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Special Report

National Kidney Foundation Laboratory Engagement Working Group Recommendations for Implementing the CKD-EPI 2021 Race-Free Equations for Estimated Glomerular Filtration Rate: Practical Guidance for Clinical Laboratories

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Recognizing that race is a social and not a biological construct, healthcare professionals and the public have called for removal of race in clinical algorithms. In response, the National Kidney Foundation and the American Society of Nephrology created the Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases to examine the issue and provide recommendations.

The final report from the Task Force recommends calculating estimated glomerular filtration rate (eGFR) without a race coefficient using the recently published CKD-EPI 2021 creatinine (cr) and creatinine-cystatin C (cr-cys) equations. The Task Force recommends immediately replacing older $eGFR_{cr}$ equations (MDRD Study and CKD-EPI 2009) with the new CKD-EPI 2021 equation.

In a 2019 survey by the College of American Pathologists, 23% of 6200 laboratories reporting $eGFR_{cr}$ used an incorrect equation that is not suitable for use with standardized creatinine measurements, 34% used the CKD-EPI 2009 equation and 43% used the MDRD Study 2006 equation re-expressed for standardized creatinine measurement.

Rapid transition to using the CKD-EPI 2021 equation is an opportunity for laboratories to standardize to a single equation to eliminate differences in $eGFR_{cr}$ due to different equations used by different laboratories, and to report eGFR without use of race. We provide guidance to laboratories for implementing the CKD-EPI 2021 equations for both $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$.

Introduction

Glomerular filtration rate (GFR) is essential to many aspects of medical care, public health, and research. Clinical laboratories provide an important role in the assessment of GFR and diagnosis of kidney disease. Measuring serum creatinine along with an estimated glomerular filtration rate ($eGFR_{cr}$) is recommended as the first step in GFR evaluation by current clinical practice guidelines (1, 2). Confirmatory tests include serum cystatin C for calculation of eGFR alone or with creatinine ($eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$, respectively) or measured clearances of creatinine or exogenous filtration markers (1, 2).

Serum creatinine may be ordered alone but most frequently it is ordered as part of the basic and comprehensive metabolic panels, and the renal function panel. The recently introduced kidney profile includes $eGFR_{cr}$ with urine albumin–creatinine ratio (uACR) to detect albuminuria. For over 20 years, $eGFR_{cr}$ has been calculated using equations such as the Modification of Diet in Renal Disease (MDRD) Study 1999 equation (3), the MDRD Study 2006 equation re-expressed for use with standardized creatinine results (4), and more recently the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation (5). Based on a 2019 College of American Pathologists (CAP) Survey of 6200 laboratories, $eGFR_{cr}$ was reported by 92% of laboratories with 23% using an incorrect equation that is not suitable for use with standardized creatinine measurements (MDRD Study 1999 4-variable and

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6-variable, and Cockcroft–Gault), 43% using the MDRD Study 2006 equation, and only 34% using the CKD-EPI 2009 equation (6). In 2012, CKD-EPI developed equations using cystatin C, either alone ($eGFR_{cys}$) or in addition to creatinine ($eGFR_{cr\text{-}cys}$) (7). However, use of cystatin C is limited as few clinical laboratories perform this test; in the same 2019 CAP Survey, 3900 US respondents reported that 2% offered cystatin C in their laboratories, 90% sent specimens to referral laboratories, and 8% did not answer the question.

The MDRD Study, CKD-EPI 2009 $eGFR_{cr}$, and 2012 $eGFR_{cr\text{-}cys}$ equations include a coefficient for Black vs non-Black race groups that was intended to improve the accuracy of the eGFR for both groups in the data sets used to develop the equations (3, 5, 7). The terms "Black" and "African American" have been applied interchangeably in past studies although not all Blacks self-identify as African American. We use the term "Black" in this report. Race is a social, not biological, construct, and as such its definition lacks precision and tends to be dynamic over time and in different places. In the past several years, healthcare professionals and the public have increasingly called for the removal of race from clinical algorithms (8–11).

