

This memo provides information supporting our recommendations related to the use of cystatin C in estimating GFR for the CRIC study. The following are our 4 principal recommendations:

1. We provide a race-free eGFR estimating equation that includes age, sex, serum creatinine, and cystatin C for use with CRIC data. This equation provides very good estimation of GFR for CRIC study participants but should not be used for datasets outside of CRIC.
2. The 2012 CRIC eGFR equation (Anderson et al. 2012) that includes age, sex, race, serum creatinine, and cystatin C remains available for investigators analyzing CRIC data and provides excellent estimation of GFR for CRIC Study participants.
3. We do not recommend the use of the CKD-EPI race-free eGFR equation that incorporates cystatin C (Inker et al. 2021) for analyses of CRIC Study data because the international standardization of cystatin C data used by this study group does not align with the CRIC cystatin C data.
4. Researchers seeking to compare eGFR between the CRIC Study population and groups outside of the CRIC Study are advised to use creatinine-based equations such as the CKD-EPI equation that incorporates age, sex, serum creatinine (Inker et al. 2021).

Background

The CKD-EPI group published eGFR estimating equations that include the use of cystatin C. To use these equations, cystatin C must be calibrated to the international standard.

Inker et al. (2012; Table S2) described an approach to calibrate the cystatin C to the international standard for CRIC samples in the development of the CKD-EPI equations.

The CRIC study has also implemented two complementary approaches for calibrating the cystatin C values. The first was developed to address lot-to-lot variation in assay reagents and is referred to as “internal calibration.” This approach was used to develop the CRIC eGFR estimating equation and described in the publication describing it (Anderson et al. 2012). The second approach was to calibrate CRIC cystatin C data to the international standard, implementing this calibration after internal calibration had been performed.

Assessing the Usability of the CKD-EPI Equation that Incorporates Cystatin C for CRIC Data

Using the samples within the CRIC iGFR subcohort (the group of study participants who underwent clearance studies with exogenous iothalamate to measure GFR), we examined the performance of CKD-EPI 2021 equation (that includes age, sex, serum creatinine and cystatin C; Inker et al. 2021) comparing the two different international cystatin C calibration methods (CKD-EPI and CRIC).

We also separately examined the CRIC eGFR estimating equation (that includes age, sex, race, serum creatinine and cystatin C; Anderson et al. 2012) and a newly developed CRIC equation

without using the race information (i.e., the equation includes only age, sex, serum creatinine and cystatin C). The cystatin C was only internally calibrated in both of these CRIC equations.

The differences between the iGFR and eGFR were calculated in the entire iGFR subcohort and in subgroups defined by race and study visit and are depicted in the Figure.

