AACC Guidance Document on Chronic Kidney Disease Diagnosis- Improving Equity in Chronic Kidney Disease

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LIST OF ABBREVIATIONS

4v-MDRD, 4-variable Modification of Diet in Renal Disease
6v-MDRD, 6-variable Modification of Diet in Renal Disease
AKI, acute kidney injury
APOL1, apolipoprotein 1
ASN, American Society of Nephrology
CDC, Centers for Disease Control and Prevention
CKD, chronic kidney disease
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
CMS, Centers for Medicare and Medicaid Services
CPT, Current Procedure Terminology
DSD, differences in sexual development
eGFR, estimated glomerular filtration rate
$eGFR_{cr}$, estimated glomerular filtration rate calculated with creatinine
$eGFR_{cr\text{-}cys}$, estimated glomerular filtration rate calculated with creatinine and cystatin C
$eGFR_{cys}$, estimated glomerular filtration rate calculated with cystatin C
EHR, electronic health record
ESKD, end stage kidney disease
GFR, glomerular filtration rate
KFRE, kidney failure risk equation
KDIGO, Kidney Disease Improving Global Outcomes
KDOQI, Kidney Disease Outcomes Quality Initiative
KPMP, Kidney Precision Medicine Project
LIS, lab information system
MDRD, Modification of Diet in Renal Disease
mGFR, measured glomerular filtration rate
NKF, National Kidney Foundation
POC, point of care
SDI, social deprivation index
uACR, urine albumin to creatinine ratio
uPCR, urine protein to creatinine ratio
USPSTF, United States Preventative Services Task Force

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Abstract

Background

Kidney disease is an important health equity issue with Black, Hispanic, and socioeconomically disadvantaged individuals experiencing a disproportionate burden of disease. Prior to 2021, the most common estimated glomerular filtration rate (eGFR) equations incorporated coefficients for Black race that conferred higher GFR estimates for Black individuals compared to non-Black individuals of the same sex, age and blood creatinine concentration. With a recognition that race does not delineate distinct biological categories, a joint task force of the National Kidney Foundation and the American Society of Nephrology recommended the adoption of the CKD-EPI 2021 race-agnostic equations.

Content

This document provides guidance on implementation of the CKD-EPI 2021 equations. Kidney disease biomarker testing and strategies that clinical laboratories can use to improve kidney disease detection in high-risk populations are also detailed. Further, the document provides guidance on the appropriate use of cystatin C, and eGFR in gender-diverse populations.

Summary

Implementation of the CKD-EPI 2021 eGFR equations represents progress towards health equity in the management of kidney disease. Ongoing efforts by multidisciplinary teams, including clinical laboratorians, should focus on improved disease detection in clinically and socially high-risk populations. Routine use of cystatin C is recommended to improve the accuracy of eGFR, particularly in patients whose blood creatinine concentrations are confounded by processes outside of the kidney. Because currently available eGFR equations incorporate a sex coefficient, calculations that use male and female coefficients are important when managing gender diverse individuals and a more holistic management approach should be employed at important clinical decision points.

Introduction

Despite significant progress in disease diagnosis and treatment, racial and ethnic minorities experience lower quality of care and poorer outcomes for several health conditions compared to non-minorities. These disparities have been researched extensively, and acknowledged by the federal government for more than three decades (1). In 2020, the widely publicized and tragic deaths of multiple Black individuals heightened collective calls to examine and mitigate the impacts of systemic racism on racialized minority populations. On the heels of these events, the disproportionate burden of COVID-19 morbidity and mortality experienced by racialized minorities galvanized momentum for change across several institutions, including healthcare (2,3). Racial and ethnic healthcare disparities are influenced by a complex interplay of biological and social factors, and in some instances, can be perpetuated and exacerbated by systemic healthcare practices (2–4). One such practice, the use of Black race coefficients in estimated glomerular filtration rate (eGFR) equations, prompted the formation of a joint task force by the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) to reassess the inclusion of race in diagnosing kidney diseases, risk stratification and staging. The recommendations stemming from the work of the NKF-ASN Task Force and the rationale for the proposed recommendations were detailed in interim and final reports (4,5) and can be summarized as follows:

1. For US adults, the CKD-EPI 2021 (Chronic Kidney Disease Epidemiology Collaboration) creatinine-based eGFR ($eGFR_{cr}$) equation that was developed without the use of the race coefficient should be implemented immediately in all laboratories.
2. National efforts should be undertaken to facilitate increased, routine, and timely use of cystatin C, in populations at risk for chronic kidney disease (CKD) or who have CKD. The race-neutral CKD-EPI 2012 $eGFR_{cys}$ and CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equations should be adopted to provide more accurate first-line or confirmatory testing, as appropriate for the clinical setting.

3. Research on GFR (glomerular filtration rate) estimation with new endogenous filtration markers and on interventions to eliminate racial and ethnic disparities in kidney disease should be encouraged and funded.

The purpose of this guidance document is to provide a tool for clinical laboratorians to facilitate implementation of the NKF-ASN Task Force recommendations. In addition to discussing practical aspects of implementing the CKD-EPI 2021 $eGFR_{cr}$ equation and cystatin C testing, the document explores CKD risk factors, laboratory tests that are used to diagnose and manage CKD, and recommendations on appropriate utilization of cystatin C-based eGFR equations. In addition, this document provides a framework for understanding the nuances and potential harms of utilizing race as a biologic classifier in eGFR and details evidence-based, actionable measures that clinical laboratorians can take to improve equity in kidney health. Race, ethnicity and gender identity can intersect to impact how individuals receive healthcare (6). Greater attention on GFR reporting and its challenges, also highlights the importance of appropriate use of eGFR in transgender and gender diverse individuals and therefore, considerations for eGFR reporting in these populations are also discussed.

What groups are at risk for worse disease burdens and outcomes from CKD?

Key Summary Points:

- *Clinical risk factors for kidney disease include diabetes, hypertension, a family history of kidney failure and older age.*
- *Racial and ethnic minorities and individuals with low socioeconomic status experience worse kidney health and clinical outcomes*
- *Individuals with two APOL1 risk alleles have a significantly greater risk of kidney disease; these have been reported to be most prevalent in individuals of recent West African ancestry*

CKD is the gradual loss of kidney function and remains a global public health concern (7). The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines define CKD as

abnormalities of kidney structure or function, present for >3 months, with implications for health (8). For CKD diagnosis one or more markers of kidney damage must be present for >3 months. CKD staging is performed on a continuum and is determined based on clinical manifestation of kidney damage, reductions in GFR, increases in albuminuria, or anomalies in other kidney biomarkers. CKD is classified by identifying the cause of CKD (C), assigning a GFR category (G) and assigning an albuminuria category (A), which is collectively known as "CGA Staging" (8). CKD is classified into six GFR categories as described in **Table 1**.

In 2021, the Centers for Disease Control and Prevention (CDC) estimated that 37 million adults in the United States have CKD (7). Complex interactions of social, environmental, and biologic factors are associated with CKD. Women exhibit a higher prevalence of CKD (14.3% versus 12.4%) (7), however men have a higher risk of developing kidney failure (9–11). CKD is more prevalent in Black non-Hispanic (16.3%), and Black Hispanic (13.6%) adults than White and Asian non-Hispanic and White Hispanic adults (12.7% and 12.9%, respectively) (7,12). Further, Black and Hispanic persons have a 3.3- and 1.9-fold higher risk, respectively, of developing kidney failure requiring dialysis as compared to White individuals (13,14). However, White persons are more likely to be placed on the waitlist for a kidney transplant prior to dialysis initiation, and more likely to receive a living donor kidney transplant while on dialysis as compared to Black and Hispanic individuals (15).

Clinical risk factors for CKD include diabetes mellitus, hypertension, cardiovascular disease, obesity, history of acute kidney injury, older age (≥65 years), suboptimal diet (including high intake of animal protein and low intake of fruits and vegetables) (7,16,17), hereditary kidney disorders (18,19) and the presence of kidney disease risk variants (7,20). Social determinants of health also contribute to CKD incidence, prevalence and morbidity. Socioeconomic variation in health outcomes can be quantified using the social deprivation index (SDI), which measures area level deprivation based on seven demographic characteristics (income, education, employment, housing, household characteristics, transportation and

demographics) collected in the American Community Survey (21). A higher SDI indicates a higher level of combined socioeconomic stressors. Individuals who experience the most deprivation also experience worse kidney health and healthcare compared to those in low SDI neighborhoods, irrespective of race (15). Nevertheless, within SDI cohorts, racial and ethnic disparities in end-stage kidney disease (ESKD) incidence and preemptive kidney transplant remain evident (4).

