EVALUATION OF RISK DATA IN 4.5 MILLION PATIENTS FOR IMPLEMENTING NEW GUIDELINES FOR KIDNEY FUNCTION REPORTING

by

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A thesis submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Science.

Baltimore, Maryland

April, 2018

Abstract

Background:

Clinical guidelines recommend reporting estimated glomerular filtration rate (eGFR) from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, still organizations report eGFR mainly using alternative equations.

Objective:

To evaluate the risk relationship of eGFR from the CKD-EPI equation relative to the Modification of Diet in Renal Disease (MDRD) and Mayo Clinic Quadratic (MCQ), describe differences in interpretation of eGFR values, and implications associated with switching to the CKD-EPI equation, in a large patient population receiving ambulatory care in the United States.

Results:

Overall, 4.5 million patients aged 18–99 were included in the study, with 37,000 events for ESRD and 195,000 for all-cause mortality. The average eGFR was considerably lower for CKD-EPI (82.7 ml/min/1.73m^2) and MDRD (79.7 ml/min/1.73m^2), compared to MCQ (94.9 ml/min/1.73m^2). Accordingly, the prevalence of GFR category 3–5 (<60 mL/min/1.73 m²) was 15.8% with CKD-EPI, 17.3% with MDRD, and 6.4% with MCQ. The CKD-EPI equation had a similarly steep risk gradient to the MDRD equation in GFR 3-5 range, both steeper than the risk gradient for the MCQ equation. The risk gradient at higher estimates of GFR was steeper for the CKD-EPI equation relative to MDRD, but shallower than MCQ. The CKD-EPI equation, compared to MDRD, reclassified more patients upward to higher categories of eGFR (2.6% downward vs.15.7% upward), and many more patients downward to lower categories compared to the MCQ (39.1% downward vs. 1.3% upward). Net reclassification improvement favored the

CKD-EPI to MDRD equation for ESRD (0.12) and all-cause mortality (0.19), and favored the CKD-EPI to MCQ for all-cause mortality (0.06) but not ESRD (– 0.07).

Conclusion:

Regarding risk stratification, the recommended CKD-EPI equation is superior to MDRD. Similar estimates of GFR from the two equations, especially in GFR 3–5 range, facilitate transitioning to the CKD-EPI equation from MDRD. MCQ largely shifted the distribution of eGFR and eGFR-risk relationship to higher levels of eGFR, warranting its careful interpretation particularly at referral or transition from or to facilities using other equations.

Advisor: Josef Coresh, MD, PhD

Reader: Kunihiro Matsushita, MD, PhD

Acknowledgements

First, I would like to thank the following people for their support and contributions to this thesis: Yingying Sang, Kunihiro Matsushita, Andrew Levey, Richard Stempniewicz, Elizabeth Ciemins, John Cuddeback, Shoshana Ballew, Morgan Grams, and Josef Coresh. I would also like to thank AMGA and Optum, in addition to the AMGA members and the patients they serve, whose data are used for this research.

I would like to express deep gratitude to my advisor Josef Coresh, for his continuous support and encouragement for this project and others during my time at graduate school. I am also particularly grateful for the guidance provided by Kunihiro Matsushita, and his valuable time and insights during the span this project. In addition, I would like to thank Drs. Coresh and Matsushita for their prior work in the area of Chronic Kidney Disease, and GFR estimating equation development and evaluation, which made this research possible.

I would like to offer a special thanks to John Cuddeback, for his role as a mentor and his contagious passion for improving population health through clinical analytics. Among many more things, working with John I have developed an interest for effectively communicating data, and he is deserving of some of the credit for any nice figure or table in this thesis.

Finally, I would like to thank my family and friends for everything, specifically, my parents, and my brother Stan. Perhaps most importantly, I would like to apologize and thank Cait, my soon to be wife, whose work ethic and compassion as a Baltimore city school teacher served as a constant inspiration, and who always knew when to encourage my use of “pretty Christmas colors”.