Some laboratories modified the current equations for reporting eGFR by removing the race coefficients from computation of the eGFR values. This approach leads to lower eGFR values only for Black individuals and could impact many aspects of medical care. For example, lower eGFR might lead to earlier recognition of CKD and initiation of CKD care, but could also lead to an inappropriate decrease in drug usage or dosing of medications that are cleared by the kidneys (e.g., cancer chemotherapies or antibiotics), or used as contrast agents (12). To ensure that any change was done with consideration of all perspectives and potential consequences, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) created the Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases to examine the issue and provide recommendations for the United States. The charge for the Task Force included consideration of the laboratory community given the importance of eGFR reporting to successful implementation of any recommendation (11).

The recommendations from the Task Force are summarized in the following list (13).

1. For US adults (>85% of whom have normal kidney function), we recommend immediate implementation of the CKD-EPI 2021 creatinine equation refit without the race variable (14) in all laboratories in the US because it does not include race in the calculation and reporting, includes diversity in its development, is immediately available to all labs in the US, and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals.
2. We recommend national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in adults who are at risk for or have chronic kidney disease, because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone. If ongoing evidence supports acceptable performance, the CKD-EPI 2012 eGFR-cystatin C ($eGFR_{cys}$) and the 2021 eGFR creatinine-cystatin C ($eGFR_{cr\text{-}cys}$) equations should be adopted to provide another first-line test in addition to confirmatory testing.
3. Research on GFR estimation with new endogenous filtration markers and on interventions to eliminate race and ethnic disparities should be encouraged and funded. An investment in science is needed for newer approaches that generate accurate, unbiased, and precise GFR measurement and estimation without the inclusion of race, and that promote health equity and do not generate disparate care.

The first recommendation is to calculate eGFR using the recently published CKD-EPI 2021 creatinine and creatinine-cystatin C equations that were refit without a race coefficient using the development data sets from the 2009 and 2012 equations (14). Both 2021 equations included a diverse development population, consisting of 32% and 40% Black participants, respectively, did not include a variable for race group in development of the equations, nor in the equations, had acceptable performance characteristics in all groups, and the potential consequences of their use are not anticipated to disproportionately affect any one group of individuals. The Task Force recommended immediately replacing older $eGFR_{cr}$ equations (MDRD Study and CKD-EPI 2009) with the new CKD-EPI 2021 equation. "Immediately" in this context is interpreted as promptly based on capabilities of laboratories to make the change following the guidance provided here.

The second recommendation from the Task Force was to increase education of clinicians as to when a cystatin C test should be ordered. The $eGFR_{cr\text{-}cys}$ equation provides a more accurate estimate of GFR than the equations that include only serum creatinine or cystatin C alone (14). Laboratories should offer cystatin C performed either in their own laboratory or sent to a referral laboratory so the test is readily available as a follow-up for $eGFR_{cr}$ when needed (see below). Cystatin

C testing on site allows a more rapid turnaround time and will facilitate using the $eGFR_{cr\text{-}cys}$ equation because the creatinine and cystatin C results will both be available to perform the calculation. When the cystatin C result comes from a referral laboratory, there are challenges to incorporate that value with a previously measured creatinine result in the calculation.

Laboratories should promptly replace the currently used CKD-EPI 2012 equation for combined creatinine–cystatin C that has a race coefficient (7) with the new CKD-EPI 2021 equation without a race coefficient (14). Calculating eGFR from cystatin C alone is unaffected because the currently recommended CKD-EPI 2012 equation does not have a race coefficient, although use of this equation was not a primary recommendation of the Task Force final report.

This report is intended to assist clinical laboratories in implementing the new CKD-EPI 2021 equations to standardize calculation of eGFR using equations developed without a race coefficient. The recommendations are summarized in Table 1 and expanded in the text. Patients and physicians are best served when clinical laboratories report standardized results across all communities wherever patients obtain testing. Using the same equation for each filtration marker or combination of filtration markers is important to standardize GFR evaluation for clinical practice, research, and public health.

Use of GFR Estimates in Clinical Practice

Together with albuminuria, GFR is used to detect and risk stratify chronic kidney disease into actionable categories for monitoring and treatment, including efforts to slow disease progression (1, 2). For patients with severe CKD, GFR is recommended to determine nephrology referral (1), medical nutrition benefit (15, 16), timing of vascular access, and transplant eligibility (17, 18). In other aspects of medicine, GFR is a risk factor for cardiovascular morbidity and mortality. GFR is also used for drug dose adjustments (19, 20), including use of contrast agents, and kidney donor evaluation (21, 22).

