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Comparison between Old and New GFR Estimating Equations in Children and Adults with Glomerular Disease in the NEPTUNE Study

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GFR estimation · CKD-EPI · U25 · EKFC · Agreement

Abstract
Introduction: New equations developed in the USA for estimating glomerular filtration rate (GFR) eliminated race for adults and widened the age range for children and young adults. The European Kidney Function Consortium (EKFC) equation was also validated and updated for a US adult population. The aftereffects of adopting these new equations on previous research results among patients with glomerular disease are unknown. This study compared eGFR using old and new estimating equations and their impacts on eGFR-based outcomes. ***Methods:*** Longitudinal serum creatinine measurements from children and adults enrolled in the Nephrotic Syndrome Study Network (NEPTUNE) were used to calculate eGFR using old bedside Schwartz and CKD-EPI 2009 equations, new U25 and race-free CKD-EPI 2021 equations, and the EKFC equation. Time to disease progression (40% eGFR decline or kidney failure) outcomes were compared using Kaplan-Meier curves and Cox models and longitudinal eGFR outcomes were compared using linear mixed-effects models to assess effects of demographics, clinical characteristics, pathology descriptors, a serum and urine biomarker, and the APOL1 genetic trait. ***Results:*** N = 756 NEPTUNE study participants were included (median age 21 years, 41% female, and 25% who reported Black race). Disease progression outcomes were similar between using old versus new age-specific equations, whereas event rates were lower using EKFC. Survival curves were largely overlapping, and selected risk factor effects on disease progression were similar. Only sex and race effects on longitudinal eGFR differed between old versus new age-specific equations, whereas larger differences were observed for disease diagnosis effects when using EKFC. ***Conclusion:*** New U25 and race-free CKD-EPI 2021 equations had little impact on estimated GFR values and results of survival and longitudinal regression analyses. EKFC results differed and were likely driven by those with very high eGFR.

Introduction

Due to the infeasibility of directly measuring kidney function in routine clinical care and most research studies, estimation equations are primarily used to estimate glomerular filtration rate (GFR) based on

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biomarkers – most commonly serum creatinine. The 2009 CKD-EPI creatinine-based equation [1] has been widely validated and used for estimating GFR in adults and includes several demographic factors including age, sex, and race. The coefficient for Black race results in higher estimated GFR values for Black adults compared to non-Black adults with the same age, sex, and serum creatinine (sCr). Estimating higher kidney function based on race can compound the effects of structural racism in healthcare resulting in later diagnosis of chronic kidney disease (CKD), categorization into higher CKD stages, and reducing eligibility for kidney transplantation. However, since race is a social construct rather than a biological attribute and therefore the use of race-based eGFR estimating equations contributes to inequities in access to care for Black Americans, a new CKD-EPI creatinine equation without race was developed [2] and has been quickly adopted in the field.

Estimating equations for eGFR in children have also been updated within the last 2 decades. In 2009, the Chronic Kidney Disease in Children (CKiD) Study revised the original Schwartz equation [3] that estimates GFR for children using height and sCr [4]. This revised equation, known as the CKiD bedside Schwartz equation, was commonly used both clinically and in research. However, the sample used to develop this revised equation came primarily from children aged 8–15 years. Since then, CKiD has enrolled children <5 years and continued to follow the original participants into ages 16 to <25. In 2020, new eGFR equations for children and young adults were developed in the CKiD study, known as the CKiD Under 25 (U25) equations, based on sex, age, height, and sCr [5]. These new equations reduced bias in eGFR and had higher accuracy values [5].

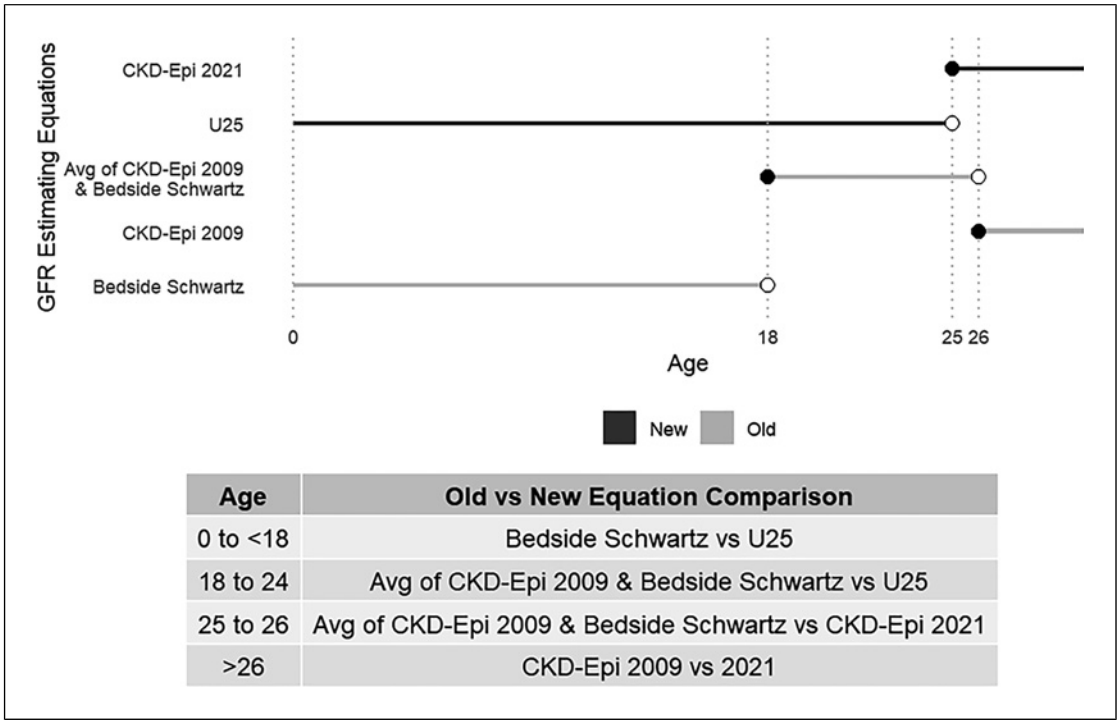
A known limitation of equations developed separately for specific age-groups is the implausible jump in estimated GFR with a switch in equations as children or young adults age [6]. To address this, Full Age Spectrum (FAS) eGFR estimating equations were initially developed [7] and the European Kidney Function Consortium (EKFC) equation further improved on FAS to address its known issues of overestimating GFR at very low sCr values and in CKD patients [8]. These equations include age- and sex-specific or height-specific Q values that correspond to the median sCr values from healthy populations and are used to rescale sCr to account for differences in sCr generation by age and sex or by height. While these equations were developed and validated in European populations and do not include race as a factor, the age-based EKFC was further validated among US adults with US adult-specific Q values [9, 10]. Among children and young adults, the EKFC equation has not been validated in the USA [11] although the older FAS equations with height-specific Q values were validated in the North American CKiD cohort [5].