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1 Background

In the United States, approximately 14% of adults have chronic kidney disease (CKD) which is estimated to cost $49 billion to treat annually.[1, 2] Less than 10% of adults in GFR category 1–3 are aware of their renal impairment, and less than half even for GFR category 4.[3] Early detection of CKD is important to slow down or prevent progression to kidney failure, avoid nephrotoxic medications, and reduce overall morbidity and mortality.[4]

Glomerular filtration rate (GFR) measures the rate at which the kidneys filter the blood and is considered the gold standard for evaluating kidney function. GFR can be measured by administrating a filtration marker, generally through injection or infusion, and measuring the presence of the filtration marker during a clearance period through repeated measurements (e.g., urine or blood), but is considered too cumbersome and costly for day to day monitoring of kidney function. Thus, estimated GFR (eGFR) using endogenous filtration markers from a blood sample is generally considered an accepted alternative.[5, 6]

Serum creatinine (SCr) is one of the components of the basic metabolic panel, a commonly ordered lab in primary care, and when combined with demographics (e.g., age, sex, and race), can be used to estimate GFR. Kidney Disease: Improving Global Outcomes (KDIGO): Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, recommends using serum creatinine for eGFR.[7] In addition to the diagnosis and management of CKD, eGFR is used to determine contraindications and avoid nephrotoxic medications, e.g., metformin, a first line therapy for diabetes contraindicated in patients with eGFR < 30 (and not generally recommended < 60 mL/min/1.73 m²).[8]

In response to recommendations by guidelines for use of estimating equations[7-9], clinical laboratories reporting eGFR with creatinine measurements have increased dramatically in the

last 15 years (3% in 2003 to 89% in 2017).[10] Guidelines recommend reporting eGFR in adults using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation to diagnose and stage CKD with known risk relationships.[7, 8] Still a survey in 2017 found the majority of laboratories report eGFR using equations no longer (or never) recommended by guidelines, mainly the Modification of Diet in Renal Disease (MDRD) equation, or other less frequently used equations, e.g., Mayo Clinic Quadratic (MCQ).[10]

While all three equations require serum creatinine to estimate GFR, the CKD-EPI and MDRD are expressed for use with standardized assays (e.g., traceable to isotope dilution mass spectrometry), while the MCQ is not. In addition to serum creatinine, the CKD-EPI and MDRD equations require age, sex, and race, whereas the MCQ equation requires age and sex only. Since 2011, meaningful use has incentivized the systematic collection and standardization of race in electronic health records (EHR), facilitating the transition for health care organizations to using the CKD-EPI equation, from other estimating equations which ignore race.[11, 12]

Prior studies suggest relative to measured GFR, estimates from the CKD-EPI equation are more accurate than those from MDRD, most recently established in a systematic review of 48 studies with primary care populations.[13] A study comparing the accuracy of the CKD-EPI, MDRD, and MCQ equations directly among solid organ transplant recipients, found the CKD-EPI and MDRD more accurate than the MCQ equation, which overestimated kidney function.[14] Other studies among kidney donors,[15, 16] and in a clinical setting,[17] found the MDRD equation more accurate than MCQ. While among patients with diabetes, the MCQ was more accurate, but only for patients with higher estimates of kidney function.[18, 19]

It has been established that the CKD-EPI equation more accurately categorizes risk of adverse events than the MDRD equation in a broad range of populations,[20-25] but these studies

did not include the MCQ equation. Research among 500,000 middle aged Swedish men and women, found a stronger risk association with myocardial infarction and all-cause mortality for GFR values estimated with the MCQ equation, compared to MDRD.[26] Two other studies found a similar relationship with risk of mortality and coronary artery disease for the CKD-EPI and MCQ equations, both stronger than MDRD.[27, 28]

Electronic heath record data from health care organizations provide the opportunity to compare estimating equations and their ability to risk-stratify patients and describe the implications of switching to the recommended CKD-EPI, from the MDRD or MCQ equations, using "real world" serum creatinine measurements from a large and diverse patient population. The goal of this study was to compare eGFR calculated with the CKD-EPI equation relative to the MDRD and MCQ equations, for classification of end stage renal disease (ESRD) and all-cause mortality risk, and describe the implications associated with using the different estimating equations on a large patient population receiving ambulatory care in the United States. Results from this study will contribute to information from prior research on the relative ability of creatinine based estimating equations to classify risk of adverse events, describe how interpretation of eGFR values differ between equations, and provide implications for switching equations to the CKD-EPI, from MDRD or MCQ. These provide useful evidence to patients, health care organizations and providers, clinical laboratories, researchers, policy makers, among others.

