; 385:1737–1749. [PubMed: 34554658] Development of the CKD-EPI 2021 creatinine race-free eGFR equation.

6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3:1–150.

7■. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383:1436–1446. [PubMed: 32970396] Dapagliflozin lowered the risk of kidney disease progression, end-stage kidney disease, or mortality from cardiac and kidney causes in those with diabetic and nondiabetic CKD.

8. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol 2011; 12:211–214. [PubMed: 21376284]

9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(Suppl 1):S1–S266. [PubMed: 11904577]

10. Earley A, Miskulin D, Lamb EJ, et al. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann Intern Med 2012; 156:785–795. [PubMed: 22312131]

11■. Kashani K, Rosner MH, Ostermann M. Creatinine: from physiology to clinical application. Eur J Intern Med 2020; 72:9–14. [PubMed: 31708357] A review of the metabolism and physiology of serum creatinine and its benefits and limitations as an endogenous filtration marker.

12. Brenner & Rector's The Kidney. Philadelphia, PA: Elsevier; 2020.

13. Allon M Renal abnormalities in sickle cell disease. Arch Intern Med 1990; 150:501–504. [PubMed: 2178577]

14. van Acker BA, Koomen GC, Koopman MG, et al. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. Lancet 1992; 340:1326–1329. [PubMed: 1360044]

15. Patel SS, Molnar MZ, Tayek JA, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. J Cachexia Sarcopenia Muscle 2013; 4:19–29. [PubMed: 22777757]

16. Rizk JG, Streja E, Wenziger C, et al. Serum creatinine-to-cystatin-C ratio as a potential muscle mass surrogate and racial differences in mortality. J Ren Nutr 2021; S1051–2276:00294–6.

17. Yoo JJ, Kim SG, Kim YS, et al. Estimation of renal function in patients with liver cirrhosis: impact of muscle mass and sex. J Hepatol 2019; 70:847–854. [PubMed: 30630010]

18. Andreev E, Koopman M, Arisz L. A rise in plasma creatinine that is not a sign of renal failure: which drugs can be responsible? J Intern Med 1999; 246:247–252. [PubMed: 10475992]

19. Willis J, Jones R, Nwokolo N, Levy J. Protein and creatine supplements and misdiagnosis of kidney disease. BMJ 2010; 340:b5027. [PubMed: 20061359]

20. Tangri N, Stevens LA, Schmid CH, et al. Changes in dietary protein intake has no effect on serum cystatin C levels independent of the glomerular filtration rate. Kidney Int 2011; 79:471–477. [PubMed: 20980977]

21. Crim MC, Calloway DH, Margen S. Creatine metabolism in men: urinary creatine and creatinine excretions with creatine feeding. J Nutr 1975; 105:428–438. [PubMed: 1113209]

22. Preiss DJ, Godber IM, Lamb EJ, et al. The influence of a cooked-meat meal on estimated glomerular filtration rate. Ann Clin Biochem 2007; 44(Pt 1):35–42. [PubMed: 17270090]

23. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! Nephron 2017; 136:302–308. [PubMed: 28441651]

24. Toffaletti JG, Hammett-Stabler C, Handel EA. Effect of beef ingestion by humans on plasma concentrations of creatinine, urea, and cystatin C. Clin Biochem 2018; 58:26–31. [PubMed: 29842868]