In addition to the disparities in health related to social determinants, genetic variants play a clear role in increasing risk of kidney disease in some Black individuals. Individuals with two risk variants for the gene that encodes apolipoprotein 1 (*APOL1*) are at significantly greater risk for developing many types of severe kidney disease (22,23). These risk alleles are more prevalent in individuals of recent West African ancestry (22,23). The presence of two risk alleles confers a significantly greater risk of hypertension-attributed ESKD, focal segmental glomerulosclerosis and HIV associated nephropathy. *APOL1* 'kidney disease variants' are not 100% penetrant and more research is needed to assess the impact of environmental and psychosocial factors on gene expression in kidney disease.

What tests are used to diagnose and manage chronic kidney disease?

Key Summary Points:

- *Patients with risk factors for CKD should be evaluated and followed with measurements of creatinine and/or cystatin C to determine eGFR and with uACR*
- *The Kidney Profile test order, which combines eGFR and uACR together under one heading on the laboratory requisition form or electronic health record order, can simplify test ordering for detection and diagnosis of CKD*

Clinical laboratory tests used to diagnose and manage CKD include creatinine, cystatin C, GFR (measured or estimated), and urine albumin-creatinine ratio (uACR). A brief summary of recommendations for measurement and reporting of each test or equation can be found in **Table 4**.

Creatinine

Creatinine, a catabolic product of muscle metabolism, is measurable in blood and urine. Normally, creatinine is generated at a constant rate and creatinine in the blood is freely filtered by the glomerulus. In addition, 10-30% of creatinine excretion is due to tubular secretion (24). Of note, creatinine is an imperfect marker of GFR because several non-GFR determinants can affect systemic creatinine concentrations in the absence of kidney damage. Non-GFR determinants of blood creatinine are described in **Table 2**.

Cystatin C

Cystatin C is a 13.3 kDa protease inhibitor that is synthesized in all nucleated cells, freely filtered through the glomerular membrane, and resorbed and catabolized in the proximal tubules (25). Cystatin C has been established as an alternative and adjunct to creatinine in GFR estimation (25–27), with equations that incorporate both markers showing superior performance than those relying solely on creatinine (26,27). Furthermore, cystatin C has shown utility as a marker for acute kidney injury (AKI) in certain settings (28,29). Cystatin C also has non-GFR determinants, as described in **Table 2**, and these determinants may be enriched in hospitalized individuals (9).

Estimated glomerular filtration rate

Direct evaluation of GFR requires blood or urinary clearance of exogenous analytes that are filtered, but not resorbed, by the kidney. Common agents used to directly measure GFR include inulin (traditionally the gold standard for measured GFR (mGFR) but not currently available in the US), iothalamate and iohexol. For the direct measurement of GFR, serial blood samples are generally collected to determine clearance kinetics of these agents. eGFR has predominantly replaced mGFR and timed urine collections for creatinine clearance in most clinical practice due to practical and cost considerations. GFR estimation equations utilize the concentration of kidney biomarkers such as creatinine and/or cystatin C in the blood to evaluate GFR. Prior to the introduction of the CKD-EPI 2021 refit equations, the 4v-MDRD

and 2009 CKD-EPI$_{cr}$ equations were the most commonly used creatinine-based eGFR equations in the US, with more than 70% of laboratory users reporting eGFR using the 4v-MDRD equation (30). As previously described, both equations were derived using blood creatinine in conjunction with age, sex and a Black race coefficient, resulting in an indexed eGFR that is standardized to a body surface area (BSA) of 1.73 m^2 (the average BSA of a 70 kg man). The CKD-EPI 2021 refit equations incorporate blood creatinine (eGFR$_{cr}$), or creatinine and cystatin C (eGFR$_{cr\text{-}cys}$), along with age and sex. eGFR equations are detailed in **Appendix 1**.

Urine albumin to creatinine ratio

The uACR helps estimate the amount of albumin excreted in the urine over 24 hours based on assumptions regarding creatinine excretion. While uACR does not directly assess eGFR, when there is aberrant filtration due to kidney damage, this value is typically elevated and is used to assess risk for progression in conjunction with eGFR. Normally, only small quantities of albumin are filtered by the glomerulus; however, albumin is usually nearly completely resorbed in the proximal tubules via active transport processes. In the setting of compromised tubular function, or when high quantities of albumin enter the filtrate due to glomerular disease, active transport mechanisms become saturated, leading to excretion of albumin into the urine. Urinary albumin should be normalized to urine creatinine and reported as a ratio, uACR, due to variability in dilution and concentration of the urine and overall water balance. uACR may be determined from a random urine sample or a 24-hour collection. Normalization of urine albumin to urine creatinine in a 24-hour or other timed urine collection may not be necessary if the value of interest is the albumin excretion rate in mg/min or mg/24hrs. uACR results <10 mg/g of creatinine are optimal, 10-30 mg/g is mildly increased, 30-300 mg/g is moderately increased and >300 mg/g is markedly increased (8,31). Historically, the term microalbumin was used as a pseudonym for urine albumin or uACR determinations. This term is a misnomer, and current recommendations advocate that

the term urine albumin be used to describe the individual measurement, and uACR be used as the indicator of albuminuria (8).

Urine albumin assays are not standardized, which precludes the application of uniform clinical decision points in the assessment of albuminuria between laboratories that use different assays (32,33). While most urine albumin assays are relatively precise, with coefficients of variation ranging between 5.2-8.1%, assay, bias relative to isotope dilution-liquid chromatography-mass spectrometry reference assays causes lack of agreement among assays (32,33). Patients should be screened and monitored using serial urine albumin measurements by the same assay to calculate the uACR. Standardization efforts are underway to enable better agreement between measurements performed at different laboratories (32,33). It should be emphasized that urine albumin and uACR exhibit large intra-individual biological variation, which can be larger than the differences observed between albumin measurements using assays from different manufacturers (32–34).

Several commercially available urine albumin assays are limited by their lower limit of quantification (LLOQ), which prevents precise calculation of the uACR when urine albumin is below the LLOQ. In these instances, Miller *et al.* recommend utilizing the manufacturer-defined LLOQ as the numerator in the uACR calculation; however, this strategy can result in falsely increased rates of uACRs above the clinically important threshold of 30 mg/g (35,36). As an alternative, lower limits of quantification can be validated by the clinical laboratory (36). Changing the LLOQ would render an assay FDA-modified, and as such a thorough validation study by the clinical laboratory would be required. Greene *et al.* validated a decreased LLOQ of 3mg/L for urine albumin, compared to the manufacturer-defined LLOQ of 12 mg/L. Linearity at the lower LLOQ was assessed by making serial dilutions of urine samples such that the dilutions spanned the LLOQ. The limit of blank and limit of detection were calculated using serial measurements of diluent blank and low concentration samples. Imprecision of ≤10% was considered acceptable for a reduced LLOQ. Urine samples with measured albumin concentrations < 12

mg/L were compared with an external laboratory's assay with a validated LLOQ of 3 mg/L. This study found that among specimens with urine albumin concentrations of < 12 mg/dL, 0.4% (n=499) had uACRs of >30mg/g, compared to 21.4% specimens when the manufacturer-defined LLOQ was substituted as the numerator in the uACR calculation (36). Validating dilutions to increase the upper end of the reportable range can also improve the utility of uACR for risk prediction and disease progression.

Compared to other markers, such as urine protein to creatinine ratios (uPCR), uACR in mg/g is the preferred urinary marker of kidney damage due to its improved clinical specificity and sensitivity (37). Currently, KDIGO guidelines stratify three uACR categories, as shown in **Table 1**. Further, in a recent meta-analysis, efforts were made to correlate uPCR or qualitative urine protein results with uACR results (**Table 3**) (38); such correlations may prove useful in their ability to categorize patients by albuminuria stage in instances where only urinary protein measurements are available.

The Kidney Profile

To improve screening in high-risk patients, a Kidney Profile order panel was recommended in 2018 as part of the NKF's Laboratory Engagement Plan and consists of blood creatinine, eGFR and uACR (39). Results from the CAP 2020-Chemistry Survey showed that among US participants, only 15% offered the Kidney Profile (40). The Kidney Profile is aimed, in part, at increasing utilization of uACR, which is used in combination with eGFR for CKD diagnosis, risk-stratification and therapy; however, it is significantly underutilized (41–43). The reasons underlying uACR underutilization are multifactorial, but include non-standardized reporting (40) and clinician uncertainty around test utility and interpretation (37,44). The frequency of CKD monitoring with the Kidney Profile should be tailored to the underlying cause of CKD, the rate of change of eGFR or uACR, the presence of one or more clinical risk factors, changes to medication management, intercurrent illness, and active vs conservative management of CKD.

What equations were most commonly used for eGFR prior to the introduction of the CKD-EPI 2021 equations?

