



Hypertension and Kidney Specialists

Race and eGFR

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Hypertension and Kidney Specialists.

What in the world is eGFR

- Calculated number derived from various factors attempted to standardize the measurement of renal function
- Creatinine historically primary method of measuring kidney function
- Cr is derived from skeletal muscle breakdown and dietary factors and cleared by the kidneys
- Cr is completely filtered at the glomerulus
- Cr is also secreted by the renal tubules
- It is an imperfect marker due to various variables

eGFR and creatinine



True glomerular filtration is measured by a substance that is freely filtered at the glomerulus and not reabsorbed or secreted post filtration.



Iothalamate and inulin have these qualities but not able to be measured on clinical and routine bases



Studies and equations created to help standardize the interpretation of cr

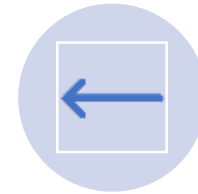
Creatinine downfalls



Dependent on muscle mass



Dietary influences (vegan vs non vegan diet)



Kidney tubular secretion
-Nephrotic syndrome
-Sickle cell



Non renal clearance
(bacterial overgrowth)



Interference of the assay used by most labs
- Acetoacetate
- bilirubin



Requirement for a stable creatinine

Non GFR determinants of creatinine

TABLE 5: FACTORS AFFECTING SERUM CREATININE CONCENTRATION

	Effect on Serum Creatinine	Mechanism/Comment
Older Age	Decrease	Reduction in creatinine generation due to age-related decline in muscle mass
Female Sex	Decrease	Reduced creatinine generation due to reduced muscle mass
Diet		
Restriction of Dietary Protein	Decrease	Decrease in creatinine generation
Ingestion of Cooked Meats	Increase	Transient increase in creatinine generation; however, this may be blunted by transient increase in GFR
Body Habitus		
Muscular	Increase	Increased creatinine generation due to increased muscle mass ± increased protein intake
Malnutrition/muscle wasting/amputation	Decrease	Reduced creatinine generation due to reduced muscle mass ± reduced protein intake
Obesity	No Change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation

*From Levey AS. *Am J Kidney Dis.* 1993;22:207-214.

History of eGFR

Cockcroft-Gault equation. 1976

- 249 White men with measured creatinine clearance ranging from 30 to 130 mL/m² to estimate creatinine clearance
- Lack of race and sex diversity
- $eClcr = \left\{ \frac{(140 - \text{age}) \times \text{weight}}{72 \times SCr} \right\} \times 0.85$ if female

MDRD 1999

- Derived from a randomized control trial evaluated dietary protein restriction and blood-pressure control interventions; recorded race as reported by individual. No options for mixed race given
- 1628 participants. 12% black
- Reported that egfr was 18% higher in self identified black participants.
- Re validated among 1700 individuals and 21% higher in self identified black participants
- $eGFR = 175 \times (\text{Standardized S})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$

History of eGFR

CKD Epi 2009; 5504 total patients

Regression analysis to determine gfr.

Black vs non black

16% higher in reported black

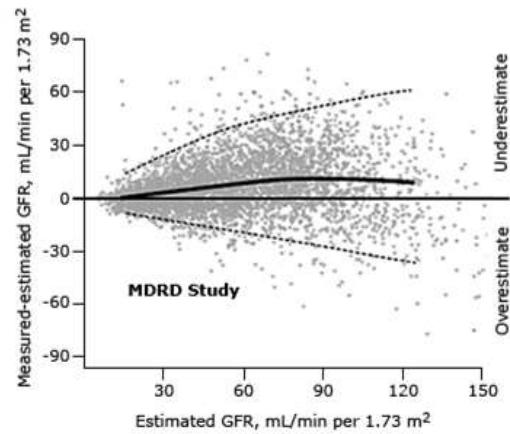
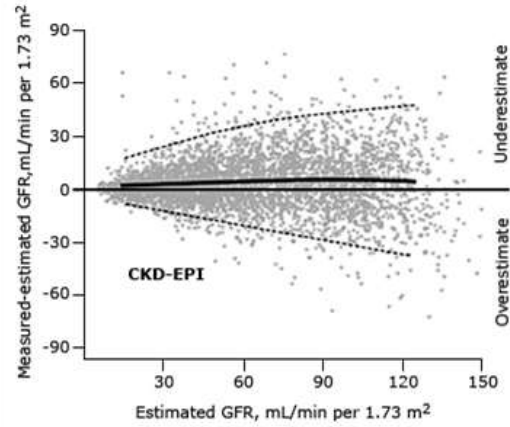
Table 1. Race/ethnicity Composition of CKD-EPI eGFR equation cohorts. ³	Development (n = 5,504)	Internal Validation (n = 2,750)	External Validation (n = 3,896)
Black	1728 (32%)	857 (31%)	384 (10%)
Hispanic	247 (5%)	106 (4%)	67 (2%)
Asian	62 (1%)	38 (1%)	67 (2%)
White and other	3467 (63%)	1749 (64%)	3378 (87%)

