OPTN

Request for Feedback

Reassess Inclusion of Race in Estimated Glomerular Filtration Rate (eGFR) Calculation

OPTN Minority Affairs and Kidney Transplantation Committees

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Contents

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Reassess Inclusion of Race in Estimated Glomerular Filtration Rate (eGFR) Calculation

Sponsoring Committees: *Minority Affairs and Kidney Transplantation*
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Executive Summary

The estimated glomerular filtration rate (eGFR) is a tool used to measure kidney function. Some eGFR formulas include a Black race coefficient. Currently, Organ Procurement and Transplantation Network (OPTN) policy is not prescriptive as to which eGFR coefficients or formulas or other methods may or may not be used. For this reason, equations that include and exclude the Black race coefficient are permitted to initiate qualified waiting time on the kidney transplant waiting list. Recent research suggests that the use of the Black race coefficient has the potential to disadvantage this population by overestimating eGFR function for Black individuals.[1,2,3,4,5] Consequences of overestimated eGFR values could include delayed referral to transplant and initiation of qualified waiting time in addition to overall worse Chronic Kidney Disease (CKD) outcomes.[6,7]

This document is not a proposal, but instead a request for feedback (RFF) on potential changes to the use of the Black race coefficient and eGFR in OPTN policy. The feedback received will be used to develop a future proposal that would support the OPTN strategic goal of providing equity in access to transplants. Details of the specific input being requested can be found in the Community Feedback section of this document and specific questions are posed in the Summary.

[1] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. *American Medical Association*. 2019. 322(2):113-114
[2] Vyas DA, Einstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. The New England Journal of Medicine. 2020. 383(9): 874-882.
[3] Ahmed S, Nutt CT, Eneanya ND, Reese PR, Sivashanker K, Morse M, Sequist T, Mendu ML. Examining the Potential Impact of Race Multiplier Utilization in Estimated Glomerular Filtration Rate Calculation on African-American Care Outcomes. Journal of General Internal Medicine. 2020. 36(2):464–71DOI: 10.1007/s11606-020-06280-5
[4] Delagdo C, Baweja M, Rios Burros N, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey- Mims MM, Roberts GV, St. Peter WL, Warfield C, Powe NR. Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report from the NKF-ASN Task Force. Journal of the American Society of Nephrology. 2021. 32: 1305- 1317.
[5] Reese PP, Sumit M, King KL, Williams WW, Potluri VS, Harhay MN, Eneanya ND. Racial disparities in preemptive waitlisting and deceased donor kidney transplantation: Ethics and solutions. The American Journal of Transplant. 2020. 21:958–967. https://doi.org/10.1111/ajt.16392
[6] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. American Medical Association. 2019. 322(2):113-114
[7] Ahmed S, Nutt CT, Eneanya ND, Reese PR, Sivashanker K, Morse M, Sequist T, Mendu ML. Examining the Potential Impact of Race Multiplier Utilization in Estimated Glomerular Filtration Rate Calculation on African-American Care Outcomes. Journal of General Internal Medicine. 2020. 36(2):464–71DOI: 10.1007/s11606-020-06280-5

Background

The eGFR is a tool used to estimate the rate at which the kidneys remove waste products from the blood and helps determine the severity of a patient's kidney disease. The eGFR value represents how well the kidneys function.[8] The average eGFR declines with age, but for adults ages 20- 59 a normal eGFR is greater than 90 milliliter/minute (mL/min). eGFR values less than 60 (mL/min) for more than three months indicate moderate to severe CKD.[9] The most severe stage of CKD is stage 5 which is defined by an eGFR value less than 15(mL/min). Patients with stage 5 CKD eventually need regular dialysis and/or a kidney transplant to survive.[10]

eGFR values are used as qualifying measures throughout OPTN policy. Policy 8.4.A: *Waiting Time for Candidates Registered at Age 18 or Older* requires one of the following to initiate candidate waiting time accrual[11]:

1. The candidate's registration date with a measured or calculated creatinine clearance or GFR less than or equal to 20 (mL/min).
2. The date after registration that a candidate's measured or calculated creatinine clearance or GFR becomes less than or equal to 20 mL/min.
3. The date that the candidate began regularly administered dialysis as an End Stage Renal Disease (ESRD) patient in a hospital based, independent non-hospital based, or home setting.