Key Summary Points:

- *The most commonly used eGFR equations prior to 2021 were the 4v-MDRD and CKD-EPI 2009, which both incorporate Black race coefficients.*
- *Race and ethnicity are imprecise, nebulously defined systems of classification as they pertain to genetic ancestry, physiologic characteristics, and socioeconomic status and therefore should not be used to classify individuals into distinct biological categories*
- *The CKD-EPI 2021 refit equations were developed because a race-free, equitable approach to eGFR was desired and needed.*

Creatinine has been used to assess GFR since the 1970s, first via nomograms and later with the Cockcroft-Gault equation to estimate creatinine clearance. The latter was considered a reasonable surrogate for evaluation of GFR and utilized to interpret pharmacologic data and establish medication dosing recommendations (45). In 1999, the 6-variable Modification of Diet in Renal Disease (6v-MDRD) study equation was published (46). This equation was developed from a predominantly White cohort of 800 men and 500 women enrolled in a clinical study to assess the potential effects of low protein diets on progression of CKD. The study evaluated 16 patient variables and subsequently derived equations to estimate GFR. The 6-variable (and subsequent 4-variable) MDRD equations, which incorporated a Black race coefficient, yielded the best goodness of fit (R^2 value), best precision and the least bias when applied to the original cohort. The studies used to generate the MDRD equations were not consistent in the way that race was assigned (46). The Kidney Disease Outcomes Quality Initiative (KDOQI) embraced the 4-variable Modification of Diet in Renal Disease (4v-MDRD) eGFR equation and recommended its use as a foundation for diagnosis and staging of CKD (31). Use of the Black race coefficient in these equations became widely accepted. Subsequently, automated reporting of eGFR was endorsed and adopted by

clinical laboratories to help providers to interpret kidney function based on systemic creatinine concentration.

In 2009, the CKD Epidemiology Collaboration (CKD-EPI) derived an equation based on a pooled analysis of 10 studies and validated in 16 international cohort studies, which involved both mGFR and blood creatinine (47). These studies included individuals across a wide range of age, race, GFR and creatinine concentrations. The resulting CKD-EPI 2009 equation exhibited improved performance, including greater accuracy and precision at higher GFRs as compared to the 4v-MDRD eGFR equation. However, similar to the 4v-MDRD equation, the derived CKD-EPI 2009 equation incorporated a Black race coefficient, albeit with a smaller modification coefficient (1.16 vs 1.21) (47). As with the 4v-MDRD equation, the studies used to generate the equation were not consistent in the way that race was assigned. The 4v-MDRD remained the predominant equation used in the US over the past decade (40).

Why is it problematic to include race as a demographic variable in medical algorithms, including estimated glomerular filtration rate (eGFR) equations?

Race, ethnicity, genetic ancestry and consequently, genetic variants that influence disease and health outcomes, are inextricably linked; however, race and ethnicity are imperfect surrogates for genetic ancestry (48). Notably, African populations exhibit a significant degree of genetic diversity (49). This diversity, combined with historic and ongoing admixture between persons of different ancestries within the US has contributed to genetic divergence within racial groups (50,51). Further, no clinical gold standard exists to determine racial classifications (52). Instead, race and ethnicity are self- or socially-ascribed identities that are often inferred based on physical characteristics such as skin color (48). The definitions of race vary widely and have changed over time based on cultural and social contexts, geography, and geopolitical events (48,52). While race and ethnicity may partially represent genetic ancestry, their use also highlights the effects of negative social determinants of health on racial and ethnic minority groups due to inequitable access to, and allocation of, health and social resources (4,48). Racial

and ethnic minorities in the U.S. are more likely to experience negative social determinants of health despite being socioeconomically diverse (13). The NKF-ASN Task Force acknowledged that the inclusion of race in the practice of medicine is challenging and problematic due to the complex and changing racial and ethnic makeup of persons (4).

The use of race and ethnicity in clinical algorithms and laboratory calculations may introduce disparities in healthcare, as race and ethnicity are social, rather than biologic, constructs (48,49). Efforts over the last several years have intensified in recommending the removal of race and ethnicity from laboratory calculations and other medical algorithms, including eGFR equations, due to concerns that their inclusion appears to endorse a biological basis for race (53). There are racial and ethnic disparities in both kidney health and healthcare that are influenced by social, environmental, and biologic factors (4). Black Americans have a higher prevalence of kidney failure and are less likely to receive patient-centric kidney failure replacement therapies, including home dialysis, and kidney transplantation, as compared to non-Hispanic White Americans (15). In the development of the 4v-MDRD and CKD-EPI 2009 equations, coefficients were included in calculating eGFR in Black patients to account for higher serum creatinine concentrations observed in Black patients relative to their mGFRs and to improve accuracy (27,46,47). These equations exhibit a higher positive bias, i.e. overestimate GFR, in Black individuals compared to non-Black individuals (46,47). This practice has the potential to introduce systematic differences in care between races (4,5). For example, studies have shown that use of the Black race coefficient results in delayed achievement of a clinical threshold for kidney transplant referral and eligibility in Black patients (54,55).

While studies have reported that the proportion of African ancestry found in an individual positively correlates with serum creatinine concentration, a similar association between African ancestry and mGFR has not been demonstrated (56,57). Although equations utilizing a Black race coefficient were rapidly adopted in the United States (U.S.), multiple studies conducted in Black populations outside of the

US demonstrated limited evidence for the appropriate use of these coefficients in eGFR equations. A recent systematic review utilized an evidenced-based approach to examine the utility of Black race coefficients in eGFR equations in African and Brazilian populations (58). Across ten studies representing 1,749 participants that directly compared mGFR to the 4v-MDRD or CKD-EPI 2009 eGFR equations, exclusion of the Black race coefficient led to improved agreement with mGFR in Black persons (58). Furthermore, in studies conducted in the US and the United Kingdom, inclusion of Black race coefficients in estimating equations led to eGFR results that were discordant markers of kidney disease-related metabolic dysfunction (e.g. secondary hyperparathyroidsim) and overestimation of eGFR relative to mGFR in prospective kidney donors (58).

In summary, race and ethnicity are imprecise, nebulously defined systems of classification as they pertain to genetic ancestry, physiologic characteristics, and socioeconomic status (8).

What are the new equations and how were they derived?

Key Summary Points:

- *The CKD-EPI 2021 equations are listed in **Table 4**, and were derived in a diverse cohort of participants with respect to age, sex, BMI and GFR, in which race was mostly self-reported.*
- *The CKD-EPI 2021 $eGFR_{cr}$ equation performs similarly to the CKD-EPI 2009 equation with respect to the percentage of measured GFR values within ±30% of the corresponding eGFR value (P_{30}) and CKD staging.*
- *The CKD-EPI 2021 $eGFR_{cr}$ equation underestimates GFR in Black individuals by 3.6 ml/min/1.73m^2 and overestimates GFR in non-Black individuals by 3.9 ml/min/1.73m^2.*
- *The CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equation exhibits less bias, a higher P_{30} and improved CKD staging in both Black and non-Black patients compared to the CKD-EPI 2021 $eGFR_{cr}$ equation.*

In 2020, a reexamination of the use of race in medical practice prompted the NKF and ASN to create a task force that scrutinized the use of race as a variable in eGFR equations (53). The NKF-ASN Task Force ultimately issued a unifying report recommending the removal of race in the eGFR reports and endorsing newer 2021 refit equations, which do not include a Black race coefficient (5).

The CKD-EPI 2021 equations are listed in **Table 4**. The equations were derived using the same data pools used in the original derivation of CKD-EPI 2009 development data set ($eGFR_{cr}$), which consisted of 10 studies with a total of 8254 participants, and the CKD-EPI 2012 development data set ($eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$), which consisted of 13 studies with a total of 5,352 participants. For both CKD-EPI 2021 equations, the regression function that was used for the 2009 and 2012 equations was used to fit new models that excluded race as an explanatory variable. The equations were validated in a pooled analysis of 12 studies comprising 4,050 participants with and without CKD, who self-reported as Black or non-Black in most studies. Black participants accounted for 31.5% of the 2009 development data set, 39.7% of the 2012 development data set, and 14.3% of the 2021 validation data set.

The CKD-EPI 2021 $eGFR_{cr}$ equation performed similarly to the CKD-EPI 2009 equation with respect to the percentage of measured GFR values within ±30% of the corresponding eGFR value (P_{30}) and assignment of GFR stages. Whereas the CKD-EPI 2009 equation overestimated GFR in Black participants by 3.7 ml/min/1.73m^2, the CKD-EPI 2021 $eGFR_{cr}$ equation underestimated GFR by 3.6 ml/min/1.73m^2. The magnitude of bias in non-Black participants increased to an overestimate of 3.9 ml/min/1.73m^2 with the CKD-EPI 2021 $eGFR_{cr}$ equation compared to 0.5 ml/min/1.73m^2 with the CKD-EPI 2009 equation. The CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equation performed similarly to the CKD-EPI 2012 $eGFR_{cr\text{-}cys}$ equation with respect to P_{30} and assignment of GFR stage with an underestimate of 0.1 ml/min/1.73m^2 in Black participants relative to the overestimate of 2.5 ml/min/1.73m^2 observed with the CKD-EPI 2012 $eGFR_{cr\text{-}cys}$ equation. In non-Black participants, overestimates of 0.6 and 2.9 ml/min/1.73m^2 were observed using the CKD-EPI 2012 $eGFR_{cr\text{-}cys}$ and CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equations respectively.