2 Methods

2.1 Data Source

This study was conducted using longitudinal EHR data from 25 health care organizations, a subset of Optum Analytics' clinical data asset. The organizations who contribute data are

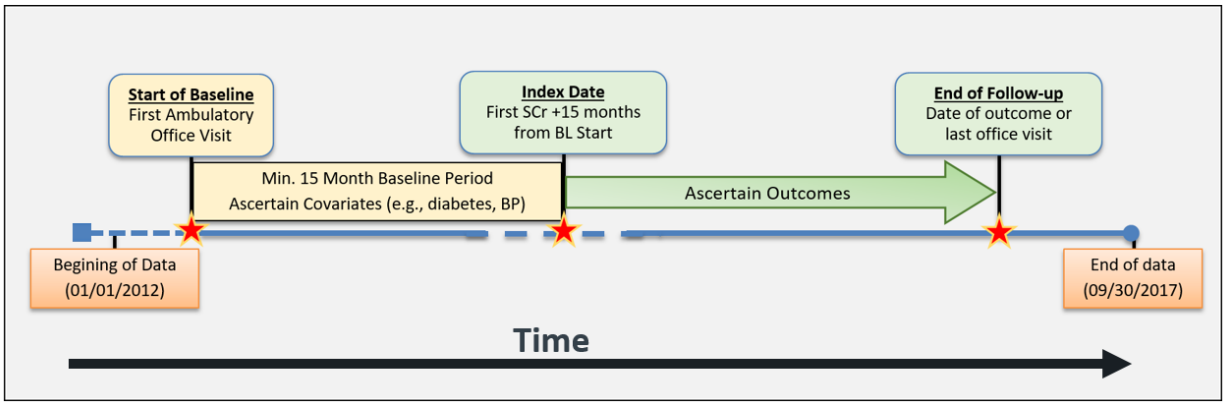
integrated delivery systems, multispecialty medical groups, and academic faculty practices that are members of AMGA and participate in a learning collaborative, AMGA Analytics for Improvement, focused on enhancing value in population health. These organizations are diverse in size (~100 to 2,000 FTE physicians), structure, geography, and patient demographics.

The Optum Analytics EHR database, derived from a variety of different EHR systems and normalized across health care organizations, contains longitudinal, patient-level detail, including clinical observations (e.g., blood pressure, body mass index), laboratory measurements (e.g., hemoglobin A1c, cholesterol, serum creatinine), medical procedures, diagnoses (on a claim, e.g., for an evaluation and management ambulatory visit, or on the patient's problem list in the EHR), medications (using prescriptions or the patient's medication list in the EHR), physician notes, patient reported outcomes (e.g., smoking, physical activity, pain score), demographics (e.g., age, race, ethnicity, gender), socio-demographics (imputed from five-digit zip code), healthcare utilization metrics (e.g., office visits, inpatient admissions), and other data collected in the course of health care delivery.

2.2 Study Population

Patients with data between 01/01/2012 – 09/30/2017 were eligible for this study. We implemented the baseline period of at least 15 months to capture data of covariates. Then, we identified the first creatinine measurement after the baseline period, which corresponded to the index date for follow-up for clinical outcomes. Patients with no outcomes during the follow-up period were censored on the date of their last office visit after index date (Figure 1). We excluded patients younger than 18 and older than 99 years from this study, as well as those with evidence of ESRD prior to the index date. Patients with less than 3 months of follow-up were also excluded from the analysis (9.3% of study population).