GFR and dialysis criteria are used for initiation of wait time accrual and are not required for kidney candidate registration. A transplant program may register a kidney transplant candidate with any eGFR value, but the candidate will not accrue waiting time until one of the criteria listed in *Policy 8.4.A: Waiting Time for Candidates Registered at Age 18 or Older* is met.[12] Qualified waiting time plays a significant role in the prioritization of kidney offers. Generally, the earlier a candidate qualifies to accrue waiting time, the sooner they will receive access to a transplant absent other qualifying criteria.[13]

Current OPTN policy is not prescriptive as to what methods of GFR measurement or estimation programs should or should not use when registering kidney candidates.[14] There are several widely used eGFR formulas with varying composition that sometimes feature a Black race coefficient. Because current OPTN policy is not prescriptive, equations that include and exclude the race coefficient are permitted for, initiation of qualified waiting time and to receive priority for a kidney after a liver transplant.

[8] National Kidney Foundation. (2013). GFR (Glomerular Filtration Rate) A Key to Understanding How Well Your Kidneys Are Working. National Kidney Foundation, Inc. https://www.kidney.org/sites/default/files/docs/11-10 1813_abe_patbro_gfr_b.pdf
[9]Ibid.
[10]Ibid.
[11]OPTN Policy 8.4.A: *Waiting Time for Candidates Registered at Age 18 or Older*
[12]Organ Procurement and Transplantation Network (2014). The New Kidney Allocation System (KAS) Frequently Asked Questions. https://optn.transplant.hrsa.gov/media/1235/kas_faqs.pdf
[13]OPTN Policy 8.3: *Kidney Allocation Score*
[14] OPTN Policy 8.4.A: Waiting Time for Candidates Registered at Age 18 or Older

Introduction and rationale for including Black race in eGFR

Modification of Diet in Renal Disease (MDRD) Study

In 1999, the Modification of Diet in Renal Disease (MDRD) study developed an equation to improve prediction of GFR from serum creatinine concentration. Included in the results of this study were findings that suggested Black race was associated with higher serum creatinine levels at the same measured GFR than for White persons. [15] 12% of the study's participants were Black (n = 127) and 88% (n= 1,304) participants were White.[16] This study resulted in assignment of a multiplication factor for Black patients' eGFR values.

Chronic Kidney Disease Epidemiology Collaboration (CKD- EPI)

In 2009, researchers developed the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as a more accurate method for measuring eGFR.[17] This equation aimed to calibrate and standardize traditional serum creatinine–based measures of kidney function and is currently one of the most widely used formulas.[18] It was developed through analysis of a number of independent studies and combined data from thousands of individuals. Results observed similar racial differences in serum creatinine levels at the same level of measured as in the MDRD study. The Black race coefficient in the CKD- EPI equation increases eGFR values by 16% for Black individuals[19]

Limitations of the original and subsequent study

Recent research suggests that the design of the studies that resulted in development of the Black race coefficient have considerable limitations. Both the MDRD and CKD-EPI studies used Black study populations that are not representative of the Black population as a whole. Additionally, researchers used incomplete data that excluded participants' sociodemographic characteristics, diet, clinical conditions, and medications, all of which can affect creatinine levels.[20, 21] At the conclusion of the CKD-EPI study, Levey et al. advised that further research would be necessary to improve GFR estimation.[22] As a result of limited representation of other minority groups in this study population, these groups were not included in large enough numbers to draw conclusions racial differences in serum creatinine levels of kidney function.[23]

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[15] Levey AS, Bosch JP, Lewis JB, Green T, Rogers N, Roth D. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Annals of Internal Medicine. 1999. 130(6): 461-470

[16] Ibid.

[17] Levey AS, Stevens LA, Schmid CH, Zhang YP, Castro III AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A New Equation to Estimate Glomerular Filtration Rate. Annals of Internal Medicine. 2009. 150(9): 604–612

[18]Ibid.