The NKF-ASN task force recommended immediate implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation. While all estimating equations have limitations, the CKD-EPI 2021 $eGFR_{cr}$ equation was developed in a diverse cohort, exhibits performance characteristics that are acceptable for clinical use, does not disproportionately affect any one group of individuals and achieves the goal of eliminating the use of race in estimating GFR. Immediate implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation is feasible as creatinine is measured in most clinical laboratories. Given the improved performance achieved through use of both cystatin C and creatinine, the Task Force also recommended increased use of the CKD-EPI 2021 $eGFR_{cr\text{-}cys}$, but acknowledged that several limitations related to cystatin C testing that are discussed in detail in this document must be overcome to facilitate more widespread implementation.

How can the clinical laboratory contribute towards closing racial/ethnic disparities in CKD?

Key Summary Points:

- *Early detection and awareness of kidney disease in clinically and socioeconomically high-risk populations is critical to achieving equitable kidney care*
- *Laboratorians can contribute towards closing racial/ethnic disparities in CKD through:*
    - *Harmonization of CKD biomarker testing and reporting*
    - *Optimization of CKD biomarker test utilization and interpretation*
    - *Integration of data-driven population health initiatives*

Negative social determinants of health contribute to poorer kidney health and worse kidney disease outcomes. Black and Hispanic Medicare recipients are over-represented in high SDI neighborhoods (58.6% & 65.1% respectively) compared to White Medicare recipients (21.5%), are at higher risk for kidney failure and less likely to receive a kidney transplant (5). Racial and ethnic disparities

in kidney disease also include late referral for nephrology care, highlighting the importance of screening in the primary care setting. Specifically, several kidney disease stakeholders have focused advocacy efforts on earlier detection, practitioner recognition and patient awareness of kidney disease, as these provide opportunities for clinical and lifestyle interventions that can slow CKD progression, but remain a significant challenge (5–7). Underutilization of screening is well recognized; however, there are no consensus screening guidelines for kidney disease (8). Furthermore, more than 88% of individuals with CKD are unaware of their disease (4) and almost half are in advanced stages when they receive a definitive diagnosis (8). Therefore, the achievement of equity in kidney care will require key stakeholder collaboration to increase early detection and awareness of kidney disease in clinically and socioeconomically high-risk (high SDI) populations (59).

Since diagnosis and staging of CKD are based on laboratory testing, laboratorians are well-poised to participate in efforts to improve CKD recognition through harmonization of CKD biomarker testing and reporting (8,31), optimization of CKD biomarker test utilization and interpretation, and integration of data-driven population health initiatives (59,60). These efforts must be executed in collaboration with interdisciplinary clinicians across the kidney care continuum, align with nationally-recommended CKD quality objectives and metrics (61–66), and be outcome driven (61).

Guidelines and recommendations for harmonization of testing and reporting for creatinine, cystatin C, uACR and eGFR are listed in **Table 4** (8,31,67). Efforts to improve utilization of kidney screening tests should focus on increasing targeted screening of high risk populations, particularly in primary care settings, at least annually using eGFR and uACR combined or within the Kidney Profile (8,31,59,68). Clinical laboratories can improve test interpretation for both eGFR and uACR by listing guideline-defined GFR and albuminuria CKD categories with test results. The Kidney Profile (eGFR and uACR) should be offered as a separate, distinct test from a Kidney Function Panel (blood albumin, urea nitrogen, urea nitrogen: creatinine ratio, calcium, carbon dioxide, chloride, creatinine, glucose, phosphorus, potassium),

566 which is an American Medical Association -recognized test panel that is better suited for monitoring
567 patients with established CKD (37). Near patient testing and direct-to-consumer testing may offer
568 advantages to traditional approaches in some instances to reach high-risk groups (19–21).

569 Clinical laboratory leaders can significantly contribute to decreasing the racial and ethnic
570 disparities in CKD by leading multi-disciplinary kidney quality improvement initiatives that include
571 characterizing the populations served and unserved, identifying testing strategies that align with expert
572 guidelines, and developing appropriate test menus and clinical decision support tools within their
573 healthcare systems. Laboratory personnel can also advocate (e.g., at the local, state, national and
574 professional levels and medical and clinical pathology societies) for care for uninsured patients, since lack
575 of insurance is an independent risk factor for early death and ESKD in patients with CKD (69). Several
576 healthcare systems have implemented kidney quality improvement initiatives and reported positive
577 screening and patient outcomes that include increased uACR testing, improved CKD recognition,
578 increased nephrology referrals and reduced hospitalizations (23–26). For example, one system
579 implemented a “creatinine safety program” to increase follow-up evaluation of all single abnormal
580 creatinine results recorded in the electronic health record (EHR), since diagnosis of CKD requires
581 establishing chronicity (23). The EHR was used to identify patients with abnormal creatinine results that
582 did not have repeat creatinine evaluation within 90 days, who were then contacted to coordinate repeat
583 testing. This initiative led to 3,668 CKD diagnoses, 1,550 patients with chart documentation of CKD and
584 336 nephrology consults (23). Laboratories can also leverage electronic health record and laboratory
585 information system (LIS) data to measure the impact of kidney disease interventions, e.g., implementing
586 race-neutral eGFR equations, on patient kidney health and outcomes. Specific quality indicators can
587 include, utilization of kidney screening tests in high-risk groups, appropriate and timely referral care,
588 implementation of therapeutic or lifestyle interventions, living donor candidate rates, and high-risk group

589 transplant rates. Health record-based CKD registries that identify patients with CKD based on laboratory
590 data to target interventions have improved clinical outcomes (70,71).

591 While expert panels currently recommend against screening in the general population in favor of
592 targeted testing for CKD among high-risk populations (31,68), laboratory data collected during routine
593 care, urgent care or emergency department visits can provide early, clinically-actionable insight as seen
594 in the "creatinine safety net" example (26). Creatinine is measured in basic and comprehensive metabolic
595 panels, and eGFR is reported in 92% of clinical laboratories (40). Patient results can:

596 • be flagged and/or annotated using LIS and middleware rules;
597 • trigger clinical decision support tools if the results meet guideline-defined criteria for CKD
598 diagnosis (eGFR < 60 mL/min/1.73 m^2) for 3 or more months or referral to nephrology including:
599 ○ GFR < 30 mL/min/1.73 m^2, a decline in GFR category accompanied by a ≥25% drop in
600 eGFR from baseline,
601 ○ a decline in eGFR of more than 5 mL/min/1.73 m^2/year, uACR > 300 mg/g (consider
602 referral if unexplained), and
603 ○ uACR > 2200 mg/g (nephrotic range albuminuria).

604

605 ## How should CKD-EPI 2021 equations be deployed by clinical laboratories?

606 *Key Summary Points:*
607 • *Calculations from programmed and pre-programmed CKD-EPI 2021 equations must be*
608 *extensively verified for accuracy across different creatinine concentrations, races, ages and*
609 *sexes.*
610 • *eGFR can be reported as integers > 60 mL/min/1.73 m^2 when calculated using the CKD-EPI 2021*
611 *equations.*

- *eGFR results should include a comment or should be named to indicate which equation was used.*
- *CKD-EPI 2021 $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ should not trend with results from older equations.*

The NKF Laboratory Engagement Working Group and CKD-EPI collaboration provide comprehensive guides for implementation of the CKD-EPI 2021 equations (67,72). Reporting recommendations are detailed in **Table 4**.

General programming instructions for the equations are included in **Appendix 1**. Of note, several LISs provide the CKD-EPI 2021 $eGFR_{cr}$ equation in their foundational programming, making it more feasible for laboratories to transition to the new equation. All LIS vendors should offer updated equations as ready-to-use, thereby alleviating laboratories of the need to conduct site-specific programming and further aiding in standardization of result reporting. However, even with the availability of pre-programmed equations in the LIS or middleware solutions, laboratories should carefully verify the accuracy of these equations. This may be achieved by calculating eGFR using the CKD-EPI equations in patients with different creatinine and cystatin concentrations, ages, sexes and races, and comparing the results with those derived from calculators provided by the NKF. It is critical for laboratories to confirm that the same eGFR is generated for a Black and non-Black person of the same age, sex, and blood creatinine concentration. Online calculators and mobile applications created or endorsed by the NKF may be used during equation performance verification (73). It is also recommended that laboratories test the correct flagging of abnormal results and correct triggering of testing algorithms (e.g. reflex testing), as appropriate. Of note, the NKF has created a table with different conditions for testing CKD-EPI 2021 $eGFR_{cr}$ and CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equations (72). KDIGO recommends that eGFR values <60 min/mL/1.73m^2 should be reported as decreased, however, diagnosis of CKD requires establishing chronicity of kidney abnormalities to distinguish chronic from acute kidney disease (8,31). Therefore, clinical context and previous eGFR values must be considered to guide appropriate follow-up. Further, the values that should

be flagged as abnormal may vary depending on the patient population being served (e.g. inpatient versus outpatient). Most importantly, primary care providers and nephrologist must be familiar with institution-, department- or site-specific flagging rules. Result comments describing the GFR categories of CGA staging can augment result flagging to facilitate interpretation of eGFR values.