While revisions to eGFR estimating equations have improved accuracy in CKD populations and may impact existing health disparities in kidney disease, these changes make comparing published results over time challenging and the implications among glomerular disease populations have not been studied. Prior to 2020, older eGFR estimating equations were used, including the 2009 CKD-EPI creatinine equation for adults >26 years, bedside Schwartz equation for children <18 years, and sometimes an average of estimates from these two equations for participants 18–26 years [12]. Since then, as newer equations have become available, large research studies are starting to publish using the updated equations, including the 2021 CKD-EPI creatinine equation without race for adults ≥25 years and CKiD U25 creatinine equation for children and young adults <25 years or the EKFC equation across all ages. In this study, we describe and compare old versus new age-specific calculations of eGFR and new age-specific versus EKFC calculations of eGFR among patients with glomerular disease and assess impacts on results from typical research analyses that use eGFR as an outcome. This work can therefore inform interpretation of prior published studies and comparisons of ongoing work to the published literature.

Methods

NEPTUNE Study Sample and Data

The Nephrotic Syndrome Study Network (NEPTUNE) is an ongoing multi-site prospective observational cohort study that has provided invaluable knowledge about glomerular disease over the last decade. eGFR has been widely used in NEPTUNE research studies, both as an outcome variable and baseline control factor. NEPTUNE enrolls adult and pediatric patients with proteinuria >0.5 g/day (or >1.5 g/day after 2014) in North America with glomerular diseases. Enrollment began in 2010. No limits on eGFR were required for study eligibility, and other details of inclusion and exclusion criteria were previously published [13]. Study participants were enrolled after informed consent (and assent, as appropriate) at the time of their first clinically indicated kidney biopsy or at initial presentation of disease for pediatric patients without biopsy and followed prospectively 2–3 times per year. Demographic and clinical variables were collected at the time of NEPTUNE study



Age	Old vs New Equation Comparison
0 to <18	Bedside Schwartz vs U25
18 to 24	Avg of CKD-Epi 2009 & Bedside Schwartz vs U25
25 to 26	Avg of CKD-Epi 2009 & Bedside Schwartz vs CKD-Epi 2021
>26	CKD-Epi 2009 vs 2021

Fig. 1. Old and new age-specific eGFR equations and comparisons of equations across age timeline.

enrollment (baseline) and each follow-up visit, including laboratory values, family history, and comorbidities. sCr was collected at study enrollment and each follow-up visit through blood sample tests and between-study visits by review of study participants' medical charts. Race was self-reported or reported by parents of children, and reporting race in NEPTUNE was mandated by the US National Institutes of Health, consistent with the Inclusion of Women, Minorities, and Children policy. The current study includes NEPTUNE participants ≥2 years old who had at least one eGFR that could be calculated from sCr.

Calculation of eGFR

For children and young adults through age 26 at the time of sCr measurement, we calculated eGFR using the bedside Schwartz equation based on height and sCr [4]. For children and young adults <25 years, we also calculated eGFR using the CKiD U25 equation based on height and sCr [5]. These two equations are calculated in the same form: eGFR = $K \times$ (height in meters/sCr in mg/dL). The K multiplier coefficients used by each of the equations, by age and sex, are plotted for reference in online supplementary Figure 1a (for all online suppl. material, see https://doi.org/10.1159/000545934). K is constant at 41.3 in the bedside Schwartz equation and is sex- and age-dependent in the U25 equation, resulting in differences ranging from −19.9% to 23.0%. For adults ≥18 years, we calculated eGFR using the 2009 CKD-EPI equation based on age, sex, race, and sCr and using the 2021 CKD-EPI equation based on age, sex, and sCr [1, 2]. eGFR values for different levels of sCr, by age, sex, and race, are plotted for reference in online supplementary Figure 1b. Generally, eGFR is similar between 2009 and 2021 CKD-EPI equations for those with non-Black race and values are lower using 2021 CKD-EPI equations for those with Black race.

The set of "old" eGFR equations includes bedside Schwartz for children (<18), the average of bedside Schwartz and 2009 CKD-EPI for adults 18–26 [12], and 2009 CKD-EPI for adults >26 (Fig. 1). The set of "new age-specific" eGFR equations includes U25 for children and adults <25 and 2021 CKD-EPI for adults ≥25. Given the different age ranges for old and new age-specific equations, there were four age-groups (<18 years, 18–24 years, 25–26 years, and >26 years), within which comparisons between different equations could be made. In our analyses, we combined 18–24 years and 25–26 years into one age-group due to their relatively small group sizes.

Additionally, we calculated eGFR using the sCr-based EKFC equation [8] with age- and sex-specific Q values

that correspond to the median sCr values in age- and sex-specific healthy populations. For children and young adults <25 years old, we used Q values from the original equation, reflecting median sCr values from the European population, as such data are not available from the US yet. For adults ≥25 years, we used race-free Q values (0.97 mg/dL in males and 0.73 mg/dL in females) from a US adult population [10] that was also validated [9]. Similarly, we plotted eGFR values for different levels of sCr by age and sex for reference (online suppl. Fig. 1b) and for comparison with the 2021 CKD-EPI equation among adults ≥25 years. Generally, the EKFC equation gave similar or slightly lower eGFR values.

Statistical Analysis

Descriptive statistics including median and interquartile range (IQR) for continuous variables and frequency and percentages for categorical variables were used to summarize demographics and clinical characteristics of the study sample at the time of study enrollment. Scatterplots were used to compare eGFR values calculated using old versus new age-specific equations and new age-specific versus EKFC equations in NEPTUNE, by age groups, sex, and Black race. We also used Bland-Altman plots to show the relative difference in old versus new age-specific equation eGFR values and new age-specific versus EKFC equation eGFR values over their average, stratified first by sex, then by age group, and calculated intraclass correlation coefficient (ICC) [14] to assess agreement. Finally, we assessed the impact of using old versus new age-specific versus EKFC equations for calculating eGFR values on two eGFR-based outcomes that have been commonly analyzed in the NEPTUNE study, including (1) time from study enrollment to disease progression, defined as ≥40% decline in eGFR [15] with eGFR <90 mL/min/1.73 m^2 or kidney failure (KF, defined as dialysis, transplant, or eGFR <15), and (2) longitudinal eGFR.