[19] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. American Medical Association. 2019. 322(2):113-114

[20] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. American Medical Association. 2019. 322(2):113-114

[21] Schmidt IM, Waikar SS. Separate and Unequal: Race-Based Algorithms and Implications for Nephrology. Journal of the American Society of Nephrology. 2021. 32(3): 529-533.

[22]Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. American Medical Association. 2019. 322(2):113-114

[23] Delagdo C, Baweja M, Rios Burros N, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey- Mims MM, Roberts GV, St. Peter WL, Warfield C, Powe NR. Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report from the NKF-ASN Task Force. *Journal of the American Society of Nephrology.* 2021. 32: 1305- 1317.

Issues with binary distinction on race

Currently when the Black race coefficient is used in formulas, eGFR calculators only offer two response options: Black or Not Black. These options do not include a designation for mixed race or multi- racial individuals and do not account for the existing genetic diversity within the Black population.[24] The concept of race is a social construct and an unreliable proxy for genetic difference, therefore not a biological marker or clinical measure.[25]

Effect of using eGFR

A recent study examined the impact of the race multiplier for the Black population in the CKD-EPI eGFR equation on CKD classification and care delivery by hypothetically removing the Black race coefficient from the eGFR formula. Results found:

- 16% increase in the total number of Black patients classified as having CKD in this study's registry
- 33.4% of Black participants who were already diagnosed with CKD would have been reclassified to a more severe stage
- 3% or 64 patients were reclassified from an eGFR greater than 20 ml/min to an eGFR equal to or less than 20 ml/min

Overestimated eGFR values resulting from race adjustments have the potential to delay referral for kidney transplantation and the initiation of qualifying waiting time.[26] Black patients with CKD have poorer outcomes and an increased rate of ESRD when compared with other racial groups.[27] They are also less likely to be added to the transplant waiting list and receive a transplant.[28] The use of race adjustments in the calculation of eGFR has the potential to exacerbate existing disparities and negatively impact patient outcomes. Timely assessment and intervention is critical for outcomes of CKD patients, as the disease can progress quickly towards kidney failure. Earlier detection of CKD could improve efforts to prevent progression.[29]

Community efforts

The nephrology community is also currently reconsidering the use of race- based adjustments in clinical algorithms, including eGFR. In July 2020 the issue gained the attention of the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN). These organizations collaborated to form a task force to reassess the inclusion of race in diagnosing kidney diseases. This task force

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[24] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. *American Medical Association*. 2019. 322(2):113-114

[25] Vyas DA, Einstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. The New England Journal of Medicine. 2020. 383(9): 874-882.

[26] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. American Medical Association. 2019. 322(2):113-114

[27] Ahmed S, Nutt CT, Eneanya ND, Reese PR, Sivashanker K, Morse M, Sequist T, Mendu ML. Examining the Potential Impact of Race Multiplier Utilization in Estimated Glomerular Filtration Rate Calculation on African-American Care Outcomes. Journal of General Internal Medicine. 2020. 36(2):464–71DOI: 10.1007/s11606-020-06280-5

[28] Zelnick LR, Leca N, Young B, Bansal N. Association of the Estimated Glomerular Filtration Rate With vs Without a Coefficient for Race with Time to Eligibility for Kidney Transplant. The Journal of the American Medical Association. 2021;4(1):e2034004. doi:10.1001/jamanetworkopen.2020.34004

[29] Reese PP, Sumit M, King KL, Williams WW, Potluri VS, Harhay MN, Eneanya ND. Racial disparities in preemptive waitlisting and deceased donor kidney transplantation: Ethics and solutions. The American Journal of Transplant. 2020. 21:958–967. https://doi.org/10.1111/ajt.16392

specifically aims to examine the inclusion of race in estimation of GFR and its implications for diagnosis and subsequent management of patients with, or at risk for, kidney disease. In March 2021, leaders at both ASN and NFK released a statement asserting that "Race modifiers should not be included in equations to estimate kidney function and current race-based equations should be replaced by a suitable approach that is accurate, inclusive, and standardized in every laboratory in the United States. Any such approach must not differentially introduce bias, inaccuracy, or inequalities."[30] In June 2021 the task force released an interim report which outlined their work to date and informed the nephrology community that final recommendations regarding estimation of eGFR without the Black race coefficient would be released at a future date.[31]