eGFR=

$141 \times \min(S_{Cr}/k, 1) \alpha \times \max(S_{Cr}/k, 1)^{-1.209} \times 0.993_{Age} \times 1.018$ [if female]

1.159 [if Black]

Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR



Reproduced with permission from: Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604. Copyright © 2009 American College of Physicians.

Cystatin C

Low molecular weight protein of the superfamily of cysteine protease inhibitors.

Freely filtered.

Not reabsorbed.

Metabolized in the tubules

Non gfr determinants of cystatin C

- Male sex
- Lean body mass
- High levels of inflammatory markers
- Thyroid disease
- Steroid use
- Race and age to a less degree

Cystatin C eGFR

Most accurate results when both cystatin c and cr equations are combined

2012 CKD-EPI cystatin C and creatinine-cystatin C equation developed

Data pooled from 10 studies against direct gfr measurement.

Recommended for use when confirmation of eGFR is needed

- Significant non-GFR determinants of serum creatinine:
- Confirmation of ckd when egfr is 45-60 with no other sign of ckd.
- Kidney donation evaluation.

Confirmation of eGFR

TABLE 6: INDICATIONS FOR A CONFIRMATORY TEST*

Patient factor leading to inaccurate eGFRcr

Extremes of body size

Severe malnutrition or obesity

Disease of skeletal muscle

Paraplegia or quadriplegia

Vegetarian diet

Rapidly changing kidney function

Pregnancy

Transgender

Drug factors

Drugs that effect tubular secretion

Drugs that effect creatinine assay

Clinical settings in which accurate GFR assessment is required

Kidney donation evaluation

Treatment with drugs with significant toxicity that are excreted by the kidneys

*From Inker LA, Titan S. *Am J Kidney Dis.* 2021;78:736-749.

Race and eGFR

Race was added as a coefficient to account for non gfr determinants of creatinine

Race is a social construct. Self reported in the 1999 vs self reporting in 2022 differs.

Does Race really add value to the eGFR

History of health care system and research in African americans

Definition of race

- First recorded in 1490–1500; from Middle French *race* “group of people of common descent,” from Italian *razza* “kind, species”; further origin uncertain.
- Term used to define a large body of persons who may be thought of as a unit because of common characteristics.
- Describes a body of persons united usually by common interests, ideals, or culture but sometimes also by a common history, or language.
- No longer used as a biological or anthropological system of classification.

Why does it matter

- Kidney disease disproportionately affects black
- More likely to be on dialysis at a younger age for the same disease process. 1 in 12 black men will require dialysis in their lifetime. (2.4 fold) increase.
- HTN is more aggressive and leads to end organ damage
 - APOL1 Mutation
- Less access to health care
- Later referrals to nephrology
- Less likely to be referred to home therapies
- Less likely to get a kidney transplant
- More likely to crash into dialysis
- Deceased donor kidneys from black patients more likely to be discarded

Removing the race coefficient

More patients diagnosed with ckd.