For the time-to-event disease progression outcome, we restricted analyses to study participants with baseline eGFR and at least one follow-up eGFR. We calculated event rates and plotted Kaplan-Meier (KM) curves to compare outcome event indicators and event times. We also used multivariable Cox proportional hazard models to estimate associations between known risk factors and the time-to-event outcome. Risk factors of interest included pathology descriptors (percent of global sclerosis, percent of interstitial fibrosis, and percent of tubular atrophy), serum anti-phospholipase A2 receptor antibodies (PLA2R), urine protein creatinine ratio (UPCR), and high-risk (2 risk alleles) versus low-risk (0 or 1 risk allele) apolipoprotein L1 (APOL1) status. Only study participants with membranous nephropathy were included in the model for PLA2R and only black study participants were included in the model for APOL1. Both PLA2R and UPCR were log-2 transformed such that results could be interpreted as a doubling of biomarker values. Adjustment covariates included age, Black race, sex, disease diagnosis, enrollment time, eGFR, UPCR, immunosuppression use, and RAAS blockade use. Adjustment for race was included to facilitate comparison with previous studies. Due to a limited number of outcome events, backward selection was used to select adjustment covariates included in each model.

For the longitudinal eGFR outcome, we used linear mixed-effects models, with random intercept and slope to account for repeated eGFR measurements within study participants. We first fitted a "base" model with only adjustment covariates (same as for the multivariable Cox model above) and then fitted a set of models that included both adjustment covariates and each of the risk factors above. All analyses were conducted using old equations, new age-specific equations, and EKFC equations to calculate eGFR values separately and results were then compared.

R software, version 4.4.0 (R Core Team, Vienna) and SAS software, version 9.4 (SAS Institute, Cary, NC) were used for all analyses. The current study was considered not human subjects research and did not require formal IRB review by The Children's Hospital of Philadelphia Institutional Review Board (IRB #22–020363).

Results

A total of N = 756 NEPTUNE participants were included in the current study (Table 1). The median age was 21 years (IQR = 7–47 years); 47% were <18 years, 6% were between 18 and 24 years, 2% were 25 or 26, and 45% were >26. Overall, 41% of participants were female, 25% reported African American or Black race, and 21% reported Hispanic ethnicity. Minimal change disease (MCD) and focal segmental glomerulosclerosis were the most common histologic diagnoses (26% and 27%, respectively) with 14% membranous nephropathy, 16% other diagnosis, and the remaining 16% pediatric patients who did not have biopsy to allow for a specific pathology-based disease classification. Median (IQR) eGFR at baseline was 88 (59, 111), 84 (60, 105), and 83 (58, 106) mL/min/1.73 m^2 based on old, new age-specific, and EKFC eGFR calculation equations, respectively, and median (IQR) UPCR was 2.4 (0.5, 5.9) mg/mg. Median (IQR) length of follow-up was 2.9 (1.3, 4.3) years.

Table 1. Study participant characteristics at study enrollment and study outcomes

	All patients (n = 756)
Age, median (IQR), years	21 (7, 47)
Children <18	47% (354)
Young adults 18–<25	6% (45)
Young adults 25–26	2% (14)
Adults >26	45% (343)
Female	41% (310)
Race	
African American or Black	25% (182)
Multiracial and Other races[a]	19% (135)
White or Caucasian	56% (407)
Hispanic or Latino ethnicity[b]	21% (157)
Disease cohort	
MCD	26% (200)
FSGS	27% (202)
MN	14% (109)
Other	16% (121)
NS not specified (no biopsy)	16% (124)
Baseline eGFR, median (IQR)[b], mL/min/1.73 m^2	
Using old eGFR calculation equations	87.9 (58.5, 110.7)
Using new age-specific eGFR calculation equations	84.2 (60.0, 104.6)
Using EKFC eGFR calculation equation	83.3 (58.4, 106.3)
Baseline UPCR, median (IQR)[b], mg/mg	2.4 (0.5, 5.9)
Length of follow-up, median (IQR), years	2.9 (1.3, 4.3)
Disease progression (≥40% decline in eGFR and eGFR ≤90 or KF) events per 100 person-years[c]	
Using old eGFR calculation equations	6.34
Using new age-specific eGFR calculation equations	6.33
Using EKFC eGFR calculation equation	5.50

Values for categorical variables are given as number (percentage); values for continuous variables are given as median (Q1, Q3). IQR, interquartile range; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; eGFR, estimated glomerular filtration rate; UPCR, urine protein creatinine ratio; KRT, kidney replacement therapy (dialysis or transplant). [a]Other category includes multiracial, American Indian/Alaska Native/First Nation, Asian/Asian American, and Native Hawaiian/Other Pacific Islander. [b]Missing 1%–5%. [c]Among n = 663 who were at least 2 years old, had eGFR at baseline, and have at least one follow-up eGFR.

Impact on eGFR Values in NEPTUNE Using Old versus New Age-Specific eGFR Calculation Equations

Among participants <18 years (Fig. 2a), new eGFR values using U25 were similar or higher than old values using bedside Schwartz for males and similar or slightly lower for females. Note that neither equation was developed to accurately estimate very high eGFR values (bedside Schwartz eGFR range 30–90; U25-measured GFR [mGFR] values <140); however, some very high eGFR values (>140 mL/min/1.73 m^2) were observed in our sample, particularly among participants <18 years. Among participants 18–26 years (Fig. 2b), new eGFR values tended to be similar or higher than old values for non-Black males, similar for Black males and non-Black females, and tended to be lower for Black females. Among participants >26 years (Fig. 2c), new eGFR values using the CKD-EPI 2021 equation were systematically lower than old values using the CKD-EPI 2009 equation among Black study participants, with differences increasing as eGFR increased; for non-Black study participants, new eGFR values were similar or slightly higher than old values, with a small proportion of new values lower than

