Supplemental Methods

A. Development of equations to estimate GFR and evaluation of their performance compared to measured GFR

Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)

CKD-EPI is a research group funded by the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) to address challenges in the study and care of CKD, including development and validation of improved GFR estimating equations by pooling data from research studies and clinical populations (hereafter referred to as "studies"). The design and studies have been previously described and are briefly reviewed here.[1-3] Full information can be found here https://www.tuftsmedicalcenter.org/research-clinical-trials/institutes-centers-labs/chronic-kidney-disease-epidemiology-collaboration/overview

The first and last authors are co-directors of CKD-EPI. They drafted the first draft and subsequent revisions with the participation of a subgroup of the authors (Crews, Coresh, Eneanya, Grams, Gutierrez and Powe). Hocine Tighiouart performed the analyses under the direction of the first and last authors. The remainder of the writing group reviewed the near to final draft and provided input. All authors approved the final version. The first, fourth, and last authors take responsibility for all the analyses and directed the development and validation of the GFR estimating equations. Drs. Coresh and Selvin and analyst Dan Wang directed the NAHANES analyses.

Data sources

The institutional review boards of all participating institutions approved each study and Tufts Medical Center's institutional review board approved the current analysis.

Collaborators provided data from research studies and clinical populations. **Figure S1** and **Table S2** shows the division of these studies into development and external validation for the CKD-EPI 2009 creatinine ($eGFR_{cr}$) equation, CKD-EPI 2012 cystatin C ($eGFR_{cys}$) and creatinine-cystatin C equations ($eGFR_{cr\text{-}cys}$) and the CKD-EPI 2021 equations described here. GFR was measured using urinary or plasma clearance of exogenous filtration markers (**Table S1**). For development of new equations, we used existing development populations: CKD-EPI 2009 for $eGFR_{cr}$ (**Table S6,** 10 studies, 8254 participants) and CKD-EPI 2012 for $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ (**Table S7,** 13 studies, 5352 participants). For external validation of all equations, we used a new population (CKD-EPI 2021) consisting of CKD-EPI 2012 external validation studies and new studies (**Table S8** 12 studies, 4050 participants). Separately, for external validation of $eGFR_{cr}$, we also used CKD-EPI 2009 external validation population, as it is larger than CKD-EPI 2021. Race was self-reported by participants in most studies (**Table S3**).

Information on race and ethnicity groups were provided in the original study data. In our past work, we had explored use of 2-level variable for race (Black vs. White and other) and as a 4-level variable (Black, Asian, Native American and Hispanic vs. White and other). Our main publications and equations used in practice included the 2-level variable as we had insufficient representation from the other groups to have definitive results and our analyses within these small sample sizes did not demonstrate large effects.[4] Categorization of racial groups in this study was consistent with previous studies. We recognize the broad diversity within racial groups and in future studies, categorization can reflect this important concept.

Laboratory methods

Figures and Tables

Figure S1: Flow diagram of the CKD-EPI development and validation datasets

Legend: The flow diagram shows the evaluation of studies and participants included in the development and validation of the 2009, 2012 and 2021 CKD-EPI equations.[1,2] The dark gray shaded boxes show the three main datasets included in the analyses presented in the analysis. The light gray shaded box indicates a dataset used in a secondary analysis. Squares represent addition or removal of studies. Circles represent removal of subset of studies. Dashed lines indicate when studies or participants were removed. Solid lines indicate when studies were added.

The green shaded area shows the creatinine development and validation studies. A more detailed figure showing the development of those studies was previously published.[1] The yellow shaded area depicts the transition from the studies included in the creatinine datasets to those included in the development and validation of the 2012 cystatin C and creatinine-cystatin C equations. The blue shaded area depicts the studies included in the new 2021 external validation dataset.