- 16% increase in ckd stage 3
- 33% increase in ckd stage 4
- 3% increase in ckd stage 5

Prevalence among black patients increased to 18.9% from 14%

Advantages of removing the coefficient

Mitigate health disparities for those with rapid progression of ckd

Earlier referral to nephrology

Earlier establishment of alternative access

Modality education starts earlier

Earlier referral to transplant

Less deceased donor kidneys lost

Disadvantages to removing the race coefficient

- Clinical studies for new agents cut off gfr of 30
- In adequate dosing of antibiotics and chemotherapy

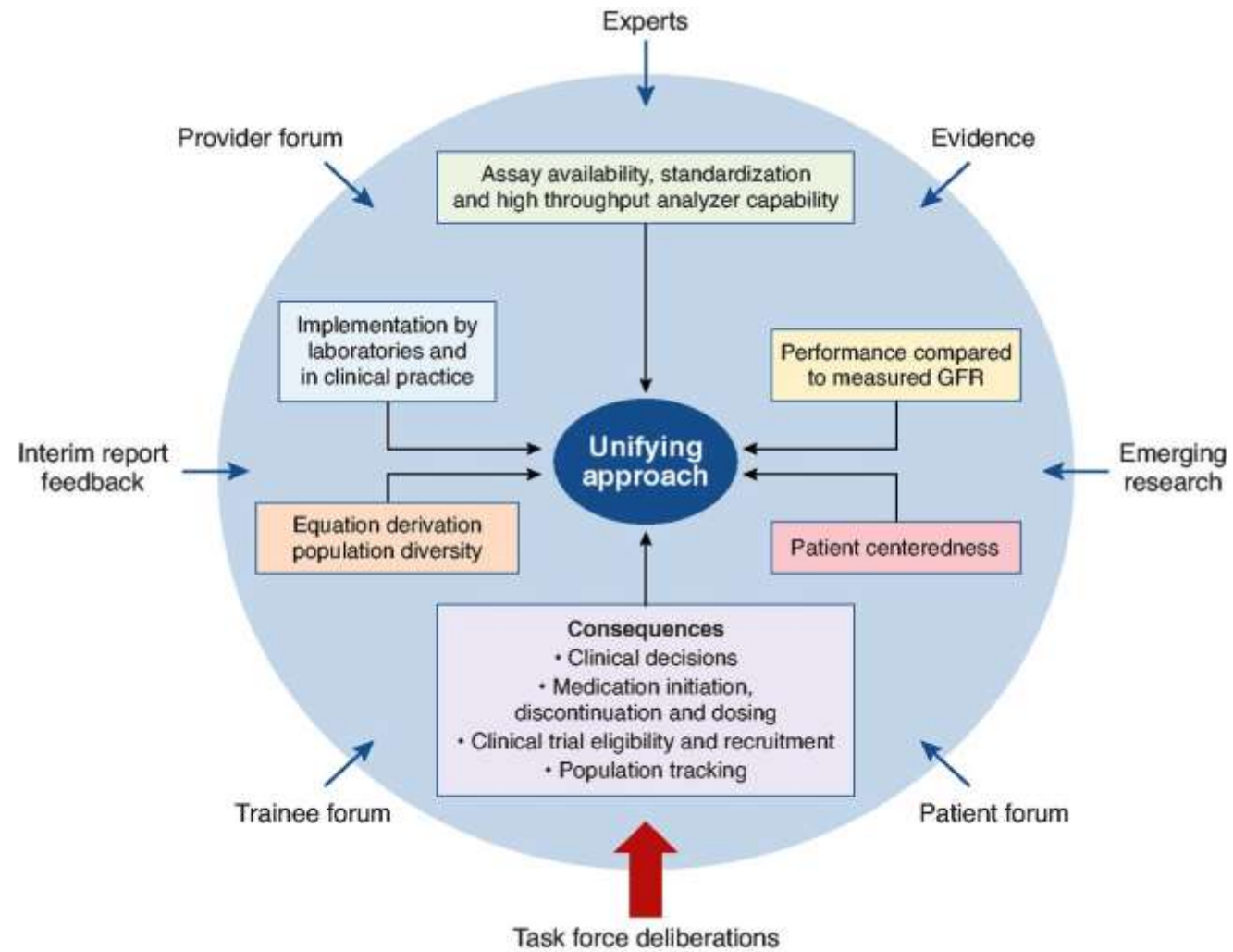
Where are we now

ASN-NKF Task Force. Formed April 2021

Outlined five domains.