25. Nair S, O'Brien SV, Hayden K, et al. Effect of a cooked meat meal on serum creatinine and estimated glomerular filtration rate in diabetes-related kidney disease. Diabetes Care 2014; 37:483–487. [PubMed: 24062331]
26. Kent R, Gopalakrishnan VP, Menon MC, Ross MJ. The case | labile creatinine levels in a patient with breast cancer. Kidney Int 2017; 91:761–762. [PubMed: 28202178]
27. Hilderink JM, van der Linden N, Kimenai DM, et al. Biological variation of creatinine, cystatin C, and eGFR over 24 hours. Clin Chem 2018; 64:851–860. [PubMed: 29483105]
28. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41. [PubMed: 1244564]
29. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. Pharmacotherapy 2012; 32:604–612. [PubMed: 22576791]
30. Brown DL, Masselink AJ, Lalla CD. Functional range of creatinine clearance for renal drug dosing: a practical solution to the controversy of which weight to use in the Cockcroft-Gault equation. Ann Pharmacother 2013; 47:1039–1044. [PubMed: 23757387]
31. Odden MC, Shlipak MG, Tager IB. Serum creatinine and functional limitation in elderly persons. J Gerontol A Biol Sci Med Sci 2009; 64:370–376. [PubMed: 19181716]
32. Burkhardt H, Bojarsky G, Gretz N, Gladisch R. Creatinine clearance, Cockcroft-Gault formula and cystatin C: estimators of true glomerular filtration rate in the elderly? Gerontology 2002; 48:140–146. [PubMed: 11961366]
33. Accetta NA, Gladstone EH, DiSogra C, et al. Prevalence of estimated GFR reporting among US clinical laboratories. Am J Kidney Dis 2008; 52:778–787. [PubMed: 18676076]
34. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007; 298:2038–2047. [PubMed: 17986697]
35. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020; 395:709–733. [PubMed: 32061315]
36. 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; 18:2749–2757. [PubMed: 17855641]
37. Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight - reconsidering the use of race correction in clinical algorithms. N Engl J Med 2020; 383:874–882. [PubMed: 32853499]
38. Hsu CY, Yang W, Parikh RV, et al. Race, genetic ancestry, and estimating kidney function in CKD. N Engl J Med 2021; 385:1750–1760. [PubMed: 34554660]
39. Grubb AO. Cystatin C—properties and use as diagnostic marker. Adv Clin Chem 2000; 35:63–99. [PubMed: 11040958]
40. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens 2015; 24:295–300. [PubMed: 26066476]
41. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009; 75:652–660. [PubMed: 19119287]
42. Liu X, Foster MC, Tighiouart H, et al. Non-GFR determinants of low-molecular-weight serum protein filtration markers in CKD. Am J Kidney Dis 2016; 68:892–900. [PubMed: 27663042]
43. Baxmann AC, Ahmed MS, Marques NC, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol 2008; 3:348–354. [PubMed: 18235143]
44. Risch L, Herklotz R, Blumberg A, Huber AR. Effects of glucocorticoid immunosuppression on serum cystatin C concentrations in renal transplant patients. Clin Chem 2001; 47:2055–2059. [PubMed: 11673383]
45. Bökenkamp A, van Wijk JA, Lentze MJ, Stoffel-Wagner B. Effect of corticosteroid therapy on serum cystatin C and beta2-microglobulin concentrations. Clin Chem 2002; 48:1123–1126. [PubMed: 12089191]
46. Schmitt R, Bachmann S. Impact of thyroid dysfunction on serum cystatin C. Kidney Int 2003; 64:1139–1140.

47■■. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. Am J Kidney Dis 2022; 79:268.e1–288.e1. [PubMed: 34563581] Most current recommendations on GFR estimation from the National Kidney Foundation and American Society of Nephrology

48. Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med 2016; 165:473–481. [PubMed: 27479614]

49■. Gregg LP, Richardson PA, Akeroyd J, et al. Effects of the 2021 CKD-EPI Creatinine eGFR Equation among a National US Veteran Cohort. Clin J Am Soc Nephrol 2022; 17:283–285. [PubMed: 34799356] Changes in CKD prevalence using the new CKD-EPI 2021 creatinine race-free equuation using real-world data.

50. Fu EL, Coresh J, Grams ME, et al. Removing race from the CKD-EPI equation and its impact on prognosis in a predominantly White European population. Nephrol Dial Transplant 2022; DOI: 10.1093/ndt/gfac197.

51. Walther CP, Winkelmayer WC, Navaneethan SD. Updated US prevalence estimates for chronic kidney disease stage and complications using the new race-free equation to estimate glomerular filtration rate. JAMA Netw Open 2022; 5:e220460. [PubMed: 35166786]

52. Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing and labeling. In: Services DoHaH, editor. Rockville, US; 1998.

53. Food and Drug Administration. Guidance for industry: pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing and labeling; draft guidance for industry. In: Services DoHaH, editor. Rockville, US; 2020.

54. Munar MY. Drug dosing adjustments in patients with chronic kidney disease. 2007. Available at: https://www.aafp.org/pubs/afp/issues/2007/0515/p1487.html.