$eGFR_{cr}$ has acceptable accuracy compared to measured GFR for many clinical decisions (80% to 90% of eGFRs are within 30% of measured GFR), but it is less accurate when non-GFR determinants of serum creatinine concentration differ from the study participants in which the equations were developed (23, 24). These conditions include variable creatinine generation (muscle wasting diseases, amputees, body builders, vegan diet), drugs that inhibit tubular secretion of creatinine such as cimetidine, cobicistat, dolutegravir, fenofibrate, ritonavir, trimethoprim and others (25), and conditions with extra-renal elimination of creatinine (gastrointestinal and "third-space" losses) (23). In addition, interferents with the laboratory assays for creatinine (significantly increased ketones, ketoacids, beta-hydroxybutyrate, glucose, protein, bilirubin, cephalosporins for the alkaline picrate methods; and flucytosine, lidocaine, bilirubin for the enzymatic assays) may make creatinine less reliable for kidney function assessment (26).

In clinical conditions when serum creatinine may be confounded, (e.g., as described above), a cystatin C based estimate may be the best choice. In general, $eGFR_{cys}$ has similar accuracy to $eGFR_{cr}$; however, cystatin C may also be confounded by non-GFR determinants of its serum concentration, including obesity, inflammation, smoking, alterations in thyroid and adrenal hormone status, and transplant history (23, 24, 27, 28). In addition, many influencing factors remain unknown. For example, both $eGFR_{cr}$ and $eGFR_{cys}$ may be inaccurate in patients with severe liver or heart disease. When there are discrepancies between eGFR estimated from creatinine and cystatin C, it would be prudent to consider the individual's clinical circumstances and to proceed to clearance measurements.

Communicating the Change to New eGFR Equations

Implementing the new CKD-EPI 2021 equations requires a comprehensive communication and collaboration plan involving key stakeholders. The laboratory director should collaborate with nephrologists to co-lead the communication plan. The communication plan should reach all practicing clinicians who rely on eGFR values in adults. In particular, internal medicine, family practice, endocrinology, and cardiology physicians manage many patients with CKD before patient referral and consultation with nephrologists. Pharmacists also need to be informed as they formulate drug dosing based on eGFR. Nutrition, dietary services, and transplant services need to be aware regarding the assessment of eligibility for medical nutrition therapy, wait-listing for deceased donor kidney transplantation, and living kidney donor evaluation. Research and clinical trial programs need to be informed since enrollment and trend monitoring may be influenced. Patients may need reassurance that true GFR has not changed even though the new eGFR values that are reported may differ from previously reported eGFR values. In general the new eGFR values will be slightly lower in Blacks and slightly higher in non-Blacks than previously reported values. Those who are not familiar with the development of the new eGFR equations may misinterpret changes in results as either a deterioration or an improvement in their true GFR. Patient advocacy groups who promote optimal kidney care should also be informed.

Table 1. Summary of recommendations for implementing the CKD-EPI 2021 equations.

Equation	Implement the CKD-EPI 2021 $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ equations
Communication	Implement a comprehensive plan for communication with key stakeholders • Physicians and advanced practitioners • Pharmacists • Clinical researchers • Patients • Patient advocates • Dietitians and nutritionists
Assays	Creatinine • Use assays (preferably enzymatic) traceable to IDMS[a] reference measurement procedures • Report results to 2 decimals in units of mg/dL (or 1 decimal in μmol/L) Cystatin C • Use assays traceable to ERM-DA471/IFCC certified reference material • Report results to 2 decimals in units of mg/L
Programming	Collaborate with information technology groups to build/update existing eGFR equations • Use KDIGO[a] recommended naming convention for reported eGFR • Creatinine based; $eGFR_{cr}$ • Cystatin C based; $eGFR_{cys}$ • Combined; $eGFR_{cr\text{-}cys}$ • Ensure new values cannot trend with older results from other equations • Test all equations thoroughly at and near splice/knot values to verify programming
Reporting	Standardize eGFR reporting systems and criteria among all laboratories • Report eGFR indexed to 1.73 m^2 of body surface area with units of mL/min/1.73m^2 • Report eGFR values as rounded whole numbers (no decimals) • Report eGFR using the CKD-EPI 2021 equations only for adults 18 years of age and older • Do not report $eGFR_{cr}$ or $eGFR_{cr\text{-}cys}$ results using the CKD-EPI 2021 equations simultaneously with values from older equations
Additional orders	Make available additional tests for assessing kidney disease • Offer the quantitative urine albumin-creatinine ratio in parallel with the eGFR • Offer the new kidney profile to help make parallel ordering convenient