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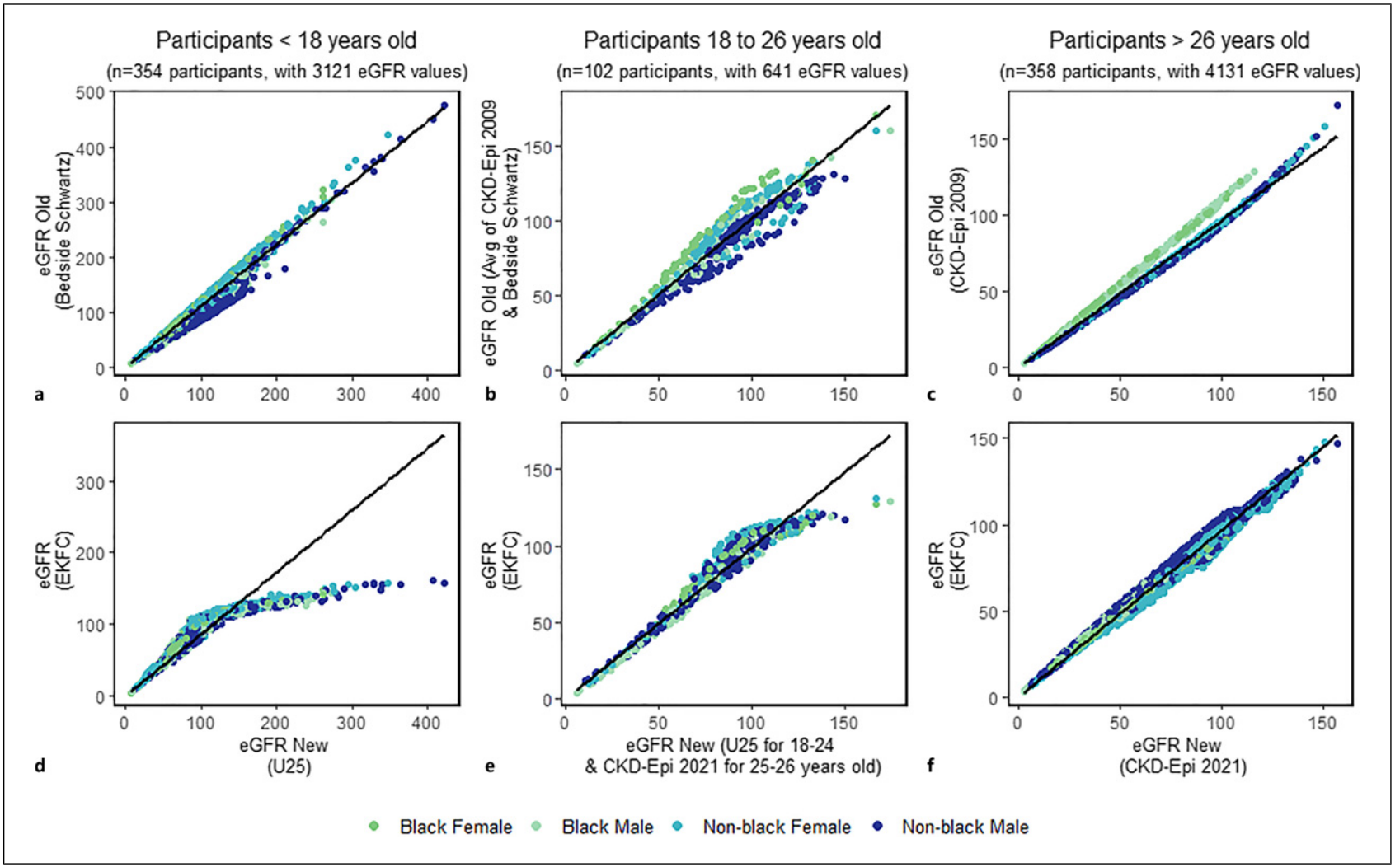

Fig. 2. Scatterplots of eGFR values using old versus new age-specific (top row) and new age-specific versus EKFC (bottom row) eGFR equations in NEPTUNE among participants <18 years old (left column), participants 18–26 years old (middle column), and participants >26 years old (right column), by sex and Black race. eGFR is in mL/min/1.73 m^2.

old values when eGFR was higher than 140. Note that during study follow-up, only small proportions (6% and 2%) of study participants crossed the thresholds at 18 and 25 years, respectively, where eGFR calculating equations would change within individuals.

On average, new eGFR values were 1.8% lower (standard deviation [SD] = 9.6%) than old values (Fig. 3a, b, solid horizontal line). The percent of new eGFR values within 10, 20, or 30% of old values were 71%, 100%, and 100%, respectively. While the majority of eGFR values were within about two SDs of the mean, there were some eGFR values for which using the new equations resulted in much larger (>17% relative difference) changes compared with the old equations. These were mostly from male study participants between the ages of 18–26 years. Agreement between the two values was high (ICC [95% CI] = 0.971 [0.970, 0.972]), indicating excellent overall agreement between old and new age-specific eGFR values among the entire study cohort.

Impact on eGFR Values in NEPTUNE Using New Age-Specific versus EKFC eGFR Calculation Equations

Among participants <18 years (Fig. 2d), EKFC eGFR values were similar or slightly higher than U25 eGFR values when U25 eGFR was <140. When U25 eGFR was >140 (acknowledging that the U25 equation was developed among mGFR values <140 and EKFC equation was developed among mGFR values <200), the U25 equation gave much higher eGFR estimates than the EKFC equation. This is due to differences in the exponents of sCr between EKFC and U25 equations, i.e., −0.322 in the EKFC equation when sCr is less than Q and −1 in the U25 equation. To illustrate this, if age and height are held constant and if sCr is less than Q, when sCr decreases from 0.5 to 0.25, the eGFR value from EKFC would increase by 1.25 times ($0.25^{-0.322}/0.5^{-0.322} = 1.25$) whereas the eGFR value from U25 would increase by 2 times ($0.25^{-1}/0.5^{-1} = 2$), a much faster increase in eGFR from U25 as sCr decreases. Among participants 18–26 years (Fig. 2e), eGFR values based on EKFC and new age-specific equations were similar, except for eGFR values >140 where eGFR values from new age-specific equations were higher than EKFC values. Among participants >26 years (Fig. 2f), eGFR values were similar across sex and race groups, even when eGFR values were higher than 140.

On average, EKFC eGFR values were 2.9% lower (SD = 9.3%) than eGFR values calculated from new age-specific equations (Fig. 3c, d, solid horizontal line). The percent of EKFC eGFR values within 10, 20, or 30% of eGFR values calculated from new age-specific equations were 78%, 95%, and 98%, respectively. While the majority of eGFR values were within about two SDs of the mean, there were some eGFR values for which using the EKFC equation resulted in much larger (>15% or < −21% relative differences) changes compared with the new age-specific equations. EKFC eGFR values that were more than 21% lower than new age-specific eGFR values were mostly from study participants <18 years with very high eGFR values, which could indicate hyperfiltration. Furthermore, some EKFC values were >15% or < −21% of new age-specific eGFR values even though differences in eGFR absolute values were small (range −3.6–2.8) due to low mean eGFR values (i.e., <20 mL/min/1.73 m^2). Finally, some EKFC values were >15% of new age-specific eGFR values while mean eGFR values were close to normal, primarily among participants <18 and 18–26 years old. Agreement between the two values was still high overall (ICC [95% CI] = 0.915 [0.912, 0.919]), indicating excellent agreement between new age-specific and EKFC equation eGFR values among the entire study cohort.