Laboratories should carefully design the reporting of the results of the revised race-agnostic eGFR equations to facilitate the correct interpretation of results by healthcare providers and patients. Re-baselining (aka parallel testing) across the new and old equations is not necessary. The concentration of creatinine can be informative in detecting changes over time (74). eGFR results should be reported and captured in the patient's medical record; for institutions where the CKD-EPI 2021 equations have not been implemented, on-line calculators available from the NKF and the CKD-EPI websites may be used. Further, reporting of eGFR should be standardized, and it is recommended that eGFR is reported as a whole number in units of mL/min/1.73m^2. Of note, while the historic upper limit of eGFR reporting was 60 mL/min/1.73 m^2, this was attributed to poor performance of 6v- and 4v-MDRD equations at higher GFRs. With improved performance of CKD-EPI equations, including the CKD-EPI 2021 refit equations, it is recommended that eGFR values above 60 mL/min/1.73 m^2 be reported to support early detection of declining kidney function (67). For example, a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year warrants investigation (8,75). Furthermore, there are patient populations in which hyperfiltration may be observed e.g. critically ill patients, or diabetic patients, where an abnormally high eGFR may prompt uACR measurement (76). eGFR values corresponding to the upper limit of creatinine reporting can be reported, but the inaccuracy of estimates relative to mGFR must be considered at higher eGFRs. A recent cross-sectional study quantified the magnitude and consequences of individual-level differences between mGFR and eGFR, using data from four community-based prospective cohort studies representing a total of 3,223 participants (77). While population level differences between mGFR and CKD-EPI 2021 $eGFR_{cr}$ (mGFR- $eGFR_{cr}$) were relatively small at -0.6 ml/min/1.73m^2, individual level differences between

660 mGFR and $eGFR_{cr}$ were relatively larger and increased with increasing eGFR (77). The range of distributions
661 of mGFR at each eGFR value examined was narrower for both the CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ and the CKD-EPI
662 2021 $eGFR_{cys}$ equations compared to the CKD-EPI 2021 $eGFR_{cr}$ equation (77). We recommend that
663 laboratories report the distribution of uncertainty between mGFR and eGFR as a reminder to providers of
664 the inaccuracy of eGFR for individual patients (77)

665 When implementing the CKD-EPI 2021 $eGFR_{cr}$ and/or CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equations, results
666 should not be trended with results from different and older equations. This may be accomplished by
667 building refit equations as new tests or test components and displaying the results in unique new rows
668 within the electronic medical record. The CKD-EPI 2021 equations have distinct LOINC codes and should
669 be resulted in distinct result fields to allow for the correct LOINC code to be applied overtime (78). When
670 applicable, healthcare systems should work to reduce complexities associated with receiving eGFR results
671 from different laboratories. Equation-specific resulting names or interpretive comments should be utilized
672 to notify providers of the equations used to estimate GFR. Sample report comments are available on the
673 NKF website and can be modified to meet the needs of the laboratory, health care professionals and
674 patients (72).

675 Laboratories should also consider creatinine measurements from point-of-care (POC) testing
676 devices, as not all POC devices have the capability to report eGFR using the 2021 refit equations. POC
677 devices used to measure creatinine should use methodologies traceable to isotope dilution mass
678 spectrometry, and have the capability to report eGFR using equations recommended by professional
679 societies. If a POC device does not have the ability to align with central laboratory testing, either in terms
680 of creatinine reporting units or eGFR equations used, results should not be trended in the medical record
681 with central laboratory results.

682

What changes can be expected in patient management, drug dosing, and transplant eligibility by implementing the CKD-EPI 2021 $eGFR_{cr}$ equation?

Key Summary Points:

- *Implementation of the CKD-EPI 2021 $eGFR_{cr}$ equation will lead to a lower eGFR in Black individuals and higher eGFR in non-Black individuals compared to eGFR calculated with formulas that included race.*
- *When the eGFR flanks a clinical decision point, confirmatory assessment can be performed using direct measurement of glomerular filtration, measurement of creatinine clearance, serial creatinine-based measurements, or estimation of GFR including cystatin C.*

Removal of the Black race coefficient and transition to the new CKD-EPI will predictably lead to a lower eGFR in individuals for whom the Black race coefficient was previously applied and an increased eGFR in those for whom it was not. Combined, changes to the calculation for eGFR will alter CKD classification in patients where eGFR was close to clinical decision thresholds (79,80).

Across the spectrum of eGFR values, transition to new equations yields a range of considerations. In individuals with an eGFR close to normal, a shift to the race-neutral equation only impacts potential kidney donor candidates whose eGFR crosses the threshold used at their transplant center. For these individuals, the shift to the new equation may prevent harm to a potential donor since the CKD-EPI 2009 equation (inclusive of the Black race coefficient) may have overestimated GFR in potential Black donors (79,81). Further, use of a CKD-EPI 2021 equation may instead prompt appropriate evaluation for kidney disease, such as screening for albuminuria. When eGFR is near (above or below) the threshold used to permit donation at a transplant center, mGFR, in conjunction with a recommended CKD-EPI eGFR including cystatin C, can be used as confirmatory testing along with an assessment for albuminuria to ensure the safety of kidney donation. The eGFR is also used to identify patients that are eligible to list for deceased donor pre-emptive kidney transplant. Although most pre-emptive transplants come from living

donors, potential recipients are typically not referred to a transplant center until they have an eGFR of ≤20 ml/min/1.73m^2. The CKD-EPI 2009 equation has the potential to delay evaluation (54). Based on these concerns, the Federal Organ Procurement Transplantation Network (OPTN) endorses a race-neutral assessment of GFR (82).

Many medications and metabolites are excreted by the kidney and a change in eGFR may prompt concerns regarding drug dosing. Since eGFR is embedded in current clinical practice, the US Food and Drug Administration (FDA) recommends use of eGFR with any "contemporary, widely accepted and clinically applicable estimating equation for the population studied"(83). Dosing parameters are of particular concern with traditional chemotherapeutic agents, antibiotics, and medications used to treat diabetes mellitus. Using eGFR to delineate who is eligible for a particular drug and define the appropriate dose has the potential for "underdosing," (ie - inappropriate cessation of a medication or inappropriate agent exclusion if the eGFR is an underestimate of GFR) and "overdosing" (ie -toxicity if the eGFR is an overestimate of kidney GFR). This is particularly salient for eGFRs at the decision points of 60 and 30 ml/min/1.73m^2, which define stages G3a and G4 of CKD, respectively. When the eGFR flanks a clinical decision point, providers may consult with a nephrologist or pharmacist for support in dosing considerations. In addition, confirmatory assessment can be performed using direct measurement of glomerular filtration, measurement of creatinine clearance, serial creatinine-based measurements, or estimation of GFR including cystatin C. Notably, when using eGFR for medication dosing, the eGFR value should be de-indexed from BSA. This is particularly important in individuals at extremes of weight, as drug clearance is related to total eGFR not indexed eGFR.

Creatinine-based eGFR equations utilize sex and age as proxies for variations in creatinine that are unrelated to filtration or non-GFR determinants of creatinine. Thus, individuals whose sex assigned at birth does not align with their gender identity may have differences in creatinine generation due to changing muscle mass that influence eGFR (84). Recommendations for gender diverse people are outlined

later in this document. Age is used as a proxy for expectations regarding muscle mass over time. For individuals with sarcopenia because of medical conditions such as cirrhosis, heart failure, spinal cord injury and progressive neurodegenerative disorders, creatinine generation is reduced and the eGFR is likely to be an overestimate (**Table 2**). In contrast, in individuals with considerable muscle such as body builders, individuals with high exogenous creatinine ingestion, and anabolic steroid users the eGFR may be an underestimate (**Table 2**). Lastly, individuals who take medications that block creatinine secretion including older medications such as cimetidine or trimethoprim and newer antivirals such as cobicistat or dolutegravir will have a small increase in creatinine and consequently, a decrease in the eGFR, without an actual decline in true GFR (**Table 2**).

How should changes to eGFR reporting be communicated?