[a]Abbreviations: IDMS, isotope dilution mass spectrometry; KDIGO, Kidney Disease Improving Global Outcomes.

The communication should summarize the expected magnitude of differences from eGFR values calculated using older equations. Table 2 shows calculations for representative creatinine concentrations and ages. While the magnitude of change in $eGFR_{cr}$ is minimal for many patients, and may not lead to any impact on clinical decisions, it may exceed 10% in patients with lower serum creatinine concentrations and at younger adult ages causing a change in the CKD classification. Changes are larger and produce lower values for Blacks compared to smaller changes and higher values for non-Blacks (14).

The communication should also emphasize that for important clinical decisions, $eGFR_{cr}$ should be the first step in laboratory GFR evaluation (1, 23). Appropriate use of cystatin C or clearance methods can be used as confirmatory tests for $eGFR_{cr}$ in situations when $eGFR_{cr}$ is less reliable or when $eGFR_{cr}$ is near a clinical decision point.

In addition, the communication about the new equations for eGFR and the importance of follow-up testing is an excellent opportunity to remind providers to order the NKF-recommended kidney profile that includes creatinine with $eGFR_{cr}$ and uACR because uACR is under-utilized in many populations at risk of CKD. These two tests are recommended by clinical practice guidelines to monitor patients at risk for CKD (e.g., diabetic, hypertensive, or with cardiac risk factors) to detect disease, and then determine the stage of disease and to monitor progression for those who have CKD (1, 29).

The online Supplemental Material includes suggested text for communicating the change to the new eGFR calculation without a race coefficient. Additional guidance for communication is available at the NKF web site (30). Communication generally involves providing multiple notices in formats that will best

Table 2. Difference in $eGFR_{cr}$ using the CKD-EPI 2021 equation compared to earlier equations.

	Age, years		20				50				80			
	Creatinine, mg/dL		0.60	1.00	1.50	2.00	0.60	1.00	1.50	2.00	0.60	1.00	1.50	2.00
Race group	Sex	Equation	mL/min/1.73m^2											
Black (African American)	Male	2021 $eGFR_{cr}$	142	110	68	48	118	92	56	40	98	76	47	33
		2009 $eGFR_{cr}$	168	125	77	54	136	101	62	44	110	82	50	35
		Difference	**-26 (-15%)**	**-15 (-12%)**	**-9 (-12%)**	**-6 (-11%)**	**-18 (-13%)**	**-9 (-9%)**	**-6 (-10%)**	**-4 (-9%)**	**-12 (-11%)**	**-6 (-7%)**	**-3 (-6%)**	**-2 (-6%)**
		2006 MDRD Study[a]	≥60	≥60	≥60	52	≥60	≥60	≥60	43	≥60	≥60	55	39
		Difference				**-4 (-8%)**				**-3 (-7%)**			**-8 (-15%)**	**-6 (-15%)**
	Female	2021 $eGFR_{cr}$	132	83	51	36	109	69	42	30	91	57	35	25
		2009 $eGFR_{cr}$	152	94	58	41	123	76	47	33	100	62	38	27
		Difference	**-20 (-13%)**	**-11 (-12%)**	**-7 (-12%)**	**-5 (-12%)**	**-14 (-11%)**	**-7 (-9%)**	**-5 (-11%)**	**-3 (-9%)**	**-7 (-9%)**	**-5 (-8%)**	**-3 (-8%)**	**-2 (-7%)**
		2006 MDRD Study	≥60	≥60	54	38	≥60	≥60	45	32	≥60	≥60	40	29
		Difference			**-3 (-6%)**	**-2 (-5%)**			**-3 (-7%)**	**-2 (-6%)**			**-5 (-13%)**	**-4 (-14%)**
Non-Black (non-African American)	Male	2021 $eGFR_{cr}$	142	110	68	48	118	92	56	40	98	76	47	33
		2009 $eGFR_{cr}$	145	108	66	47	117	87	54	38	95	71	43	31
		Difference	**-3 (-2%)**	**2 (2%)**	**2 (3%)**	**1 (2%)**	**1 (1%)**	**5 (6%)**	**2 (4%)**	**2 (5%)**	**3 (3%)**	**5 (7%)**	**4 (9%)**	**2 (6%)**
		2006 MDRD Study	≥60	≥60	≥60	43	≥60	≥60	50	36	≥60	≥60	45	32
		Difference				**5 (12%)**			**6 (12%)**	**4 (11%)**			**2 (4%)**	**1 (3%)**
	Female	2021 $eGFR_{cr}$	132	83	51	36	109	69	42	30	91	57	35	25
		2009 $eGFR_{cr}$	131	81	50	35	106	66	40	28	86	53	33	23
		Difference	**1 (1%)**	**2 (2%)**	**1 (2%)**	**1 (3%)**	**3 (3%)**	**3 (5%)**	**2 (5%)**	**2 (7%)**	**5 (6%)**	**4 (8%)**	**2 (6%)**	**2 (9%)**
		2006 MDRD Study	≥60	≥60	44	32	≥60	59	37	26	≥60	53	33	24
		Difference			**7 (16%)**	**4 (13%)**		**10 (17%)**	**5 (14%)**	**4 (15%)**		**4 (8%)**	**2 (6%)**	**1 (4%)**