55. Peters BJ, Rule AD, Kashani KB, et al. Impact of serum cystatin C-based glomerular filtration rate estimates on drug dose selection in hospitalized patients. Pharmacotherapy 2018; 38:1068–1073. [PubMed: 30120844]

56. Barreto EF, Rule AD, Murad MH, et al. Prediction of the renal elimination of drugs with cystatin C vs creatinine: a systematic review. Mayo Clin Proc 2019; 94:500–514. [PubMed: 30713050]

57. Frazee E, Rule AD, Lieske JC, et al. Cystatin C-guided vancomycin dosing in critically ill patients: a quality improvement project. Am J Kidney Dis 2017; 69:658–666. [PubMed: 28131530]

58. Suzuki A, Imanishi Y, Nakano S, et al. Usefulness of serum cystatin C to determine the dose of vancomycin in critically ill patients. J Pharm Pharmacol 2010; 62:901–907. [PubMed: 20636878]

59. Thomas F, Séronie-Vivien S, Malard L, Chatelut E. Interest of cystatin C for individual dosing of anticancer drugs cleared by the kidneys. Therapie 2007; 62:121–127. [PubMed: 17582313]

60. Schmitt A, Gladieff L, Lansiaux A, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. Clin Cancer Res 2009; 15:3633–3639. [PubMed: 19401344]

61. Iversen E, Bodilsen AC, Klausen HH, et al. Kidney function estimates using cystatin C versus creatinine: Impact on medication prescribing in acutely hospitalized elderly patients. Basic Clin Pharmacol Toxicol 2019; 124:466–478. [PubMed: 30372593]

62. Kim SM, Lee HS, Kim MJ, et al. Diagnostic value of multiple serum biomarkers for vancomycin-induced kidney injury. J Clin Med 2021; 10:5005. [PubMed: 34768522]

63■■. Shafi T, Zhu X, Lirette ST, et al. Quantifying individual-level inaccuracy in glomerular filtration rate estimation: a cross-sectional study. Ann Intern Med 2022; 175:1073–1082. [PubMed: 35785532] Pooled observational cohort study showing the individual-level inaccuracy of current methods of GFR estimation

64. Levey AS, Coresh J, Tighiouart H, et al. Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol 2020; 16:51–64. [PubMed: 31527790]

65■■. Inker LA, Titan S. Measurement and estimation of GFR for use in clinical practice: core curriculum 2021. Am J Kidney Dis 2021; 78:736–749. [PubMed: 34518032] Review of methods for measuring and estimating GFR.

KEY POINTS

- The Chronic Kidney Disease Epidemiology Collaboration serum creatinine (CKD-EPIcr) and CKD-EPIcr-cys 2021 equations are the most current methods to estimate glomerular filtration rate (GFR). The NKF-ASN task force recommends the immediate use of the CKD-EPIcr race-free equation and the increased use of cystatin C as a confirmatory testing for GFR estimation.
- Creatinine clearance by the Cockcroft--Gault equation has traditionally been used to estimate kidney function for the purpose of drug dosing, but in recent years, FDA recommendations have slowly evolved to include modern methods to estimate GFR including the use of cystatin C.
- The individual-level inaccuracies of modern GFR estimating methods are significant, with the distribution of measured GFR at a given estimated GFR value spanning several CKD stages.