Key Summary Points:

- *Pharmacists, primary care and internal medicine providers, radiologists, transplant surgeons and providers that prescribe medications that are cleared by the kidney should be informed of the implementation of the CKD-EPI 2021 equations.*
- *Communications should emphasize what changes should be expected and encourage providers to interpret eGFR based on clinical context, given the limitations of eGFR as an estimate of GFR.*

The NKF laboratory engagement working group provides sample text for communicating implementation of the CKD-EPI 2021 equations (72). Implementation requires communication with all stakeholders who care for adults. Collaboration between clinical laboratories, nephrologists, and other subject matter experts, can achieve broad coverage and dissemination of information. Although pharmacists and those practicing internal medicine may be the most affected, those practicing radiology, those who order contrast-based imaging, transplant surgeons, and providers who prescribe medications that are cleared by the kidney such as antibiotics, lithium, and antiepileptic agents, also need to be aware

of the change. Institutional communication should include provider-wide and redundant approaches to maximize the likelihood of information reaching all caregivers. Communications should be explicit and provide an educational basis, outlining the new equation and how results will be affected. Educational material should highlight that the eGFR is only an estimate rather than a measured value. The 2021 CKD-EPI_{cr} P_{30} is ~86%, meaning that 14% of eGFR values were greater than ± 30% of the measured GFR in the study cohort (26). Indeed, eGFR values perform well at a population level but for an individual, the inaccuracy of the estimate needs to be considered (77). Lastly, the educational content should reinforce that the eGFR is designed to estimate kidney function when patients are medically stable and cannot be used when the kidney function is changing, such as with AKI (67).

When should eGFR equations including cystatin C be used?

Key Summary Points:

- *eGFR calculated using the CKD-EPI 2021 $eGFR_{cr\text{-}cys}$ equation is generally more accurate compared to eGFR calculated with the CKD-EPI 2021 $eGFR_{cr}$ equation, and should be used when eGFR is close to a clinical decision point where higher accuracy is required.*
- *In cases where creatinine is confounded by non-GFR determinants (Table 2), an estimate calculated using the CKD-EPI 2012 $eGFR_{cys}$ equation may be preferred.*
- *Cystatin C has non-GFR determinants (Table 2), which may impact the accuracy of eGFR equations that incorporate cystatin C.*

Cystatin C testing may be complementary in individuals with low creatinine production, where creatinine-based eGFR overestimates true GFR, such as individuals with sarcopenia, amputees, as well as those who are frail and elderly (85,86). Cystatin C testing is also recommended in individuals where creatinine production is increased and serum creatinine-based eGFR underestimates true GFR, such as body builders and other individuals who exercise vigorously and have increased muscle mass, individuals

779 with high exogenous creatine ingestion, and anabolic steroid users (85,86). Use of the CKD-EPI 2021
780 $eGFR_{cr\text{-}cys}$ equation may offer more precise estimates near eGFR clinical decision points (26,67); however,
781 cystatin C has non-GFR determinants (Table 2), which must be considered when choosing which eGFR
782 equation may provide the best estimate of GFR (86,87).

783 Increased adiposity is associated with increased levels of circulating cystatin C, and one study
784 found that equations that incorporate both cystatin C and creatinine (CKD-EPI 2012 $eGFR_{cr\text{-}cys}$) show
785 reduced bias relative to mGFR compared to cystatin C- (CKD-EPI 2012 $eGFR_{cys}$) or creatinine-only (CKD-EPI
786 2009 $eGFR_{cr}$) equations in a cohort of 166 obese CKD patients (87). In a small cohort (n=66) of patients
787 with chronic heart failure, eGFR calculated with cystatin C (CKD-EPI 2012 $eGFR_{cys}$) exhibited a bias of −4.1
788 mL/min/1.73 m^2 relative to mGFR (88). eGFR calculated with creatinine (CKD-EPI 2009 $eGFR_{cr}$) or
789 creatinine and cystatin C (CKD-EPI 2012 $eGFR_{cr\text{-}cys}$) exhibited biases of −15.2 mL/min/1.73 m^2 and −7.8
790 mL/min/1.73 m^2 relative to mGFR, respectively (88). Further, the P_{30} for $eGFR_{cys}$ was 65% compared to
791 that of $eGFR_{cr}$, which was 33%, and $eGFR_{cys}$ agreed more closely with mGFR in classifying patients in to
792 CKD Stages 3,4 and 5 compared to $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ (88). $eGFR_{cys}$ (CKD-EPI 2012 $eGFR_{cys}$) and $eGFR_{cr\text{-}cys}$
793 (CKD-EPI 2012 $eGFR_{cr\text{-}cys}$) have been found to be more accurate compared to $eGFR_{cr}$ (CKD-EPI 2009 $eGFR_{cr}$)
794 in patients with liver cirrhosis, but both equations were less accurate at lower GFRs (89,90).

795 KDIGO 2012 guidelines recommend cystatin C testing for dosing medications with narrow
796 therapeutic indices, such as vancomycin, aminoglycosides and chemotherapeutic agents (8,91). A
797 systematic review examined the use of eGFR equations that incorporate cystatin C for drug dosing across
798 34 studies with a total of 3455 participants and 16 different medications (92). In most studies, $eGFR_{cys}$ was
799 a better predictor of drug levels and clearance compared to $eGFR_{cr}$ (92). $eGFR_{cr\text{-}cys}$ was only assessed in 5
800 studies and showed superior performance to equations incorporating either biomarker alone (92).

801 In patients in which both creatinine and cystatin C may be influenced by non-GFR determinants,
802 mGFR should be used at clinical decision points and for dosing of nephrotoxic medication and medications

with a narrow therapeutic index (93). Large differences between $eGFR_{cys}$ and $eGFR_{cr}$ ($eGFRdiff_{cys-cr}$= $eGFR_{cys}$-$eGFR_{cr}$) indicate that non-GFR determinants are causing a substantial change in one of the biomarkers and consequently, use of $eGFR_{cr-cys}$ equations can mask the influence of these factors (94). Approximately 33% of participants in the Chronic Renal Insufficiency Cohort (CRIC) Study, a multicenter observational cohort study of 5499 adults from 7 clinical centers across the US, had $eGFRdiff_{cys-cr}$ ≥15mL/min/m^2 (94). Importantly, $eGFRdiff_{cys-cr}$, is prognostic of ESKD, mortality, hospitalization and cardiovascular disease (93). Clinical judgement based on patient-specific factors should be exercised in patients with discrepant $eGFR_{cr}$, eGFRcr-cys and eGFRcys results who may benefit from a more global assessment of kidney function.

What challenges are associated with implementing cystatin C testing?

Key Summary Points:

- *Implementation of cystatin C testing should be accompanied by institutional practice guidelines or educational initiatives, annotation of results with interpretive and educational comments, and clinical decision support or reflex testing to aid provider utilization and interpretation.*

There are barriers to the widespread implementation of cystatin C testing in clinical laboratories (5). In the 2019 CAP survey of 3,900 US respondents, only 2% reported offering cystatin C in-house, as compared to 90% that sent specimens to reference laboratories for testing and 8% not answering the question (67). Reference laboratory cystatin C testing is a viable option to facilitate testing demands for CKD diagnosis and management, but may present a challenge for use in AKI and emergent settings where a shorter turnaround time is required (28,29,91). Cystatin C testing can be performed on most high-throughput automated chemistry analyzers and assay harmonization has considerably improved. In the CYS-B 2021 survey, which was the most recent cystatin C CAP survey at the time of this report, method-

specific means ranged from -11% to 6% around the all-method mean, compared to 2014 when they ranged from -12% to 29% (56,57). Several scalability challenges to cystatin C test implementation exist. Firstly, measurement of cystatin C relies predominantly on immunoturbidimetric approaches, in contrast with creatinine, which is measured using enzymatic or colorimetric assays that are rapid and cost-efficient. Incorporation of cystatin C into basic and comprehensive metabolic panels to enable routine calculation of $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ may be impractical, due to the significantly increased volume of cystatin C reagent that would be required, as vendors work to sustainably increase production. Another scalability challenge centers around a lack of clinical decision support. Currently, decision support on when to perform cystatin C testing for clinical workflows are not standardized.

The increased cost of cystatin C compared to creatinine is often cited as barrier to widespread implementation (85,95,96). The differential reagent costs will vary based on institution-vendor agreements, but cystatin C reagents are estimated to cost up to 20 times more than creatinine reagents (85,95). However, cost may decrease with more widespread implementation and increased test volumes (85). The differential cost is also reflected in the higher CMS (Centers for Medicare and Medicaid Services) 2022 reimbursement rate for cystatin C ($18.52) versus creatinine ($5.12) (97). Comparative reimbursements for the basic and comprehensive metabolic panels that are used more frequently than creatinine ordering alone are $8.46 and $10.56, respectively. The NKF-ASN Task Force highlighted the need for changes in Current Procedure Terminology (CPT) coding to encourage use of cystatin C (5). Data on hospital/system-wide cost-savings, if any, that may be realized with more accurate cystatin C-based eGFR estimates are lacking. As healthcare transitions from fee-for-service to value-based care, use of cystatin C-based eGFR estimates may become more widespread in spite of cost, if use of cystatin C can improve patient outcomes through better risk stratification and interventions.