[a]The MDRD Study equation is not intended for reporting numeric eGFR values of ≥60 mL/min/1.73m^2.

reach the intended target audiences, e.g., newsletters, announcement at department staff meetings, internal webinars, and on clinical laboratory reports.

Measuring Creatinine and Cystatin C

All eGFR equations require appropriate measurement procedures for creatinine and cystatin C. The CKD-EPI 2009 and 2021 equations were developed using creatinine results that were based on measuring systems calibrated to be traceable to isotope dilution mass spectrometry (IDMS) reference measurement procedures. Clinical laboratories must use creatinine measuring systems that are calibrated to have results traceable to IDMS reference measurement procedures. Similarly, the cystatin C measuring systems used for developing the CKD-EPI 2012 and 2021 equations had calibration traceable to the ERM-DA471/IFCC certified reference material. Clinical laboratories must use cystatin C measuring systems that are calibrated to the same certified reference material. Creatinine results should be reported to 2 decimals in mg/dL or 1 decimal in μmol/L, and cystatin C to 2 decimals in mg/L, to avoid rounding errors when calculating eGFR.

Programming the CKD-EPI 2021 eGFR Equations in a Laboratory Information System

The laboratory needs to collaborate with its information technology group to request the current eGFR calculation be changed to the new CKD-EPI 2021 equations. When changing from the older CKD-EPI 2009 $eGFR_{cr}$ or CKD-EPI 2012 $eGFR_{cr\text{-}cys}$ equations to the new CKD-EPI 2021 equations, the only changes are in the coefficients used; the form of the equations is the same so re-programming is relatively simple. The CKD-EPI equations are for use when the patient's age is 18 years or older. In most cases, the current report provides two eGFR values for adults, one for Black and one for non-Black based on the original recommendation for reporting using the older equations. Because only one value will be reported, the previous two result names are replaced with a single name. The nomenclature recommended by KDIGO is $eGFR_{cr}$ for the creatinine based estimate, $eGFR_{cr\text{-}cys}$ for the combined creatinine–cystatin C based estimate and $eGFR_{cys}$ for the cystatin C alone estimate (1, 31). Because values will differ, eGFR calculated using CKD-EPI 2021 equations should not be allowed to trend with values calculated using older equations.

PARAMETERS USED IN THE ESTIMATING EQUATIONS

The CKD-EPI 2021 equations were developed from data sets with age in whole numbers. However, age rounded to whole numbers or in fractional years are both acceptable because the influence on the eGFR is very small and not of clinical importance. For example, a person who is 52 years and 9 months could be represented as 52.75, or 53 years.