Impact of Old versus New Age-Specific versus EKFC eGFR Calculation Equations on Outcomes Analyses

A total of 663 participants with baseline eGFR and at least one follow-up eGFR were included in the analyses of disease progression. There were 109, 109, and 95 study participants who reached the outcome during study follow-up using old, new age-specific, and EKFC eGFR calculations, respectively. Comparing outcomes using old versus new age-specific eGFR equations, 104 study participants were classified as reaching the outcome using both estimating equations. Investigation of the 10 study participants with discrepant event statuses (5 with events using new eGFR but without events using old eGFR and 5 vice versa) demonstrated that eGFR slopes among these study participants were similar but outcomes censored using one equation due to end of follow-up. Comparing outcomes using new age-specific versus EKFC equations, 93 study participants were classified as reaching the outcome using both estimating equations. Investigation of the 18 study participants with discrepant event statuses (16 with events using new eGFR but without events using EKFC eGFR and 2 vice versa) demonstrated that most of these participants were from children <18 years who had very high eGFR values >140 at the beginning of study follow-up when using new age-specific eGFR values, resulting in much steeper eGFR slopes from using new age-specific eGFR values than that from using EKFC eGFR values and thus more events. Event rates were 6.34, 6.33, and 5.50 events per 100 person-years using old, new age-specific, and EKFC eGFR values, respectively. KM

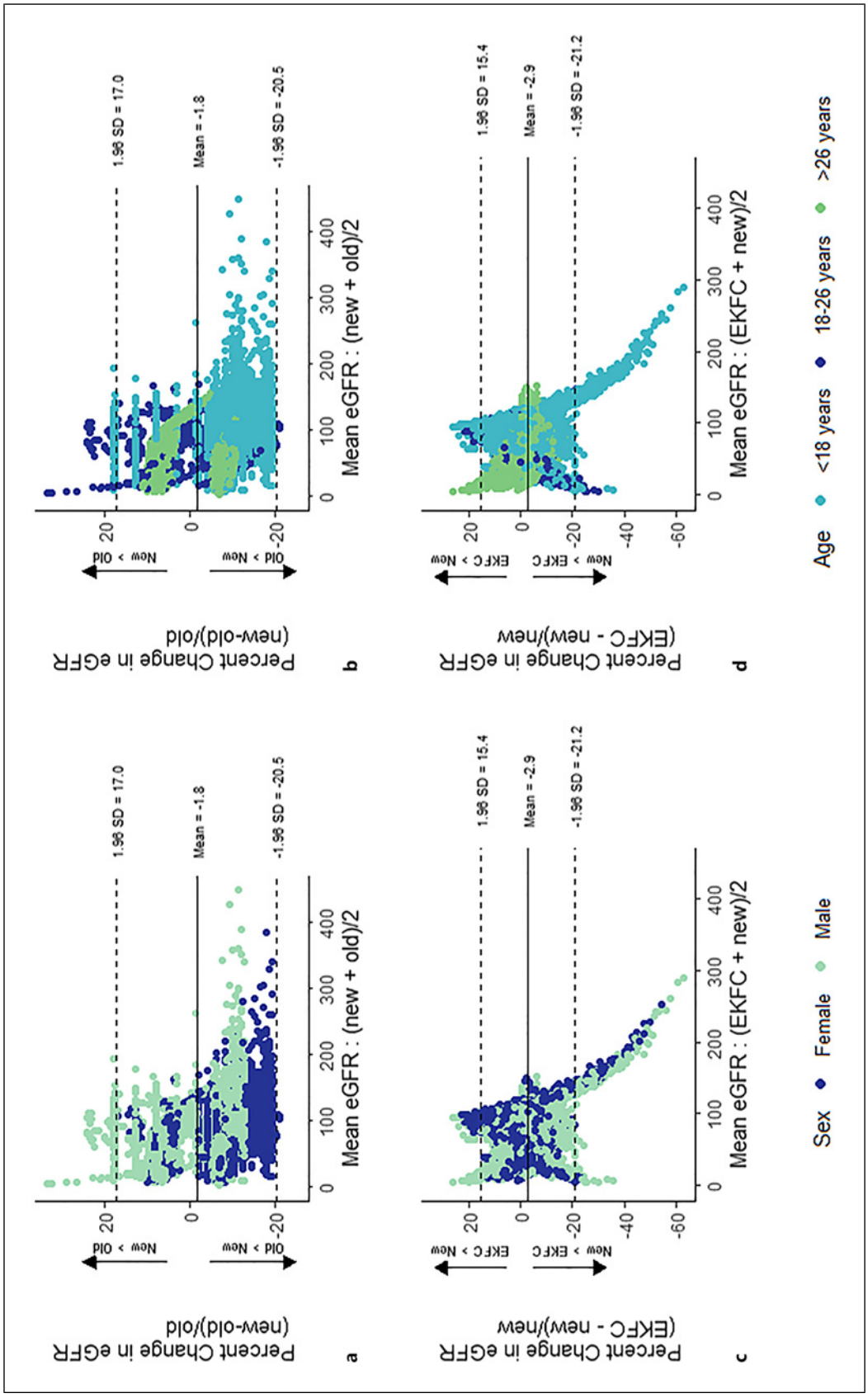

Fig. 3. Bland-Altman plot comparing eGFR values using old versus new age-specific (top row) and new age-specific versus EKFC (bottom row) eGFR calculation equations. eGFR is in mL/min/1.73 m^2.