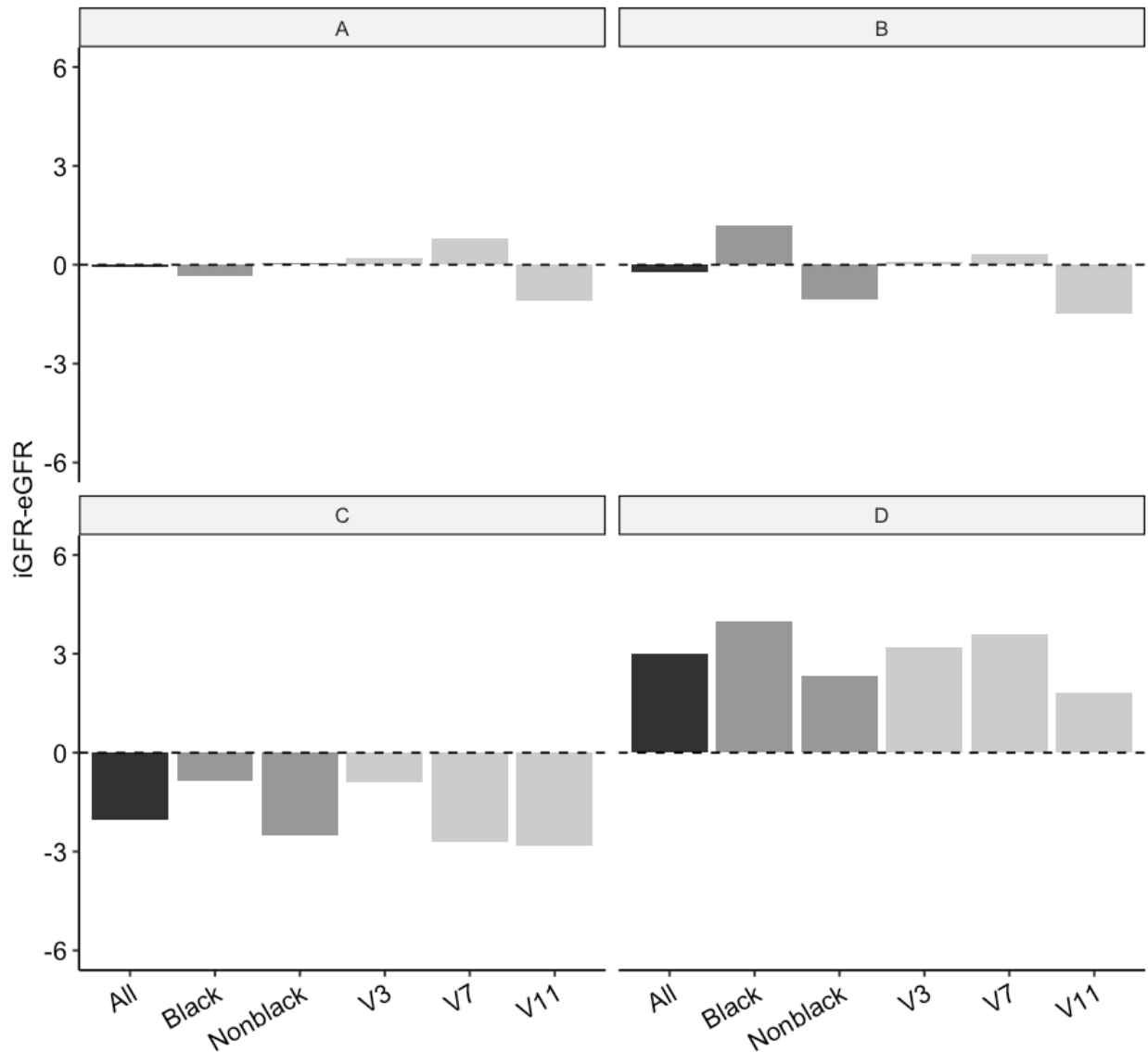


Figure: iGFR minus eGFR for different eGFR estimating equations with different cystatin C calibration methods in the overall CRIC iGFR subcohort (All) and subgroups by race (Black, Nonblack) and visit number (V3, V7 and V11). **(A):** CRIC equation that includes age, sex, race, serum creatinine and CRIC internally calibrated cystatin C; **(B):** CRIC equation that includes age, sex, serum creatinine and CRIC internally calibrated cystatin C; **(C):** CKD-EPI equation that includes age, sex, serum creatinine and cystatin C calibrated to the international standard using the CKD-EPI method; **(D):** CKD-EPI equation that includes age, sex, serum creatinine and cystatin C calibrated to the international standard using the CRIC method. V3, V7 and V11 are CRIC baseline, year 2 and year 4 visit respectively.

The bias for both CRIC equations (Panels A and B in the Figure) using CRIC internally calibrated cystatin C is smaller compared to using the CKD-EPI equation that incorporating cystatin C calibrated using either the CKD-EPI (Panel C in the Figure) or CRIC method (Panel D in the Figure) to the international standard.

The CKD-EPI equation incorporating the CKD-EPI calibrated cystatin C value performed best at the baseline visit (i.e., V3), from which the CRIC samples were used as part of the development set for the CKD-EPI estimating equation. Its performance in the CRIC follow-up visit samples (i.e., V7 and V11) was not as good. Notably, eGFR was over-estimated using the CKD-EPI equation with the CKD-EPI calibrated cystatin C data (Panel C). In contrast, eGFR was under-estimated in all subgroups using the CKD-EPI equation using the CRIC calibrated cystatin C value (Panel D).

Based on our empirical data, we believe there is need for a more formal systematized approach to calibrating cystatin C to the international standard that can be consistently implemented across different research and clinical laboratories. This is needed before we can recommend the use of eGFR estimating equations that include cystatin C for CRIC data other than the internally validated CRIC eGFR equations (either without or with the race variable). Because of these considerations, researchers seeking to compare eGFR between the CRIC Study population and groups outside of the CRIC Study are advised to use creatinine-based equations such as the CKD-EPI equation that incorporates age, sex, serum creatinine (Inker et al. 2021).

References:

- Inker, L. A., Schmid, C. H., Tighiouart, H., Eckfeldt, J. H., Feldman, H. I., Greene, T., ... & Levey, A. S. (2012). Estimating glomerular filtration rate from serum creatinine and cystatin C. *New England Journal of Medicine*, *367*(1), 20-29.
- Inker, L. A., Eneanya, N. D., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., ... & Levey, A. S. (2021). New creatinine-and cystatin C–based equations to estimate GFR without race. *New England Journal of Medicine*, *385*(19), 1737-1749.
- Anderson, A. H., Yang, W., Hsu, C. Y., Joffe, M. M., Leonard, M. B., Xie, D., ... & CRIC Study Investigators. (2012). Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) study. *American journal of kidney diseases*, *60*(2), 250-261.