The CKD-EPI 2021 equations were developed from data sets with sex described as a binary variable, male or female. Some electronic medical records can include both the biological sex and gender identity, whereas others are only able to include one sex demographic. In most cases, a laboratory is not informed if a patient identifies as transgender or is receiving gender-affirming hormone therapy and will report an eGFR based on the sex provided in the medical record.

PROGRAMMING THE EGFR CREATININE EQUATION

From (14), the equation for age ≥18 years in a single expression for $eGFR_{cr}$ is:

$$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa,\ 1)^{a} \times \max(S_{cr}/\kappa,\ 1)^{-1.200} \times 0.9938^{Age} \times 1.012\ \text{[if female]}$$

where $\kappa = 0.7$ (females) or 0.9 (males)
$a = -0.241$ (female) or -0.302 (male)
S_{cr} = serum creatinine in mg/dL; divide by 88.4 for creatinine in μmol/L
Age (years)

The coding for implementing the single equation is nuanced. The "$\min(S_{cr}/\kappa,\ 1)$" factor indicates the minimum of S_{cr}/κ or 1.0 and "$\max(S_{cr}/\kappa,\ 1)$" indicates the maximum of S_{cr}/κ or 1.0. Coding may be simpler if the single equation is expressed as 4 equations applicable to 4 logical conditions as in Table 3. See Supplemental Material for equations when SI units are used.

PROGRAMMING THE COMBINED EGFR CREATININE–CYSTATIN C EQUATION

From (14), the equation for age ≥18 years in a single expression for $eGFR_{cr\text{-}cys}$ is:

$$eGFR_{cr-cys} = 135 \times \min(S_{cr}/\kappa,\ 1)^{a} \times \max(S_{cr}/\kappa,\ 1)^{-0.544} \times \min(S_{cys}/0.8,\ 1)^{-0.323} \times \max(S_{cys}/0.8,\ 1)^{-0.778} \times 0.9961^{Age} \times 0.963\ \text{[if female]}$$

where $\kappa = 0.7$ (females) or 0.9 (males)
$a = -0.219$ (female) or -0.144 (male)
S_{cr} = serum creatinine in mg/dL; divide by 88.4 for creatinine in μmol/L
S_{cys} = serum cystatin C in mg/L
Age (years)

Similar to the creatinine equation, the coding for implementing the single equation is nuanced. The "$\min(S_{cr}/\kappa,\ 1)$" factor indicates the minimum of S_{cr}/κ or 1.0, "$\max(S_{cr}/\kappa,\ 1)$" indicates the maximum of S_{cr}/κ or 1.0, "$\min(S_{cys}/0.8,\ 1)$" indicates the minimum of $S_{cys}/0.8$ or 1.0, and "$\max(S_{cys}/0.8,\ 1)$" indicates the maximum of $S_{cys}/0.8$ or 1.0.

Table 3. Equations to calculate $eGFR_{cr}$ from serum creatinine (S_{cr}).

Logic[a]			
Age	Sex	S_{cr}, mg/dL	eGFR equation
≥18	Female	≤0.70 (or <0.71)	$= 142 \times (S_{cr}/0.7)^{-0.241} \times 0.9938^{age} \times 1.012$
		>0.70	$= 142 \times (S_{cr}/0.7)^{-1.200} \times 0.9938^{age} \times 1.012$
	Male	≤0.90 (or <0.91)	$= 142 \times (S_{cr}/0.9)^{-0.302} \times 0.9938^{age}$
		>0.90	$= 142 \times (S_{cr}/0.9)^{-1.200} \times 0.9938^{age}$

[a]Programming logic for "If" statements to select the correct equation for each set of parameters.

Table 4. Equations to calculate $eGFR_{cr\text{-}cys}$ from serum creatinine (S_{cr}) and cystatin C (S_{cys}).