Data have shown that eGFR equations that utilize cystatin C alone better predict mortality as compared to creatinine only or combined marker estimates (98–101). However, lack of provider

familiarity with cystatin C results interpretation, lack of knowledge of non-GFR determinants of cystatin C and absence of clinical practice guidelines represent additional barriers to widespread utilization (91). Interdisciplinary collaboration between nephrology and the clinical laboratory may help to overcome these challenges through development of institutional practice guidelines or educational initiatives, annotation of results with interpretive and educational comments, and clinical decision support or reflex testing for patient populations in which cystatin C-based eGFR calculations are more appropriate as described above.

How do sex and gender influence eGFR equations?

Key Summary Points:

- *In transgender, non-binary, or intersex people, eGFR should be evaluated using both the male and female constants with CKD-EPI 2021 equations. Considering both values is particularly relevant at the onset of CKD and/or when approaching important thresholds.*
- *When eGFR calculated with either sex constant crosses a clinical threshold, a holistic approach should be taken to determine appropriate management anchored to the muscle mass of the individual based on their sex hormone configuration and gender identity.*
- *More data is needed on the impact of gender-affirming hormones on cystatin C and the use of cystatin C- based eGFR estimates in gender diverse populations.*

Equations to estimate GFR include binary-dependent variables that classify individuals as male/female or as a man/woman (26). These variables were included to account for the apparent differences in muscle mass between females and males and were supported by the observed biases between mGFR and eGFR. Gender and differences in sexual development (DSD; intersex), however, were

not directly included in the development or validation of eGFR equations and may influence muscle mass through diet and behavior or variance in sex hormone administration or expression.

Increasing societal and cultural recognition of gender variance complicates the use of eGFR equations, and our ability to segregate humans based on perceived sex. In contrast to sex, which is biologically defined based on the visual appearance of external genitalia at birth or sex hormone profiles, respectively, and/or in ambiguous cases, the presence or absence of a Y chromosome, gender identity encompasses the psychosocial characteristics that define an individual's identity or expression as masculine, feminine, or non-binary (102). Cisgender people have a gender identity that aligns with their sex assigned at birth; transgender or gender diverse people have a gender identity that is incongruent with their sex assigned at birth. A transgender man was assigned female sex at birth and identifies as a man; a transgender woman was assigned male sex at birth and identifies as a woman; a non-binary person was assigned male or female sex at birth and may identify as both a man or a woman or as neither. Intersex individuals have an array of underlying mechanisms for their phenotypic differences that are either developmental due to in utero exposure of sex hormones, metabolites in sex hormone synthesis, androgen insensitivity, or to other unusual transcription factors, receptors and/or genetic mutations. Transgender people may be intersex, but people who are intersex are not necessarily transgender. Any of these gender diverse individuals may present as androgynous, masculine, feminine or fluctuate across the spectrum. Medical care for transgender and non-binary people may include gender affirming hormones testosterone and estradiol (with or without androgen blockade or progesterone), which are prescribed to promote development of masculinizing and feminizing secondary sex characteristics, respectively. The introduction of gender affirming hormones will promote physiological changes that align with gender identity, including redistribution of fat and changes in muscle mass, and hence complicate the use of sex-specific constants in eGFR equations. Additionally, some transgender and non-binary people will undergo gender affirming gonadectomies, which may further mediate sex hormone concentrations and the

898 downstream tissues they influence. Not all transgender people seek medical intervention and may appear
899 as their preferred sex even without hormones. In addition, health conditions that impact sex hormone
900 concentrations, such as polycystic ovarian syndrome may complicate visual identification.

901 A recent systematic review and meta-analysis of all studies related to eGFR in transgender
902 people confirmed that serum creatinine concentration variably changes as a person transitions to their
903 affirmed gender identity when using gender affirming therapies (103). Specifically, after ~12 months on
904 testosterone hormone therapy, creatinine concentrations increased by ~0.15 mg/dL (95%CI 0.00-0.29
905 mg/dL) in transgender men. In contrast, after a similar time frame, transgender women on estrogen
906 hormone therapy do not show a statistically significant increase or decrease in creatinine concentration
907 (average change from baseline -0.05 mg/dL; 95% CI -0.16-0.05 mg/dL). The mechanism underlying the
908 change (or lack thereof) in creatinine concentration is not defined, although it is hypothesized to result
909 from changes in muscle mass and not GFR or tubular secretion. The authors did not find any literature
910 whereby mGFR and eGFR were evaluated in transgender people, making it difficult to distinguish which
911 sex-variable or alternate variable, if any, would allow for a more accurate estimation of GFR.

912 Until additional data are available, regardless of hormone therapy or other intervention use, we
913 recommend evaluating eGFR using both the male and female constants with the CKD-EPI 2021 equations
914 in transgender, non-binary, or intersex people. If either of these results crosses a clinical threshold a
915 holistic approach should be taken to determine appropriate management anchored to the muscle mass
916 of the individual based on their sex hormone configuration and gender identity. Mathematically, the
917 higher the eGFR, the larger the difference between eGFR (male) and eGFR (female) (104); however,
918 considering both values is still relevant at the onset of CKD and/or when approaching important
919 thresholds such as for transplant referral, dialysis initiation or dosing of medications with narrow
920 therapeutic indices. Until interfacing between the electronic health record and the laboratory information
921 systems improve, there are no automated informatics solutions to identify gender diverse people and

report both eGFR values (105). Data on the impact of gender-affirming therapy on cystain C is lacking (103), however, since cystatin C is less influenced by muscle mass (106), cystatin C-based GFR estimates could, in theory, improve screening for CKD or monitoring for CKD progression. Assessment of gender in the context of eGFR is an area for shared decision-making and an evolving area for investigation.

Additional Considerations and Outstanding Gaps

Consensus Screening Guidelines

United States Preventative Services Task Force (USPSTF), the government agency responsible for outlining evidence-based guidelines for preventative medical services, has not issued recommendations for CKD screening (107). This is despite the high prevalence of CKD, low rates of detection, and current evidence supporting the need for screening of high-risk individuals. While the NKF KDOQI, KDIGO and the American Diabetes Association recommend CKD screening using eGFR and uACR in high-risk individuals, the development of USPSTF CKD screening guidelines would streamline CKD testing strategies nationally, and will be critical in achieving health equity in kidney disease. The development of consensus critical action and delta values for eGFR and uACR represent additional opportunities for improvement of CKD detection.

Novel Kidney Disease Biomarker Discovery

Notwithstanding the clinical utility of eGFR, it must be emphasized that eGFR is an estimate with multiple contributory sources of uncertainty, including uncertainty in mGFR, analytical uncertainty associated with measurement of creatinine and cystatin C, and biological variation (108). Indeed, the P_{30} values for the CKD-EPI 2021 equations ranged between 86-91% (26). Research into novel endogenous filtration markers and kidney disease biomarkers is needed to improve kidney disease diagnosis, management and treatment (5). Initiatives such as the Kidney Precision Medicine Project (KPMP) (109)

945 seek to better define the molecular underpinnings of both CKD and AKI, with the goal of kidney disease
946 biomarker discovery, and the development of novel therapeutics with companion diagnostics. The
947 findings of the KPMP and similar initiatives have the potential to enable precision medicine for kidney
948 disease. Integration of disparate data sources such as clinical imaging, cellular data, proteomic data and
949 genomic data, through EHR systems will be necessary to enable real-time decision support (110).

950 ## Guidance on the Use of Cystatin C

951 Expert practice guidelines on cystatin C are needed to facilitate its increased use in eGFR. The use
952 of cystatin C in conjunction with creatinine can improve GFR estimates, however, in contrast to creatinine,
953 providers are less familiar with indications for cystatin C-based eGFR calculations and result
954 interpretation. Additionally, the non-GFR determinants of cystatin C are relatively less studied (106,111).
955 Calculation of eGFR using CKD-EPI equations based on different biomarkers (creatinine only, cystatin C
956 only, or creatinine and cystatin) may yield different, and at times contradictory, results in certain patient
957 populations (e.g., the elderly) (111). Improved understanding of non-GFR determinants of cystatin C can
958 be used to develop algorithms to support decision making when there is discordance between estimates
959 that incorporate cystatin C versus those based on creatinine alone.