Figure 1: Study Schema



2.3 Covariates

2.3.1 Clinical measurements

Systolic blood pressure

Systolic blood pressure (BP) was taken in an ambulatory setting, when multiple blood pressures were taken on the same day, the lowest value was kept, and when there were multiple days in the baseline period with measurements, we used data from the day closest to the index date. Methods of measurement and precision of BP vary by health care organization, e.g., some use automated BP machines, and other manual sphygmomanometer. Most health care organizations contributing data were concurrently participating in a national campaign focused on improving hypertension screening, control, and detection, lasting the majority of the study period, including emphasis on proper measurement of BP and screening for high BP.[29]

Smoking

Smoking status was defined as current smoker, previous smoker, or never smoker based on patient-reported data. For patients with conflicting data on smoking status during the baseline period, e.g., a record for current smoker followed by one for never smoker, the more "severe" smoking status is used, i.e., any patient with status of current smoker during the baseline period, was classified as such regardless of other evidence.

2.3.2 Comorbid Conditions

Diagnosis codes were defined with 9th and 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10) and identified on a claim or the patients' problem list in the EHR. Procedure codes were defined with Current Procedural Terminology (CPT) and identified on a claim, and medications were available at the class level, identified on prescriptions and the patients' medication list in the EHR.

Cardiovascular disease

Cardiovascular disease (CVD) was defined using diagnosis codes or procedure codes for myocardial infarction (old or new), coronary artery bypass graft, percutaneous coronary intervention, heart failure, or stroke.

Diabetes mellitus

Diabetes mellitus was defined using diagnosis codes for type 1, type 2, or secondary diabetes (due to underlying conditions, chemical or drug induced, or other specified), or complications attributed to diabetes (diabetic retinopathy or cataract, polyneuropathy in diabetes, or diabetic nephropathy). The following medication classes were also used to define diabetes: sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonist, sodium/glucose cotransporter 2, or insulin.

Hypertension

Hypertension was defined using diagnosis codes for essential or secondary hypertension, or a prescription for a medication used to treat hypertension: angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), beta blocker, calcium channel blocker, diuretics, antiadrenergic, renin inhibitors, or vasodilator.

2.3.3 Demographics

Age

Defined on the index date in integer years.

Health care organization

Deidentified code for each organization, which was used in our models to account for correlations between patients receiving care within the same health care organization.

Race/Ethnicity

Asian, Black, Hispanic/Latino, White, Other, or unknown/missing

Sex

Female or Male

2.4 Exposure

2.4.1 Serum Creatinine

For patients with multiple serum creatinine measurements taken on the index date, we used the lowest value. Precision of serum creatinine measurements was described using the proportion of values with a 0 in the second place after the decimal (e.g., 0.90, 1.00), where with precise measurement, we expect ~10% of patients to end in each digit, including 0.

2.4.2 Estimated GFR

Serum creatinine values from the index date, and the necessary demographics were used to estimate GFR with the CKD-EPI,[30] MDRD,[31] and MCQ[32] equations, listed in Figure 2. For the same age, sex, and serum creatinine, the CKD-EPI and MDRD estimate higher estimates of kidney function for patients who are Black, compared to White or Other race (i.e., not Black). Compared to CKD-EPI, the MDRD equation has a larger adjustment for race (1.159 vs. 1.212), corresponding to larger differences in estimates of GFR between races for the MDRD equation.

The CKD-EPI and MCQ equations include splines to account for different relationships between serum creatinine and GFR at different levels of serum creatinine. For the CKD-EPI equation the splines use sex specific knots, while for MCQ the knot at 0.8 mg/dL is used for both males and females, and the slope is flat (i.e., equal to 0 when < 0.8 mg/dL). Meaning differences between GFR estimates with the MCQ equation when serum creatinine < 0.8 mg/dL are due to age and sex.