Logic[a]				
Age	Sex	S_{cr}, mg/dL	S_{cys}, mg/L	$eGFR_{cr\text{-}cys}$ equation
≥18	Female	≤0.70 (or <0.71)	≤0.80 or (<0.81)	$135 \times (S_{cr}/0.7)^{-0.219} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age} \times 0.963$
			>0.80	$135 \times (S_{cr}/0.7)^{-0.219} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age} \times 0.963$
		>0.70	≤0.80 or (<0.81)	$135 \times (S_{cr}/0.7)^{-0.544} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age} \times 0.963$
			>0.80	$135 \times (S_{cr}/0.7)^{-0.544} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age} \times 0.963$
	Male	≤0.90 (or <0.91)	≤0.80 or (<0.81)	$135 \times (S_{cr}/0.9)^{-0.144} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age}$
			>0.80	$135 \times (S_{cr}/0.9)^{-0.144} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age}$
		>0.90	≤0.80 or (<0.81)	$135 \times (S_{cr}/0.9)^{-0.544} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age}$
			>0.80	$135 \times (S_{cr}/0.9)^{-0.544} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age}$

[a]Programming logic for "If" statements to select the correct equation for each set of parameters.

Coding may be simpler if the single equation is expressed as 8 equations applicable to 8 logical conditions as in Table 4. See Supplemental Material for equations when SI units are used.

TESTING THE NEW EQUATIONS AFTER PROGRAMMING

Once the information technology team creates the new calculation in the computer test system, the laboratory must verify the program functions as expected. Online Supplemental Tables S1 and S2 include creatinine result inputs and expected $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ outputs that cover a range of values suitable for verifying correct calculations using the CKD-EPI 2021 equations. When testing, it is important to use concentration values at and just above the splice/knot values to ensure the equations were programmed correctly.

PROGRAMMING THE EGFR CYSTATIN C EQUATION

There is no change in the calculation of $eGFR_{cys}$ using the CKD-EPI 2012 equation. Programming for $eGFR_{cys}$ is provided in Supplemental Material for the convenience of readers.

Reporting eGFR Values

The Regenstrief Institute has developed new logical observation identifiers names and codes (LOINC) terms for the new CKD-EPI 2021 eGFR equations. For $eGFR_{cr}$ the LOINC is 98979-8 and for $eGFR_{cr\text{-}cys}$ the LOINC is 98980-6.

The eGFR should be reported indexed for 1.73 m^2 of body surface area (BSA) with units of mL/min/1.73m^2, and if that expression is not available as mL/min/1.73m^2, or mL/min/1.73m2. Truncating the units of measurement is highly discouraged. Some computer charting systems may not allow for a sufficient number of characters to include the units of measurement in the reference interval field in which case the units of measurement may be included in the result comment. Indexed eGFR is appropriate for comparison to normative ranges, but non-indexed eGFR (units of mL/min) is more appropriate for drug dosing for individuals with BSA very different from the index value of 1.73 m^2. Indexed eGFR can be converted to non-indexed eGFR by multiplying by the patient's BSA in m^2 and dividing by 1.73 m^2. The

accuracy of non-indexed eGFR compared to non-indexed measured GFR is similar to the accuracy of indexed eGFR relative to indexed measured GFR (32). When a patient's height and weight are available, consider reporting both indexed and non-indexed eGFR to assist in drug dose decisions.

Numeric values can be reported throughout the range of GFR, similar to the CKD-EPI 2009 equation, but unlike the MDRD Study equation where reporting numeric values were limited to results <60 mL/min/1.73m^2. The reported eGFR value should have whole numbers and no decimals. When calculating eGFR, the reported result should be rounded to the closest whole number based on the rounding logic of a laboratory information system. For example, a calculated eGFR of 59.7 mL/min/1.73m^2 will be reported as 60 mL/min/1.73m^2.

CKD is defined as a GFR <60 mL/min/1.73m^2 or the presence of kidney damage, either of which being present for >3 months. The suggested single value reference value for eGFR is either >59 mL/min/1.73m^2 or ≥60 mL/min/1.73m^2. This eGFR value is consistent with the decision value used in criteria for making a diagnosis of CKD (1).