- eGFR and measurement.
Race, racism, and genetic ancestry.
Body composition and populations used in eGFR.
Standardization and guidelines.
Patients' perspective and shared decision making.

Process and input to create a unifying approach to GFR estimation was comprehensive.



Cynthia Delgado et al. JASN 2021;32:2994-3015

ASN-NKF task force

1

Examining the inclusion of race in the estimation of GFR and implications for the diagnosis and subsequent management of patients with, or at risk for, kidney disease.

2

Examining the inclusion of race in the estimation of GFR and its implications for the diagnosis and subsequent management of patients with, or at risk for, kidney disease.

3

Recognizing that any change in eGFR reporting must consider the multiple social and clinical implications, be based on rigorous science, and be part of a national conversation about uniform reporting of eGFR across health care systems.

4

Incorporating the concerns of patients and the public, especially in marginalized and disadvantaged communities, while rigorously assessing the underlying scientific and ethical issues embedded in current practice.

5

Ensuring that GFR estimation equations provide an unbiased assessment of GFR so that laboratories, clinicians, patients, and public health officials can make informed decisions to ensure equity and personalized care for patients with kidney disease.

6

Keeping laboratories, clinicians, and other kidney health professionals apprised of any potential long-term implications of removing race from the eGFR formula.

A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease



Recommend immediate implementation of the **CKD-EPI creatinine equation refit without the race variable** in all laboratories in the U.S.

The equation refit excludes race in the calculation and reporting, includes diversity in its development, is immediately available to all labs in the U.S. and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals.



Recommend national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in clinical decision-making



Encourage and fund research on GFR estimation with new endogenous filtration markers and on interventions to eliminate racial and ethnic disparities



The Task Force gathered input from diverse stakeholders and carefully reviewed the evidence to create these recommendations

TABLE 3: EQUATIONS TO ESTIMATE GFR

EQUATION (YEAR)	CKD-EPI (2021)	CKD-EPI (2012)	MDRD Study (1999/2005)	Cockcroft-Gault (1978)
POPULATION	Diverse	Diverse	CKD	White men
REFERENCE METHODS	mGFR	mGFR	mGFR	mClcr
UNITS	mL/min/1.73 m ²	mL/min/1.73 m ²	mL/min/1.73 m ²	mL/min
FACTORS	Scr, age, sex	Scr, age, sex, race	Scr, age, sex, race	Scr, age, sex, weight
RECOMMENDATIONS (YEAR)	NKF-ASN Task Force Final Report (2021)	KDIGO (2013), KDOQI (2014), FDA (2020)	KDOQI (2002), FDA (2020)	FDA (1998), KDOQI (2002)

What's Next: Future of eGFR.

What new endogenous filtration markers that are not sensitive to social and demographic factors.

How do they perform with regard to accuracy bias and precision in estimating GFR in all populations.

What are the performance characteristics of cystatin C in more heterogenous populations (hospitalized pts).

What is the effect of recommended approaches for estimation of eGFR on all race and ethnic groups.

Are there sound new GFR approaches for real time decision making/ (Point of care testing).

What is the relation of kidney drug clearance with non indexed mGFR and indexed and non indexed eGFR across categories of diverse population.

What interventions focus on the most important drivers and are effective in prevention and elimination of race and ethnic disparities.

References:

- Delgado C, Baweja M, Burrows NR, Crews DC, Eneanya ND, Gadegbeku CA, et al: Reassessing the inclusion of race in diagnosing kidney diseases: An interim report from the NKF-ASN task force. J Am Soc Nephrol 32: 1305–1317, 2021
- ASN final comment letter AHRQRFI
- Am J Kidney Dis. 2021 July ; 78(1): 103–115. doi:10.1053/j.ajkd.2021.03.008.
- Vivekan and Jha and Gopesh K. Modi
CJASN June 2021, 16 (6) 963-965; DOI: <https://doi.org/10.2215/CJN.16001020>
- Kidney.org. frequently asked questions about gfr estimates.