Figure 2: Creatinine Based GFR Estimating Equations

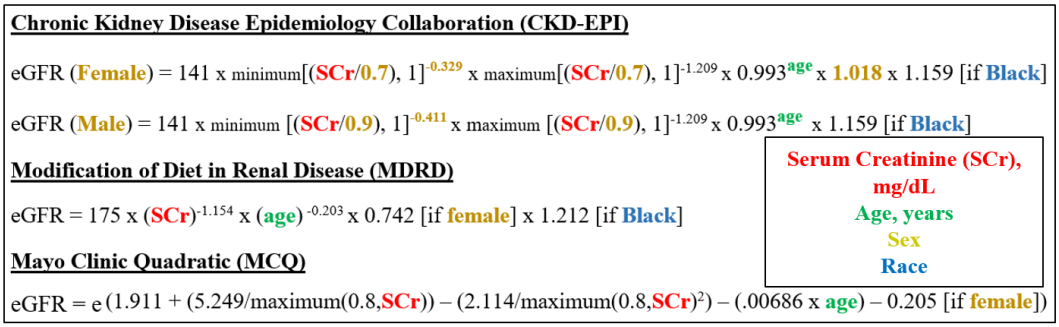
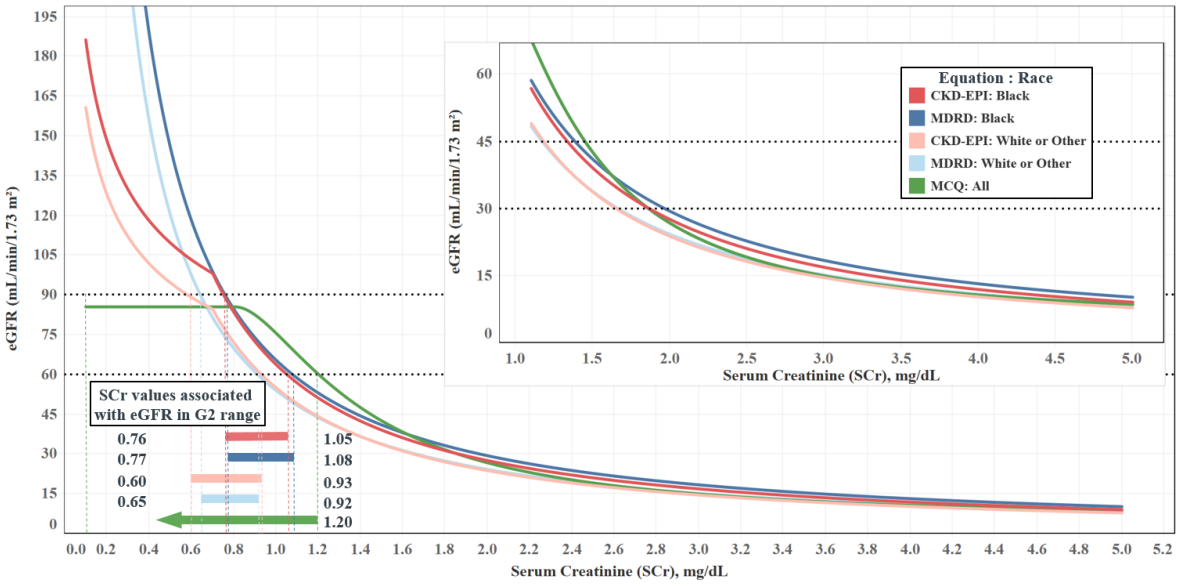


Figure 3 shows the relationship of eGFR and serum creatinine by race for the CKD-EPI, MDRD, and MCQ estimating equations, for female patients aged 75 years. The solid lines in the bottom left corner show the serum creatinine values which correspond to estimates in GFR category 2 (60–89 mL/min/1.73 m²) for each equation and race. Serum creatinine values in GFR category 2 with the CKD-EPI and MDRD equations are similar for Black patients, and for White or Other race the range is slightly wider for the CKD-EPI equation (CKD-EPI: 0.59–0.93, MDRD: 0.64–0.92 mg/dL). Using the MCQ equation, a female patient aged 75 will never have an estimate in GFR category 1 (≥ 90 mL/min/1.73 m²), and all patients with serum creatinine ≤ 1.20 mg/dL have estimates in GFR category 2. Compared to the CKD-EPI and MDRD equations, the MCQ estimates lower GFR for the smallest values of serum creatinine, e.g., < 0.7 mg/dL, higher GFR between ~0.8–1.6 mg/dL, and similar GFR for the largest values of serum creatinine.

Figure 3: Estimated GFR (eGFR) for Females Aged 75, by Serum Creatinine (SCr), Race, and Equation



The dark red and blue lines show the relationship for Black patients, and the light red and blue lines for non-Black patients, for the CKD-EPI and MDRD equations respectively. The green line reflects the relationship for all females aged 75 using the MCQ equation. The smaller box towards the top right of the figure focuses on the range of SCr corresponding to estimates of GFR of the lowest kidney function, e.g., 1.1-5.0 mg/dL.
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; MCQ, Mayo Clinic Quadratic
GFR 2 Range: eGFR 60-89 mL/min/1.73 m²

2.5 Follow-up/Outcomes

End stage renal disease (ESRD)

End stage renal disease was defined using diagnosis and procedure codes for dialysis, kidney transplant, or ESRD.