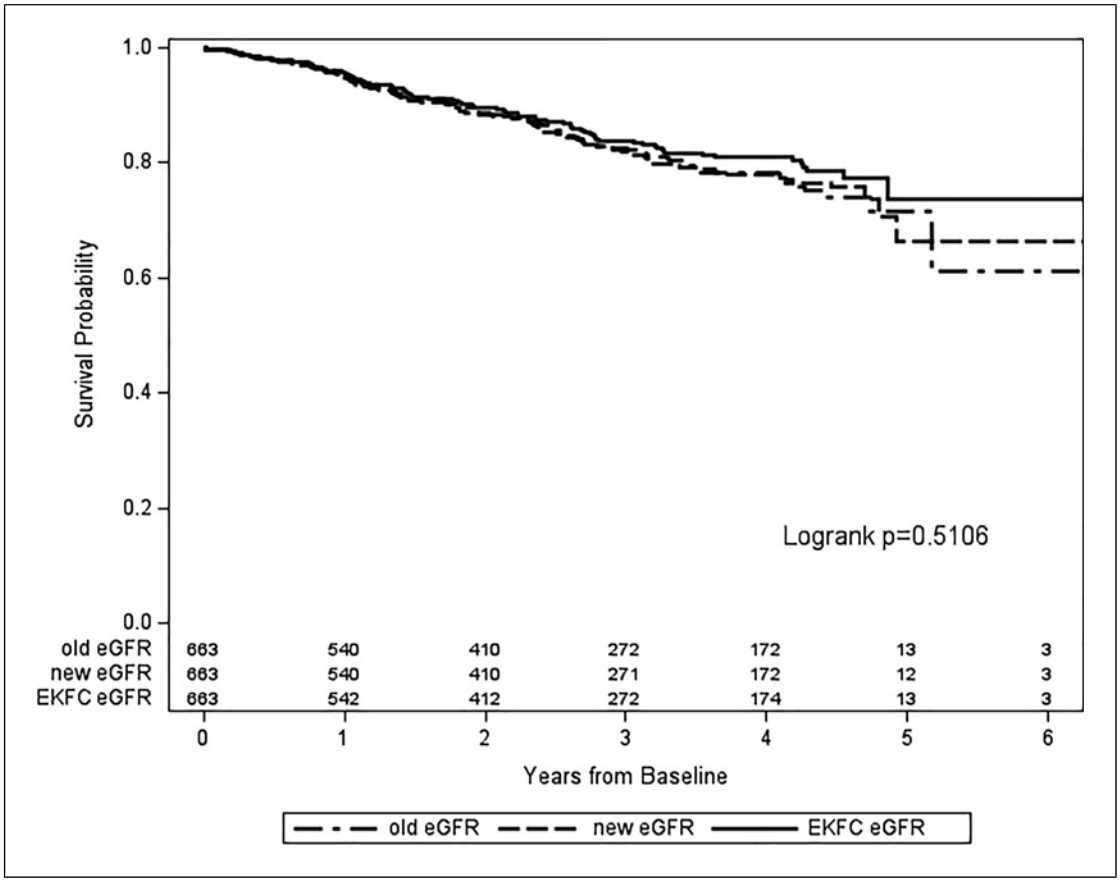

Fig. 4. KM curves of disease progression outcome based on eGFR values using old versus new age-specific versus EKFC eGFR calculation equations. Numbers at the lower bottom of the figure are the number of participants at risk.

curves were very similar and largely overlapping, with the KM curve from using EKFC eGFR values falling slightly above the other two curves when study follow-up was > 2 years (Fig. 4).

Cox model results showed similar coefficient estimates for associations between selected risk factors and disease progression across all three sets of eGFR values (Fig. 5). For example, the hazard of disease progression increased by 1.34 (95% confidence interval [CI], 1.19–1.51]), 1.34 (95% CI, 1.19–1.50]), and 1.37 (95% CI, 1.22–1.55]) times per 10% increase in global sclerosis, when using old, new age-specific, and EKFC eGFR values, respectively.

In longitudinal eGFR models, coefficients were slightly attenuated when using the new age-specific versus old eGFR estimating equations for most covariates (Table 2). For each covariate, the coefficient indicates the difference in mean eGFR between a group and the reference group or for a unit increase in a continuous covariate, holding all other covariates constant. The largest differences were seen in the sex and race coefficients, which were stronger in the model using new age-specific eGFR equations. Using old eGFR values, males and females had similar eGFR values on average (estimate [95% CI] = 1.4 [−3.0, 5.8]). However, using new eGFR values, males had 6.3 mL/min/1.73 m^2 higher eGFR than females (95% CI = 2.2, 10.4), on average. On average, Black study participants also had 9.4 (95% CI = 4.4, 14.4) lower eGFR values than non-Black study participants when using old eGFR values, as compared with 13.1 (95% CI = 8.4, 17.8) lower eGFR values when using new age-specific eGFR values.

Comparing longitudinal eGFR models using EKFC versus new age-specific equations, coefficients were similar or slightly attenuated for most covariates (Table 2). However, a larger difference in coefficient estimates for disease cohort was observed. Using new age-specific eGFR equations, compared with MCD participants, pediatric nephrotic syndrome (NS) participants without biopsy had slightly lower eGFR values that were

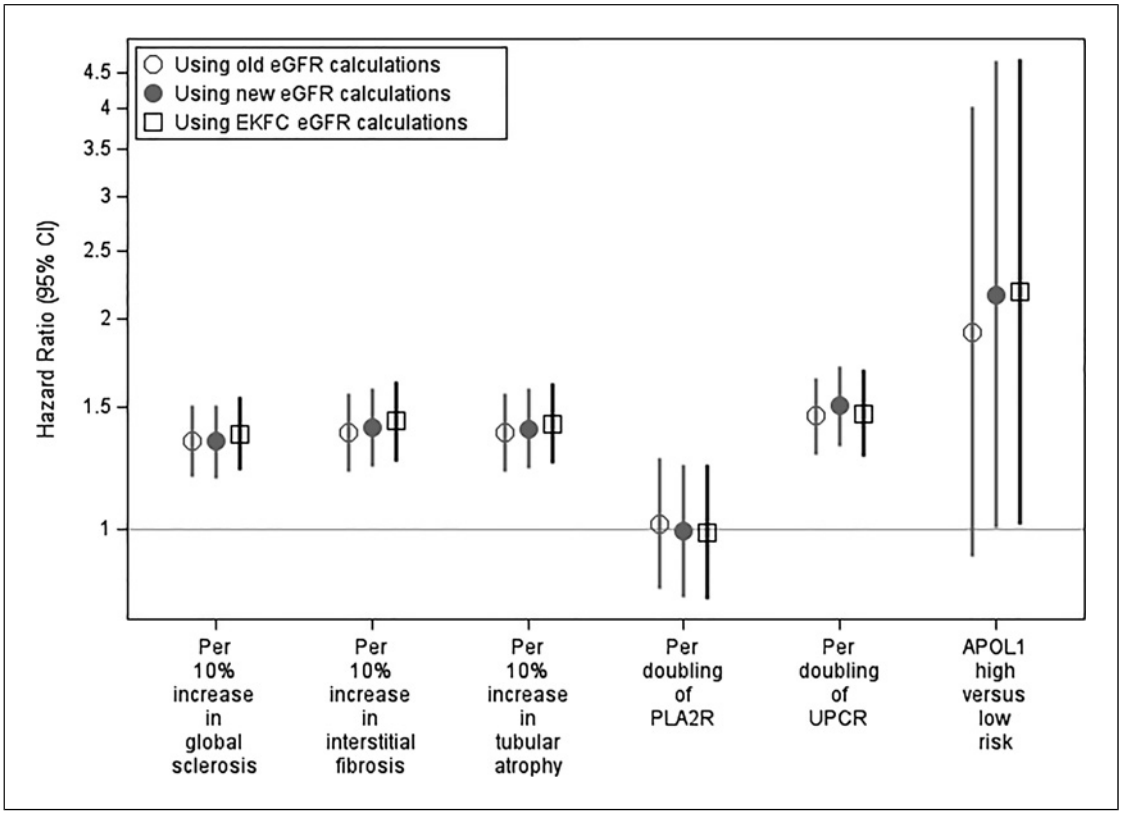

Fig. 5. Cox model results of associations between known risk factors and disease progression outcome based on eGFR values using old versus new age-specific versus EKFC eGFR calculation equations. Models for PLA2R only included MN disease diagnosis patients, and models for APOL1 only included black patients. HRs for PLA2R were unadjusted due to low number of outcome events. HRs for others risk factors were adjusted for patient age, race, sex, disease diagnosis, eGFR, UPCR, and medication use (immunosuppression and RAAS blockade), unless the number of events was limited, in which case backward selection was used to select adjustment variables.