960 ## Improved Kidney Disease Risk Assessment

961 The development of tools to improve kidney disease risk assessment and prognosis may also be
962 beneficial. Multiple risk assessment equations exist for different patient populations. The Kidney Failure
963 Risk Equations (KFRE) are the most internationally validated, widely known and widely used risk
964 assessment equation (112). The KFREs can be used to predict an individual's 2 to 5-year risk of developing
965 kidney failure and were originally developed in Canadian patients diagnosed with stages G3-5 CKD
966 (112,113). Notably, the KFREs are not impacted by the imprecision of eGFR. The KFREs have been
967 extensively validated in > 700,000 individuals across more than 30 countries and demonstrated high

discrimination between individuals who develop CKD and individuals that do not. Specifically, there are two KFREs, a 4-variable KFRE and an 8-variable KFRE. The 4-variable KFRE derives kidney failure risk from an individual's age, sex, eGFR and uACR; the 8-variable equation includes the aforementioned parameters in addition to serum albumin, bicarbonate, calcium and phosphorus measurements. Results are reported as percentage risk, ranging from <1% to 99.99% (87). The 4-variable KFRE was superior to eGFR alone at predicting 2-year risk for kidney failure (114). A KFRE score of > 20% has sensitivities ranging from 0.68 to 0.78, as compared to 0.42 to 0.66 when using a common eGFR cutoff point of <20 mL/min/1.73m^2, for dialysis referral or kidney transplant recommendation. However, these comparisons were made against eGFR equations inclusive of the Black race coefficient. Use of eGFR calculations without the Black race coefficient in KFRE calculation produced better calibration for participants that identified as Black (114). Of note, in patients diagnosed with autosomal dominant polycystic kidney disease, the KFRE underestimated risk, while in elderly patients (80 years and older) the KFRE overestimated the risk of kidney failure (113,115). Indications for calculating KFRE risk scores are not well-defined and continued validation of the equations will be necessary to define how often the risk score should be calculated. Further, the potential impact of high KFRE risk scores on insurance coverage must be considered.

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Tables

Table 1- KDIGO 2012: Prognosis of CKD by GFR and Albuminuria Categories (8)

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g	30-300 mg/g	> 300 mg/g
				< 3 mg/mmol	3-30 mg/mmol	>30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	< 15			

Green- low risk (if no other markers of kidney disease, no CKD); Yellow- moderately increased risk; Orange- high risk; Red- very high risk.

Table 2- Non-GFR determinants of blood creatinine and cystatin C concentrations

	Non-GFR Determinants	
	Creatinine	**Cystatin C**
GFR Over-estimation	**Physiologic factors:** unknown **Pathologic conditions:** amputation, frailty, anorexia, sarcopenia, liver cirrhosis, thyroid disease, chronic illness, critical illness; extra-renal elimination e.g. intestinal bacterial metabolism, spinal cord injury and progressive neuromuscular disease (87–90,116–118) **Diet:** vegan diet (118)	**Physiologic factors:** unknown **Pathologic conditions:** thyroid disease (116,118,119) **Diet:** unknown
GFR Under-estimation	**Physiologic factors:** high muscle mass e.g. bodybuilders (93,116) **Pathologic conditions:** obesity, rhabdomyolysis, thyroid disease (87,93) **Diet:** high meat consumption, creatine supplements (118) **Drugs:** Inhibition of tubular secretion-trimethoprim, cobicistat, dolutegravir, fenofibrate, olaparib, ritonavir, cimetidine (93)	**Physiologic factors:** smoking, lower lean body mass (120) **Pathologic conditions:** Obesity, diabetes, inflammation, thyroid disease, hypercortisolism (86,87,106,116,118,119) **Diet:** unknown **Drugs:** steroids(86,116)

Table 3. KDIGO recommended urine albumin to creatinine ratio (uACR) stages with corresponding 24-hour urine albumin concentrations, uACR measurements (8), and terms (Columns 1-4). Corresponding urine protein to creatinine ratio (uPCR) and dipstick protein results using approximate conversions(38) are also shown in the last two columns

Terms	**Albuminuria Category**	**Albumin (mg/ 24 hour urine)**	**uACR (mg/g)**	**uPCR**	**Dipstick Proteinuria**
Normal to mildly increased	A1	<30	<30	<150	Negative to trace
Moderately increased	A2	30-300	30-300	150-650	Trace to 1+
Severely increased	A3	>300	>300	>650	+2 or greater
Nephrotic range	A3 Nephrotic range	>2200	>2200	>3500	+2 or greater

1301 Table 4. eGFR reporting guidance (67)

CDK-EPI 2021 $eGFR_{cr}$
$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female] where, S_{cr} = serum creatinine in mg/dL, divide by 88.4 for creatinine in µmol/L κ = 0.7 (females) or 0.9 (males) α = -0.241 (female) or -0.302 (male) $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0 $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0 Age (years)
Assay: • Creatinine using methods that are traceable to IDMS reference measurement procedures. • Enzymatic assays are preferable over assays based on the Jaffe reaction, which are impacted by several interferences. • Report to 2 decimal points in mg/dL units and 1 decimal point in µmol/L units.
Reporting: Report $eGFR_{cr}$ as a whole number in units of mL/min/1.73 m^2 in adults ≥ 18 years of age. Do not allow results to trend with eGFR values calculated using older or different equations.
CDK-EPI 2021 $eGFR_{cr-cys}$
$eGFR_{cr-cys} = 135 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times \min(S_{cys}/0.8, 1)^{-0.323} \times \max(S_{cys}/0.8, 1)^{-0.778} \times 0.9961^{Age} \times 0.963$ [if female] where, S_{cr} = serum creatinine in mg/dL divide by 88.4 for creatinine in µmol/L κ = 0.7 (females) or 0.9 (males) α = -0.219 (female) or -0.144 (male) $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0 $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0 S_{cys} = serum cystatin C in mg/L Age (years)

Assays:
• Creatinine (as above)
• Cystatin C
  ○ Using methods traceable to the certified reference material ERM-DA471/IFCC.
  ○ Report to 2 decimal points in mg/L units.

Reporting: Report $eGFR_{cr-cys}$ as a whole number in units of mL/min/1.73 m^2 in adults ≥ 18 years of age. Do not allow results to be trended with eGFR values calculated using older or different equations.
CKD-EPI 2012 $eGFR_{cys}$
$eGFR_{cys} = 133 \times \min(S_{cys}/0.8, 1)^{-0.499} \times \max(S_{cys}/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$ [if female] where, eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2 S_{cys} (standardized serum cystatin C) = mg/L min = indicates the minimum of $S_{cys}/0.8$ or 1 max = indicates the maximum of $S_{cys}/0.8$ or 1 Age (years)

Assay: Cystatin c (as above)
Reporting: Report $eGFR_{cys}$ as a whole number in units of mL/min/1.73 m^2 in adults ≥ 18 years of age. Do not allow results to trend with eGFR values calculated using older or different equations.

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Appendix 1. Programming logic for "If" statements to select the correct equation for each set of parameters (67)

Logic for "if" statements		CKD-EPI 2021 $eGFR_{cr}$ Equation
Sex	**Serum Creatinine (mg/dL)**	
Female	≤0.7	$eGFR=142 \times (S_{cr}/0.7)^{-0.241} \times 0.9938^{age} \times 1.012$
	>0.7	$eGFR=142 \times (S_{cr}/0.7)^{-1.200} \times 0.9938^{age} \times 1.012$
Male	≤0.9	$eGFR=142 \times (S_{cr}/0.9)^{-0.302} \times 0.9938^{age}$
	>0.9	$eGFR=142 \times (S_{cr}/0.9)^{-1.200} \times 0.9938^{age}$

Logic for "if" statements		CKD-EPI 2012 $eGFR_{cys}$ Equation
Sex	**Serum Cystatin C (mg/L)**	
Female	≤0.8	$eGFR= 133 \times (S_{cys}/0.8)^{-0.499} \times 0.9962^{age} \times 0.932$
	>0.8	$eGFR= 133 \times (S_{cys}/0.8)^{-1.328} \times 0.9962^{age} \times 0.932$
Male	≤0.8	$eGFR= 133 \times (S_{cys}/0.8)^{-0.499} \times 0.9962^{age}$
	>0.8	$eGFR= 133 \times (S_{cys}/0.8)^{-1.328} \times 0.9962^{age}$

Logic for "if" statements			CKD-EPI 2021 $eGFR_{cr-cys}$ Equation
Sex	**Serum Creatinine (mg/dL)**	**Serum Cystatin C (mg/L)**	
Female	≤0.7	≤0.8	$eGFR= 135 \times (S_{cr}/0.7)^{-0.219} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age} \times 0.963$
	>0.7	>0.8	$eGFR= 135 \times (S_{cr}/0.7)^{-0.219} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age} \times 0.963$
	≤0.7	≤0.8	$eGFR= 135 \times (S_{cr}/0.7)^{-0.544} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age} \times 0.963$
	>0.7	>0.8	$eGFR= 135 \times (S_{cr}/0.7)^{-0.544} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age} \times 0.963$
Male	≤0.9	≤0.8	$eGFR= 135 \times (S_{cr}/0.9)^{-0.144} \times (S_{cys}/0.8)^{-0.323} \times 0.9961^{age}$
	>0.9	>0.8	$eGFR= 135 \times (S_{cr}/0.9)^{-0.144} \times (S_{cys}/0.8)^{-0.778} \times 0.9961^{age}$

	≤0.9	≤0.8	eGFR= 135 x $(S_{cr}/0.9)^{-0.544}$ x $(S_{cys}/0.8)^{-0.323}$ x 0.9961^{age}
	>0.9	>0.8	eGFR= 135 x $(S_{cr}/0.9)^{-0.544}$ x $(S_{cys}/0.8)^{-0.778}$ x 0.9961^{age}

NB. Single equations can also be programmed with more complex programming.