All-cause mortality

All-cause mortality was defined using the date of death field from the EHR. Dates were limited to month and year of death and assumed to occur on the 15th day.

Follow-up time

For ESRD and all-cause mortality separately, patient's accumulated follow-up time from the index date to the first evidence of the outcome.

2.6 Statistical Methods

2.6.1 eGFR Distribution and Classification

Distributions from the CKD-EPI, MDRD, and MCQ equations were compared continuously, using deciles (i.e., eGFR values for the 10, 20, 30, 40, 50, 60, 70, 80, 90th percentile), and using clinically meaningful eGFR categories (i.e., eGFR < 15, 15–29, 30–44, 45–59, 60–89, and ≥ 90 mL/min/1.73 m²).[7]

2.6.2 Hazard Ratios

Risk of ESRD and all-cause mortality was evaluated using unadjusted and adjusted hazard ratios estimated from Cox proportional hazards regression models. All adjusted models were adjusted for age (continuous), sex, race (Black vs. Not Black), smoking (never, previous, or current), systolic blood pressure (continuous), and history of cardiovascular disease, diabetes, and hypertension. All Cox models used cluster-adjusted standard errors to account for correlation within healthcare organizations.

2.6.3 Risk Prediction

We evaluated the risk relationship separately for each equation and outcome. Estimated GFR was included in the model as a continuous variable with 7 linear splines and knots at eGFR 30, 45, 60, 75, 90, and 105 mL/min/1.73 m², as previously modeled, to allow for potentially non-linear relationship with risk at different levels of eGFR.[33] Each equation was compared relative to a reference value of 60 mL/min/1.73 m² for the given equation.

Deciles

We included eGFR decile in the model as a categorical variable, using the 7th decile (60th to 70th percentile) for that given equation as the reference category.

2.6.4 Reclassification Matrix

First, for each equation separately, we compared the risk using crude incidence rates and adjusted hazard ratios for eGFR categories previously described, (< 15, 15–29, 30–44, 45–59, 60–89, and ≥ 90 mL/min/1.73 m²), using GFR 2 (60–89 mL/min/1.73 m²) for the given equation as the reference category. Next, comparing the CKD-EPI equation to the MDRD and MCQ equations, we cross-tabulated eGFR using the same categories. For each combination of eGFR categories we calculated the proportion of the study cohort, crude incidence rate, and adjusted hazard ratios using a reference of GFR 2 for both equations.

2.6.5 Net Reclassification Improvement (NRI)

Net Reclassification Improvement (NRI) was applied to compare the equations directly. Reclassification was calculated using eGFR categories (< 15, 15–29, 30–44, 45–59, 60–89, and ≥ 90 mL/min/1.73 m²), comparing the CKD-EPI equation to the MDRD and MCQ equations separately. Results are presented for each outcome and pair of equations, overall and stratified by event.[34]

Demographic Subgroups

To assess generalizability of results in different subpopulations we applied NRI to the subgroups by age (< 65 vs. ≥ 65), sex (male vs. female), hypertension, diabetes, cardiovascular disease, race/ethnicity (White vs. Black vs. Asian vs. Hispanic), and smoking status (current vs. previous, vs. never).

Sensitivity Analyses

Sensitivity analyses for NRI included calculating net reclassification using eGFR deciles, and applying bias corrected NRI in subgroups of $eGFR_{CKD\text{-}EPI}$ < 60 and ≥ 60 mL/min/1.73 m². [35]

2.6.6 Missing values

Missing values for race, smoking, and systolic BP, were imputed using mean values within each health care organization.