Development Process

In November 2020, the United States House of Representatives Ways and Means Committee invited a number of professional organizations, societies, and community stakeholders to comment on a Request for Information (RFI) pertaining to racial bias in clinical tools.[32] This communication specifically highlighted the connection between race adjusted eGFR calculations and the racial heath inequities in kidney transplantation. This RFI posed questions regarding the organization's plans for reevaluating the use of race in clinical algorithms and ensuring improved access to transplant for the impacted population.[33] Responses from a number of these professional organizations are available on the Ways & Means Committee's website.[34]

In March 2021, the OPTN formed the Reassess Race in eGFR Workgroup (hereinafter the Workgroup) to evaluate the use of the Black race coefficient in the eGFR calculation as it relates to wait time criteria for kidney transplant. The Workgroup consists of members from the OPTN Minority Affairs and Kidney Transplantation Committees as well as subject matter experts, including nephrologists, epidemiologists, and patients. The Workgroup first aims to determine if or what policy should be developed to address the use of the Black race coefficient in eGFR calculations.[35] The Workgroup has selected a concentrated scope as it aims to respond to the community's desire to address this growing initiative in an efficient and timely manner. Topics outside the scope of this work, such as preemptive kidney listing or donor criteria, may be addressed as a separate project.[36] The Workgroup presented this request for Feedback to the OPTN Minority Affairs and Kidney Transplantation Committees; both committees voted in support of recommending the Request for Feedback be sent out for public comment, as cosponsors.

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[30] National Kidney Foundation. (2021, March 9). Removing Race from Estimates of Kidney Function. https://www.kidney.org/news/removing-race-estimates-kidney-function

[31] Delagdo C, Baweja M, Rios Burros N, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey- Mims MM, Roberts GV, St. Peter WL, Warfield C, Powe NR. Reassessing the Inclusion of Race in Diagnosing Kidney Diseases: An Interim Report from the NKF-ASN Task Force. Journal of the American Society of Nephrology. 2021. 32: 1305- 1317.

[32] Letter to Dr. David Mulligan from the United States House of Representatives Committee on Ways and Means, November 24, 2020.

[33] Neal RE, "Clinical Corrections Invitation to Comment" Ways and Means Committee. September17, 2020. Accessed June 24, 2021 from https://waysandmeans.house.gov/sites/democrats.waysandmeans.house.gov/files/documents/ClinicalCorrectorsinvitation_final.pdf

[34] Ways and Means Committee. "Feedback from Professional Societies and RFI Respondents on the Misuse of Race Within Clinical Care" January 21, 2021. Accessed July 20, 2021 from https://waysandmeans.house.gov/media-center/press-releases/feedback-professional-societies-and-rfi-respondents-misuse-race-within-0

[35] See Reassess Race in eGFR Calculation Workgroup Meeting Summary, March 1, 2021. Available at https://optn.transplant.hrsa.gov/

[36] See Reassess Race in eGFR Calculation Workgroup Meeting Summary, May 5, 2021. Available at https://optn.transplant.hrsa.gov/

Community Feedback

The OPTN Minority Affairs and Kidney Transplantation Committees (hereinafter "the Sponsoring Committees") are seeking feedback on the following items to inform a future proposal.

Considerations for the Community

Current Transplant Program Use of eGFR Calculations

The Workgroup aims to understand the current state of GFR measurement or estimation use across transplant programs. The Workgroup seeks feedback on which eGFR formula programs use and why it is their preferred method for estimating GFR. Additionally, the Workgroup asks transplant programs if they have elected to remove the Black race coefficient and why they decided to remove or retain it. Community responses to these questions will provide the OPTN with valuable information on current trends in eGFR use and assist in estimating the overall amount of adjustment necessary should the Workgroup propose changes to policy.