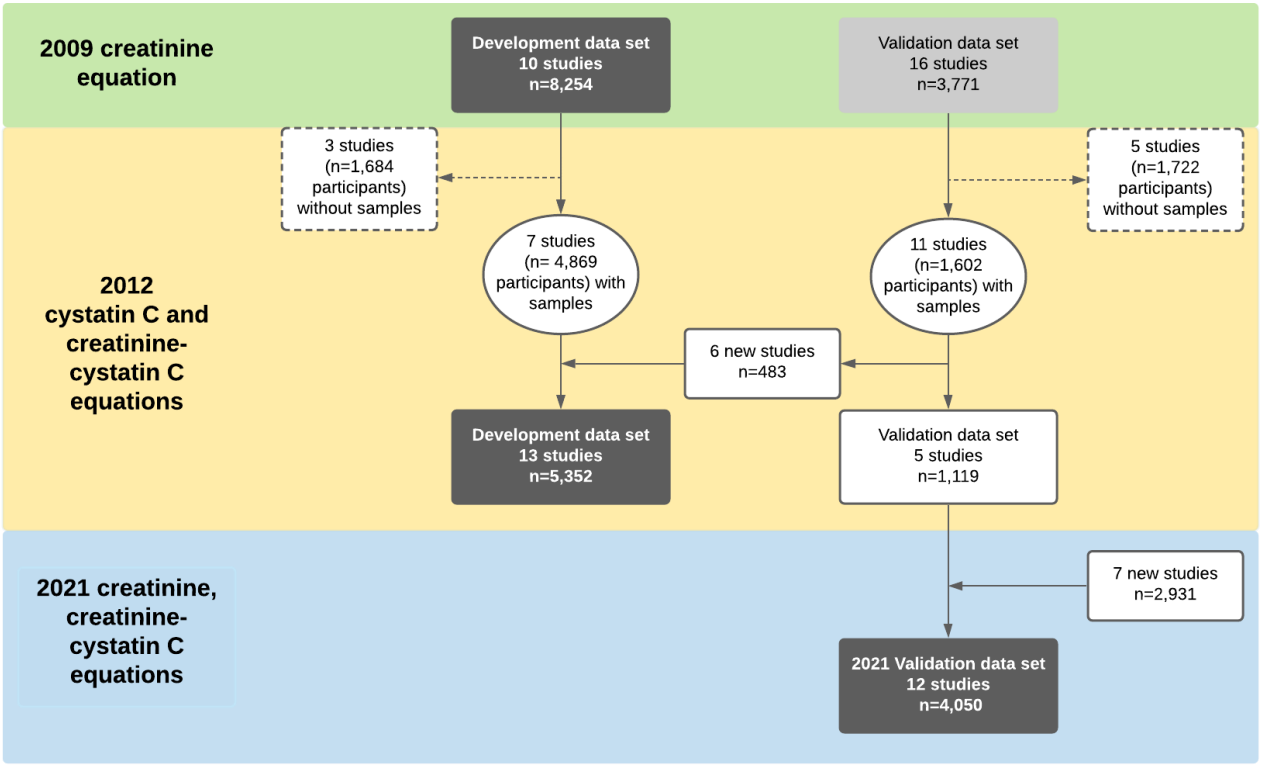

Table S1: Methods to measure GFR in each study in the 2009 and 2012 development and 2021 External Validation Datasets

Study	**Datasets**		
	2009 Creatinine Development	2012 Cystatin C Development	2021 External Validation
AASK[33]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
MDRD[34]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
DCCT[35]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
DRDS[36]	Urinary clearance of iothalamate	-	-
CSG[37]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
CRIC[38]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
CCF[39]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
Mayo[40]	Urinary clearance of iothalamate	Urinary clearance of iothalamate	-
CRISP[41]	-	Urinary clearance of iothalamate	-
Groningen[42]	-	Urinary clearance of iothalamate	-
RASS[43]		Urinary clearance of iothalamate	Plasma clearance of iohexol*[12]
AGES[44]	-	-	Plasma clearance of iohexol*[12]
STENO[45-48]	-	-	Plasma clearance of ^{51}Cr-EDTA
UMN Donor	-	-	Plasma clearance of iohexol*[12]
Lund[49]	-	-	Plasma clearance of iohexol*[12]
HIV[50]	-	-	Plasma clearance of iohexol*[12]
MACS[51]	-	-	Plasma clearance of iohexol*[12]
PERL[52]	-	-	Plasma clearance of iohexol*[12]
MESA[53]	-	-	Plasma clearance of iohexol*[12]
ALTOLD[54]	-	-	Plasma clearance of iohexol*[12]
NephroTest[55]	-	-	Plasma and urinary clearance of ^{51}Cr-EDTA

Abbreviations: MDRD Study, Modification of Diet in Renal Disease Study; AASK, African American Study of Kidney Diseases and Hypertension; DCCT, Diabetes Control and Complications Trial; DRDS, Diabetic Renal Disease Study; CSG, Collaborative Study Group: Captopril in Diabetic Nephropathy Study; CRIC, Chronic Renal Insufficiency Cohort Study; CCF, Cleveland Clinic Foundation; MACS, Multicenter Aids Cohort Study; PERL, Preventing Early Rental Loss in Diabetes; CCF, Cleveland Clinic Foundation; MESA, Multi-Ethnic Study of Atherosclerosis; ALTOLD, Assessing Long Term Outcome of Living Kidney Donors; CRIC, Chronic Renal Insufficiency Cohort Study; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study; UMN, University of Minnesota; RASS, Renin Angiotensin System Study, ^{51}Cr-EDTA, ^{51}Cr-ethylenediaminetetraacetic acid

* Calibrated to urinary clearance of iothalamate by reducing the assigned value of other methods by 5%, based on a systematic comparison of all methods. See supplemental methods for additional details