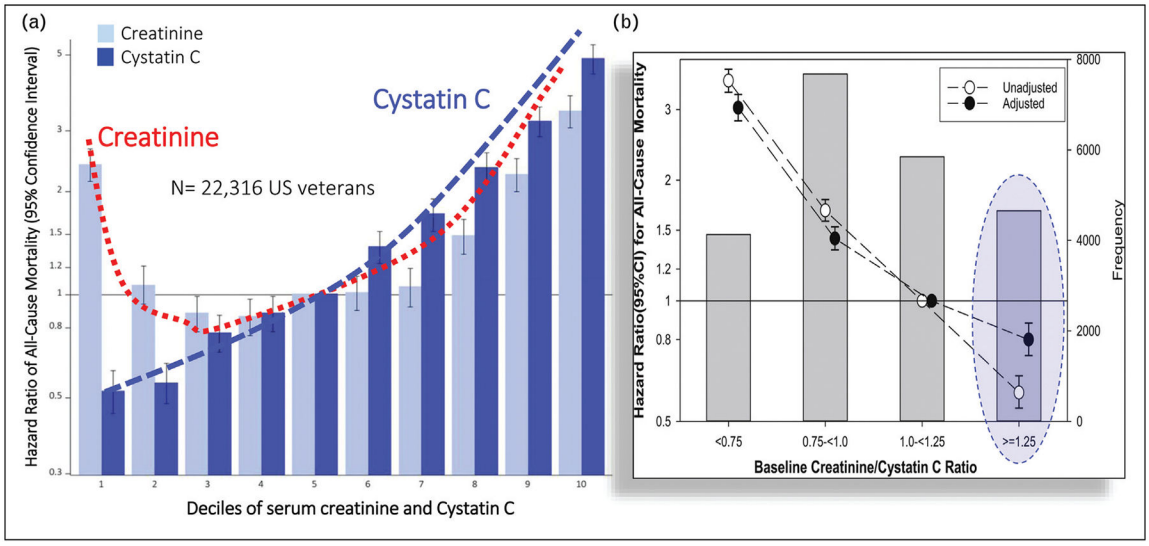

FIGURE 1.

Serum creatinine to cystatin C ratio as a marker of health status independent of kidney function. Data from a retrospective cohort study of US veterans showing the association of low creatinine-to-cystatin C ratio (<0.75 compared to the reference group 1 to <1.25) with mortality among both Black and non-Black veterans. In contrast, a higher creatinine-to-cystatin C ratio (≥1.25) was associated with reduced mortality compared to the reference group with race affecting the strength of these associations.