not statistically significantly different (estimate [95% CI] = −3.6 [−10.7, 3.6]); however, this difference was much larger and statistically significant when using EKFC equations (estimate [95% CI] = −10.0 [−15.7, −4.2]). This difference in coefficient estimates can likely be explained by the large proportion of U25 eGFR values >140 among non-biopsied NS participants (19% vs. 10% from MCD participants) and the much lower corresponding EKFC eGFR estimates. This was further confirmed by a sensitivity analysis that removed all eGFR values >140 in longitudinal models, which showed very similar coefficient estimates for disease cohort between using new age-specific and EKFC eGFR equations (online suppl. Table 1). Similar explanations can be applied to differences in coefficient estimates comparing participants with focal segmental glomerulosclerosis (2% with eGFR >140) and other disease diagnoses (1% with eGFR >140) to MCD participants. Effect estimates for selected biomarkers on longitudinal eGFR were similar when using old versus new age-specific equation eGFR values and were slightly attenuated when using EKFC versus new age-specific equation eGFR values (Table 3).

Discussion

Effect estimates between several risk factors and eGFR-based outcomes were largely similar when comparing old, new age-specific, and EKFC eGFR estimating equations in NEPTUNE study participants when eGFR <140. Differences in effect estimates were observed on a few adjustment covariates in longitudinal eGFR models, specifically age and sex when comparing old versus new age-specific eGFR equations and disease cohort when using EKFC eGFR equations and including eGFR values greater than 140. The several other studies that have

Table 2. Linear mixed-effects model results of associations between demographics and clinical characteristics and longitudinal eGFR from using old, new age-specific, and EKFC eGFR equations

	Old eGFR		New eGFR		EKFC eGFR	
	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value
Time since baseline (years)	−3.1 (−4.0, −2.2)	<0.0001	−2.7 (−3.6, −1.9)	<0.0001	−2.4 (−3.0, −1.8)	<0.0001
Age (per 10-year increase)	−9.6 (−10.9, −8.3)	<0.0001	−7.5 (−8.7, −6.3)	<0.0001	−6.8 (−7.7, −5.8)	<0.0001
Male	1.4 (−3.0, 5.8)	0.5230	6.3 (2.2, 10.4)	0.0027	3.0 (−0.3, 6.3)	0.0780
Race: Black	−9.4 (−14.4, −4.4)	0.0002	−13.1 (−17.8, −8.4)	<0.0001	−12.8 (−16.5, −9.0)	<0.0001
Ethnicity: Hispanic	−0.1 (−0.3, 0.1)	0.4577	−0.1 (−0.3, 0.1)	0.4271	−0.1 (−0.2, 0.1)	0.5259
Disease cohort		<0.0001		<0.0001		<0.0001
MCD (reference)						
FSGS	−22.3 (−28.8, −15.7)	<0.0001	−20.3 (−26.4, −14.2)	<0.0001	−15.8 (−20.7, −10.9)	<0.0001
MN	−2.9 (−11.4, 5.5)	0.4979	−1.4 (−9.3, 6.5)	0.7315	2.3 (−4.0, 8.6)	0.4757
NS not specified (no biopsy)	3.4 (−4.3, 11.0)	0.3908	−3.6 (−10.7, 3.6)	0.3307	−10.0 (−15.7, −4.2)	0.0007
Other	−25.6 (−32.9, −18.2)	<0.0001	−23.5 (−30.4, −16.6)	<0.0001	−18.0 (−23.5, −12.5)	<0.0001
UPCR, mg/mg		0.8440		0.9283		0.3004
0–0.3 (reference)						
>0.3–1.5	1.8 (−5.5, 9.1)	0.6315	1.6 (−5.3, 8.4)	0.6516	1.0 (−4.5, 6.5)	0.7122
>1.5–3.0	−1.3 (−9.1, 6.5)	0.7366	−0.7 (−8.0, 6.6)	0.8558	−2.5 (−8.4, 3.3)	0.3928
>3.0	0.9 (−5.3, 7.1)	0.7769	0.3 (−5.5, 6.1)	0.9157	−2.9 (−7.6, 1.8)	0.2237
Kidney disease duration as of baseline		0.5124		0.6101		0.7933
0–3 months (reference)						
4–12 months	3.3 (−2.4, 9.0)	0.2607	2.1 (−3.3, 7.4)	0.4438	0.3 (−4.0, 4.6)	0.8970
>12 months	0.5 (−5.4, 6.3)	0.8709	−0.9 (−6.3, 4.6)	0.7567	−1.3 (−5.7, 3.1)	0.5652
Immunosuppressant use at baseline	2.5 (−2.5, 7.6)	0.3263	1.5 (−3.3, 6.2)	0.5441	0.4 (−3.4, 4.2)	0.8449
RAAS blockade use at baseline	−2.9 (−7.9, 2.1)	0.2500	−2.3 (−6.9, 2.4)	0.3412	−0.7 (−4.5, 3.0)	0.7037

compared old and new age-specific eGFR equations largely focused on impacts on CKD prevalence, CKD staging, and nephrology referrals or were limited to specific disease and ethnic populations [16–21]. Similarly, comparisons of CKD-EPI and EFKC equations were done mostly for accuracy of eGFR values [9, 22, 23], not on eGFR-based outcomes and not in patients with glomerular diseases. To our knowledge, this is the first study that compared old, new age-specific, and EKFC eGFR equations among a glomerular disease cohort and compared effect estimates of several risk factors from statistical models of eGFR-based outcomes. Our findings suggest that previous research results using old eGFR equations may also be similar to those using new age-specific eGFR equations, facilitating comparison to prior literature for future studies. Similarly, research studies using either new age-specific or EKFC equations likely would give similar results as long as there is not a high proportion of very high eGFR values. Therefore, while the advantages of using new age-specific or EKFC equations – including removal of the social construct of race from CKD-EPI, the use of a single equation into young adulthood for U25, or an equation that spans the full age spectrum – are clear, our study provides some evidence that these benefits likely do not come at the cost of changing the majority of previous research findings.

eGFR values between old versus new age-specific equations were similar on average, although variability was high. The largest relative differences observed among males between the ages of 18 and 26 were driven by the transitions between adolescent and adult equations. The average of the bedside Schwartz and CKD-EPI 2009 equations in this age range was previously used to increase accuracy [6] and mitigate large jumps in eGFR as patients age into adulthood and switch equations. The use of the new U25 and CKD-EPI 2021 equations has increased accuracy and removed race but does not address this issue of implausible jumps in eGFR. FAS and EKFC equations that can be used across the entire age continuum address this issue. However, while the FAS equation with height-based Q values was validated among children and young adults in North America [5], such