Operational Impacts

The Workgroup requests input on any operational impacts the use of a race- neutral formula could have on transplant programs. Operational impacts could include those affecting programs' finances, day to day protocols and function, or systems such as Electronic Medical Records (EMRs). Community responses to these questions will assist the OPTN in understanding the level of complexity programs could encounter should a policy be proposed.

Implementation

The Workgroup seeks feedback on the transplant programs' implementation processes if eGFR equations requirements were changed. Community responses to these feedback questions will inform the OPTN of any foreseeable challenges various programs could experience. This will also better prepare the OPTN to develop resources to assist programs with any necessary transitions.

Patient Feedback

The Workgroup requests feedback from patients. Much of the requested information pertains specifically to programs, but the OPTN also values patient input. Responses from patients will inform the OPTN as to why patients may support or oppose changes. Expressed perspectives will inform the development of any future proposal and assist the OPTN in serving patients.

Current Workgroup Discussion

Race-Neutral eGFR Policy

The feedback received will inform ongoing Workgroup discussions regarding potential OPTN policy changes that would require the use of race- neutral formulas for the initiation of accruing qualified waiting time. The Workgroup is considering the potential impacts of removing the Black race coefficient from the eGFR equation. They are also discussing that a race- neutral formula would discontinue the binary Black/Not Black response options, as they do not account for mixed-race and multi- racial

individuals. The Workgroup will use responses to this Request for Feedback to frame a potential future proposal.

NOTA and Final Rule Analysis

The OPTN Minority Affairs and Kidney Transplantation Committees submit the following project for consideration under the authority of the OPTN Final Rule, which states the OPTN shall develop "Policies for the equitable allocation of cadaveric organs in accordance with §121.8."[37] While this Request for Feedback will not immediately result in an allocation policy change, this project may affect equitable allocation by examining the impact of race on a candidate's eGFR. Because eGFR affects a candidate's ability to be listed and to accrue wait time, the impact of the race coefficient could ultimately affect a candidate's placement on the match run. This Request for Feedback will assist the OPTN in evaluating solutions to ensure any future policy modification is consistent with the requirements of the OPTN Final Rule.

Summary

Research suggests that the use of the Black race coefficient in the eGFR formulas has the potential to disadvantage the Black patient population.[38, 39] Overestimation of eGFR has the potential to delay referral for transplant and initiation of qualifying waiting time.[40] Use of eGFR formulas that include the Black race coefficient could further exacerbate existing disparities and contribute to worse outcomes for the Black individuals with CKD.[41, 42] The Workgroup seeks feedback to assist in the development of a future proposal that aims to provide more equity in access to transplantation for these patients.

The Sponsoring Committees are seeking feedback on the following items to inform a future proposal:

Considerations for the Community

- Which method of estimating or measuring GFR is your transplant program currently using? Why?
- How would this use of a race-neutral eGFR impact your program?
- What implementation challenges could use of a race- neutral eGFR present for your transplant program?
- What resources could assist in facilitating a smooth transition for your program?
- Do patients support the use of a race- neutral eGFR formula? Why or why not?
- What potential unintended consequences should be considered during this proposal's development?

[37] 42 CFR §121.4(a)(1).
[38] Reese PP, Sumit M, King KL, Williams WW, Potluri VS, Harhay MN, Eneanya ND. Racial disparities in preemptive waitlisting and deceased donor kidney transplantation: Ethics and solutions. The American Journal of Transplant. 2020. 21:958–967. https://doi.org/10.1111/ajt.16392
[39] Vyas DA, Einstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. The New England Journal of Medicine. 2020. 383(9): 874-882.
[40] Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. American Medical Association. 2019. 322(2):113-114
[41] Ibid.
[42] Ahmed S, Nutt CT, Eneanya ND, Reese PR, Sivashanker K, Morse M, Sequist T, Mendu ML. Examining the Potential Impact of Race Multiplier Utilization in Estimated Glomerular Filtration Rate Calculation on African-American Care Outcomes. Journal of General Internal Medicine. 2020. 36(2):464–71DOI: 10.1007/s11606-020-06280-5