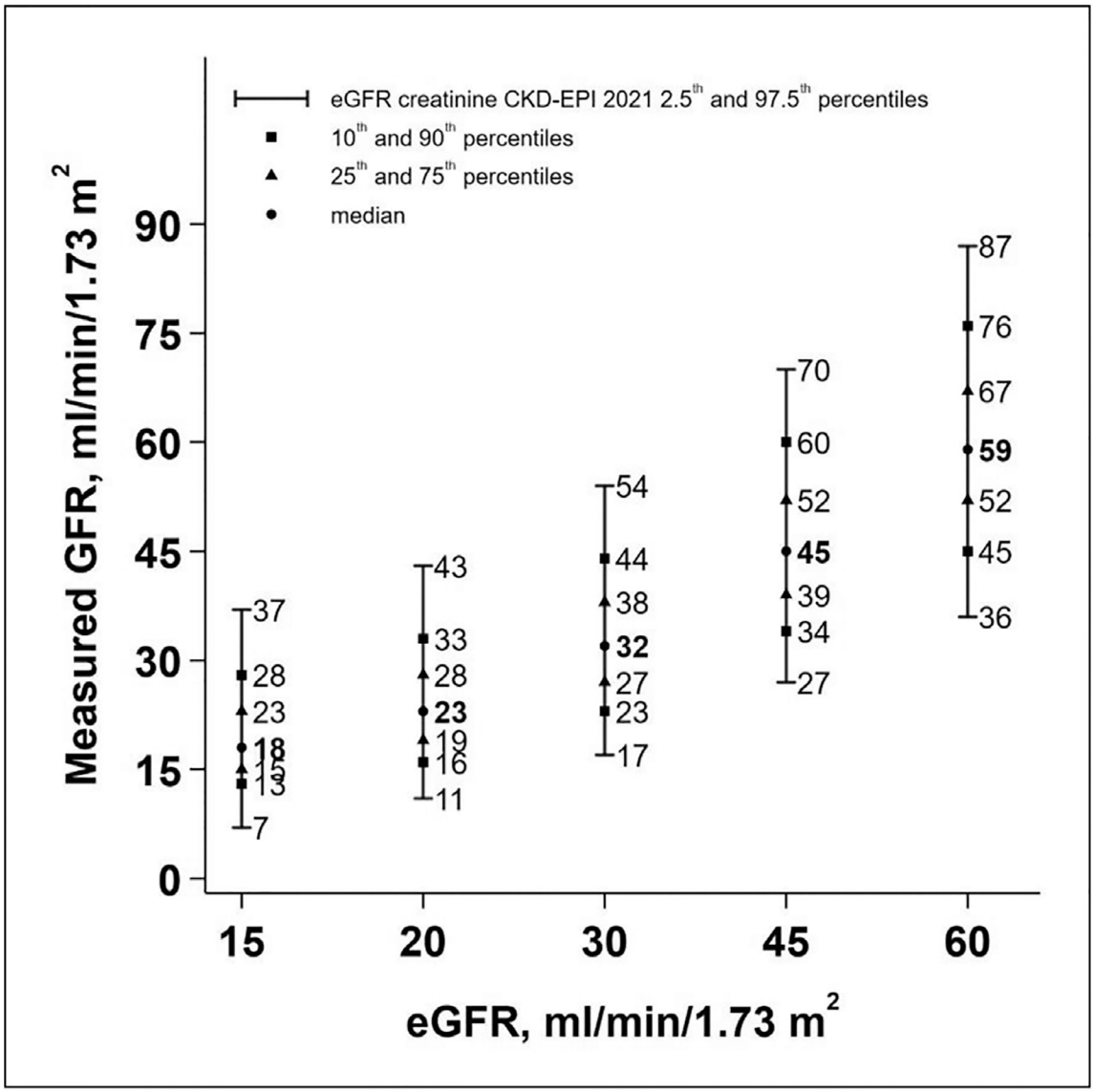

FIGURE 2.

Distribution of measured GFR at selected CKD-EPI 2021 eGFR threshold for CKD Diagnosis and Staging based on four prospective US cohorts - GENOA, ECAC, ALTOLD, and CRIC. eGFR was calculated using CKD-EPIcr 2021. Selected eGFR cut-off values correspond to the thresholds for CKD diagnosis and staging. GFR was measured using urinary clearance nonradiolabeled iothalamate in GENOA and ECAC, radiolabeled iothalamate in CRIC, and plasma clearance of iohexol in ALTOLD. Each percentile value is from a separate quantile (2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th) regression model of mGFR on CKD-EPIcr 2021. Sample interpretation: at an eGFR of 30, 50% of mGFRs ranged from 27 ml/min/1.73 m^2 to 38 ml/min/1.73 m^2, 80% of mGFRs ranged from 23 ml/min/1.73 m^2 to 44 ml/min/1.73 m^2, while 95% of mGFRs ranged from 17 ml/min/1.73 m^2 to 54 ml/min/1.73 m^2. ALTOLD, Assessing Long-term Outcomes in Living Kidney Donors Study; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort;

ECAC, Epidemiology of Coronary Artery Calcification Cohort Study; GGFR, glomerular filtration rate; ENOA, Genetic Epidemiology Network of Arteriopathy Study.

Table 1.

Narrow therapeutic index medications and adjustments based on kidney function [1–3]

Medication	Usual dosage	Threshold for adjustment
Aminoglycosides	Various	<60 ml/min
Cyclophosphamide	Various	<30 ml/min
Cisplatin	Various	<60 ml/min
Digoxin	0.125–0.25 mg/day	<60 ml/min
Direct-acting oral anticoagulants		
Apixaban	2.5–5 mg twice daily	<25 ml/min
Dabigatran	150mg twice daily	<30 ml/min
Edoxaban	60mg once daily	<30 ml/min
Rivaroxaban	20mg once daily	<50 ml/min
Glucagon-like peptide 1 receptor agonist	Various	<15 ml/min
Lithium	600–900 mg/day	<60 ml/min
Metformin	500–1000 mg/day	<45 ml/min
Mineralocorticoid receptor agonists	Various	<30 ml/min
Sodium-glucose cotransporter-2 inhibitors	Various	<25 ml/min
Vancomycin	15–20 mg/kg i.v. Q 8–12 h	<50 ml/min
Warfarin	2.5 mg/day	<60 ml/min

References:

1. Heerspink HJL, StefÃnsson BV, Correa-Rotter R, *et al.* Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.

2. Michos ED, Tuttle KR. GLP-1 Receptor agonists in diabetic kidney disease. Clin J Am Soc Nephrol. 2021;16(10):1578–80.

3. Lexicomp Online. Lexi-Drugs. Waltham, MA: UpToDate, Inc.; 2022. Available at: https://uptodate.com