The CKD-EPI 2021 eGFR equations are intended only for adults 18 years and older. When a patient's age is unknown, an eGFR cannot be reported. A comment such as 'Unable to calculate eGFR because patient age was unspecified' may be added. When the clinical laboratory has no record of the patient's sex, the report can include a comment such as 'Unable to calculate eGFR because patient sex or age was unspecified.' An alternative when sex is unknown or not disclosed, or when gender identity and not biological sex are reported in the electronic medical record, is to report eGFR values for both males and females. This would allow for shared decision making between the patient and the health care professional as to the best eGFR value to be used to guide their care. We recognize this approach to report 2 values may not be practical for computer systems. At present, there is much unknown about the accuracy of eGFR in transgender individuals (33–35). $eGFR_{cys}$ is less affected by sex than $eGFR_{cr}$ and might be considered reasonable to use as a first test for such individuals although exogenous sex hormones might affect cystatin C separately from their effect on GFR. Optimal methods to assess GFR in transgender individuals is an evolving field, and we anticipate having more guidance in the years ahead.

We discourage clinical laboratories reporting eGFR values using both CKD-EPI 2021 and the older equations with the intent to allow clinicians to "rebaseline" patients from the old to new values. Multiple eGFR results may be confusing and extend the use of race-based calculations.

Urine Albumin–Creatinine Ratio

Quantitative uACR for a random or morning first void urine is an essential laboratory test for assessing albuminuria for CKD detection, evaluation, and determining the risk of progression. uACR should be reported in units of mg of albumin per g of creatinine. uACR >30 mg/g is one of the diagnostic criteria for CKD. The level of uACR is also vital to assessing risk for and monitoring disease progression, the impact of medical interventions, and to determine when an $eGFR_{cr\text{-}cys}$ or $eGFR_{cys}$ is indicated. Laboratories are encouraged to offer the new kidney profile that includes both $eGFR_{cr}$ and uACR to assist clinical providers in consistently ordering these 2 important tests for CKD assessment (36, 37).

Conclusions

We support the NKF-ASN Task Force recommendation that clinical laboratories quickly implement the CKD-EPI 2021 equations for $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ to eliminate race as a parameter when calculating eGFR and to standardize laboratory reporting. We provide guidance for implementing these changes and recognize the burden on laboratories to make this transition. There may be challenges in implementing the internal calculations, changing reporting practices, and effectively communicating to the relevant stakeholders. However, the benefit of transitioning to a unified approach for CKD-related testing is improved quality of care for all patients. Benefits also include standardizing results for consistent interpretation from all laboratories to minimize variability in using eGFR in clinical decision making. Additional information is available at the websites of the NKF (38) and the CKD-EPI (39). The Supplemental Material includes a list of resources available from the NKF.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; $eGFR_{cr}$, estimated glomerular filtration rate using serum creatinine; MDRD, Modification in Diet Renal Disease; $eGFR_{cr\text{-}cys}$, estimated glomerular filtration rate using serum creatinine and cystatin C; GFR, glomerular filtration rate; $eGFR_{cys}$, estimated glomerular filtration rate using cystatin C; uACR, urine albumin–creatinine ratio. CKD, chronic kidney disease; NKF, National Kidney Foundation; S_{cr}, serum creatinine; S_{cys}, serum cystatin C.

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acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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Correction

This is a correction to: W Greg Miller, Harvey W Kaufman, Andrew S Levey, Joely A Straseski, Kelly W Wilhelms, Hoi-Ying (Elsie) Yu, J Stacey Klutts, Lee H Hilborne, Gary L Horowitz, John Lieske, Jennifer L Ennis, James L Bowling, Mary Jane Lewis, Elizabeth Montgomery, Joseph A Vassalotti, Lesley A Inker, National Kidney Foundation Laboratory Engagement Working Group Recommendations for Implementing the CKD-EPI 2021 Race-Free Equations for Estimated Glomerular Filtration Rate: Practical Guidance for Clinical Laboratories, *Clinical Chemistry*, Volume 68, Issue 4, April 2022, Pages 511–520, https://doi.org/10.1093/clinchem/hvab278

The originally published version of this Special Report contained errors. In the equation for age 18 years in a single expression for $eGFR_{cr\text{-}cys}$ on page 516, the exponent $^{-1.200}$ should be $^{-0.544}$.

On page 513, "ritonovir" should be "ritonavir."

These errors have been corrected online. The authors regret the errors.

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