Table 3. Comparison of associations between known risk factors and longitudinal eGFR when using old, new age-specific, and EKFC eGFR equations

	Old eGFR		New eGFR		EKFC eGFR	
	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value	estimate (95% CI)	*p* value
APOL1 high versus low risk	−19.3 (−28.4, −10.3)	<0.0001	−17.5 (−25.5, −9.6)	<0.0001	−14.8 (−22.0, −7.5)	<0.0001
Per 10% increase in global sclerosis	−7.0 (−8.5, −5.5)	<0.0001	−7.1 (−8.5, −5.7)	<0.0001	−6.5 (−7.8, −5.3)	<0.0001
Per 10% increase in interstitial fibrosis	−9.1 (−10.6, −7.6)	<0.0001	−9.1 (−10.5, −7.7)	<0.0001	−8.5 (−9.6, −7.3)	<0.0001
Per 10% increase in tubular atrophy	−9.0 (−10.5, −7.5)	<0.0001	−9.0 (−10.4, −7.6)	<0.0001	−8.4 (−9.6, −7.3)	<0.0001
Per doubling of PLA2R	−1.0 (−2.1, 0.2)	0.0943	−1.0 (−2.1, 0.1)	0.0848	−0.7 (−1.8, 0.3)	0.1654
Per doubling of UPCR	1.3 (−1.1, 3.8)	0.2821	0.8 (−1.4, 3.1)	0.4686	0.3 (−1.6, 2.2)	0.7677

Models for PLA2R only included MN disease diagnosis patients, and models for APOL1 only included black patients. Results from each row using old versus new age-specific versus EKFC eGFR is from a separate model. For each model, adjustment covariates included age, race, sex, ethnicity, disease diagnosis, UPCR, kidney disease duration, and medication use (immunosuppression and RAAS blockade), all measured at baseline.

validation for the more updated EKFC equation is still needed for US children and young adults.

There were differences between old and new age-specific eGFR equations in sex and race effect estimates with longitudinal eGFR. The higher eGFRs in males than females with the new equations was driven by sex-specific calculation of eGFR using U25, with a *K* multiplying coefficient that was larger for males than females. The lower eGFRs among black study participants was driven by the removal of race from the CKD-EPI equation that generally decreased eGFR values for black patients. While these differences are not surprising, we emphasize their existence, so research investigators, analysts, and clinicians can interpret study results with this context.

eGFR values between new age-specific and EKFC equations were very similar, except for eGFR values estimated as >140 from the U25 equation among participants <25 years old, for which eGFR values were much lower from EKFC. In our study sample of glomerular disease patients, 6% of eGFR values were >140 (when using new age-specific equations). There was also a notable difference in associations between disease diagnoses and longitudinal eGFR when using EKFC. This was also driven by large differences in estimates of GFR at very high levels and the relatively high proportions of very high eGFR values from study participants with MCD or non-biopsied NS, particularly among younger study participants. All of the GFR estimating equations were developed and validated among populations with limited numbers of study participants with very high GFRs and/or few patients with glomerular disease. For example, the one CKiD study that included participants with glomerular disease was limited to glomerular disease patients with mild to moderately impaired kidney function [5]. Therefore, it is unknown which of these equations is most accurate at very high GFRs among a glomerular disease population. Since high eGFRs are common in glomerular disease – which could reflect inaccurate estimation of GFR and/or truly high GFR through hyperfiltration – results using eGFR-based outcomes among this population must be interpreted with caution. Future studies on accurate GFR estimation and impacts of hyperfiltration on clinical outcomes are needed in this population.

There are three limitations of our study worth noting. First, we did not have measured GFR to assess accuracy of any GFR estimating equations in this study. Therefore, we used agreement measures and qualitative comparisons of model results to compare old versus new age-specific versus EKFC equations. Second, although cystatin C-based eGFR equations or the combined creatinine- and cystatin C-based equations have been shown to give more accurate eGFR values, cystatin C data were not available and thus could not be evaluated. Third, we only included a handful of known risk factors and estimated their associations with eGFR-based outcomes. Redoing all previous analyses with the new age-specific and EKFC eGFR equations would not be feasible, so we focused on several markers that spanned a variety of domains – including pathology, a serum biomarker, a urine biomarker, and a genetic trait.

Despite these limitations, our study provides the first empirical evidence that the recent 2021 CKD-EPI and

U25 and EKFC eGFR estimating equations provide comparable results to using the 2009 CKD-EPI and bedside Schwartz equations in patients with glomerular disease, particularly when eGFR <140. Our study included children, young adults, and older adults, and included patients with glomerular diseases who may or may not have CKD. By evaluating two common eGFR-based outcomes for longitudinal data, we have shown that many previous studies would likely have similar results if they used new age-specific or EKFC eGFR equations and future work can be fairly compared to past results, while caution is advised when many high eGFRs are present in the study sample.

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Statement of Ethics

This study was considered not human subjects research and did not require formal IRB review by The Children's Hospital of Philadelphia Institutional Review Board (IRB #22-020363). This study consisted of secondary data analysis of existing, de-identified data from NEPTUNE. All participants enrolled in the NEPTUNE study provided written informed consent (adults) or assent with parental written informed consent (children).

Conflict of Interest Statement

Dr. Smith has received research grant funding from Hi-Bio (Biogen). Dr. Mariani has received consulting funds from Novartis, Calliditas, Dimerix, Vera, and Travere and research grant funding from Boehringer-Ingelheim, Travere, Hi-Bio (Biogen), Takeda, Calliditas, and Reliant Glycosciences. Dr. Zee serves on a Data and Safety Monitoring Board for US Renal Care. Dr. Mariani and Dr. Zee were members of the journal's Editorial Board at the time of submission. Other authors do not have anything to disclose.

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Author Contributions

Q.L., A.R.S., C.S., L.H.M., and J.Z. conceptualized and designed the study. Q.L., V.O., and J.Z. conducted data analysis and drafted the manuscript. Q.L., V.O., A.R.S., C.S., L.H.M., and J.Z. interpreted analysis results. J.Z. provided supervision. All authors reviewed the manuscript and approved the final version.

Data Availability Statement

The data in this study were obtained from the Nephrotic Syndrome Study Network (NEPTUNE) where data sharing requires ancillary study approval and a data use agreement. The dataset may be requested from the NEPTUNE Data and Analysis Coordinating Center (DACC), www.neptune-study.org. NEPTUNE investigators are listed in online supplementary materials.

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