2.6.7 Statistical Software

All statistical analyses were conducting using Stata version 13.1

3 Results

3.1 Patient Characteristics

Table 1 shows overall, 4.5 million patients aged 18–99 with a serum creatinine measurement on the index date and no previous evidence of ESRD were included in this study. There was a total of 195,000 events for all-cause mortality, 37,000 events for ESRD, and average follow-up time was 2.4 years. Average age was 58.4 years, 84.8% White, 8.5% Black, and 58.4% female. Overall, there was 61.6% of patients with hypertension, 22.9% with diabetes, and 12.0% with cardiovascular disease. Most patients had a measurement for systolic blood pressure (SBP) and smoking during the baseline period (96.1% and 92.7%), with average SBP of 125.9 mmHg, 19.8% current smoker, 24.4% previous smoker, and 48.6% never smoker. Patient characteristics were similar between the populations with eGFR $_{\text{CKD-EPI}}$ and eGFR $_{\text{MDRD}}$ < 60 mL/min/1.73 m², and comparatively patients with eGFR $_{\text{MCQ}}$ < 60 mL/min/1.73 m² were more likely to develop ESRD or die, be older, and Black.

Table 1: Patient Characteristics Overall and by Estimated GFR < 60 mL/min/1.73 m²

		All Patients		eGFR $_{CKD-EPI}$ < 60		eGFR $_{MDRD}$ < 60		eGFR $_{MCQ}$ < 60	
Patients		4,528,015		713,351 (15.8%)		782,025 (17.3%)		289,022 (6.4%)	
Outcomes	All-cause mortality	4.3%	195,262	12.8%	91,458	11.4%	88,885	18.2%	52,550
	ESRD	0.8%	37,152	3.6%	25,716	3.3%	25,979	7.3%	20,993
SCr (mg/dL)	Mean (SD)	0.9	(0.3)	1.3	(0.5)	1.3	(0.5)	1.7	(0.6)
eGFR mL/min/1.73 m²: Mean (SD)	CKD-EPI	82.7	(22.5)	47.3	(10.2)	48.8	(10.8)	37.6	(8.5)
	MDRD	79.7	(26.8)	47.2	(9.6)	48.0	(9.5)	38.4	(8.5)
	MCQ	94.9	(21.0)	60.1	(15.5)	62.4	(16.6)	44.5	(11.5)
Age (years)	Mean (SD)	58.4	(16.3)	73.9	(11.4)	71.2	(12.6)	75.4	(11.6)
Sex	Female	58.4%	2,642,646	59.9%	427,639	61.7%	482,866	50.1%	144,772
Race/Ethnicity	Asian	1.3%	60,876	0.7%	5,020	0.7%	5,563	0.7%	2,134
	Black	8.5%	385,826	6.4%	45,384	5.5%	42,739	11.2%	32,294
	Hispanic	1.5%	68,505	0.8%	5,676	0.8%	6,571	0.8%	2,301
	Other	0.3%	14,965	0.3%	2,044	0.3%	2,295	0.3%	895
	White	84.8%	3,841,874	89.8%	640,338	90.5%	707,628	85.0%	245,561
	Unknown/Missing	3.4%	155,969	2.1%	14,889	2.2%	17,289	2.0%	5,837
Comorbid Conditions	CVD	12.0%	545,062	27.5%	196,355	25.1%	196,578	34.9%	100,741
	Diabetes	22.9%	1,035,221	36.3%	258,939	34.6%	270,310	44.7%	129,090
	Hypertension	61.6%	2,791,076	87.3%	622,500	84.0%	656,795	92.7%	267,901
Smoking	Never	48.6%	2,198,551	44.4%	316,752	45.2%	353,794	41.1%	118,805
	Previous	24.4%	1,103,534	32.2%	229,715	30.8%	240,504	34.7%	100,375
	Current	19.8%	894,997	15.0%	107,229	15.8%	123,477	15.9%	45,833
	No measurement	7.3%	330,933	8.4%	59,655	8.2%	64,310	8.3%	24,009
Systolic BP	Mean (SD)	125.9	(16.1)	128.7	(17.5)	128.0	(17.3)	128.8	(18.3)
	No measurement	3.9%	178,933	4.1%	29,027	4.1%	31,940	3.8%	10,958
Follow-up (yr)	Mean (SD)	2.4	(1.1)	2.5	(1.2)	2.5	(1.2)	2.4	(1.2)

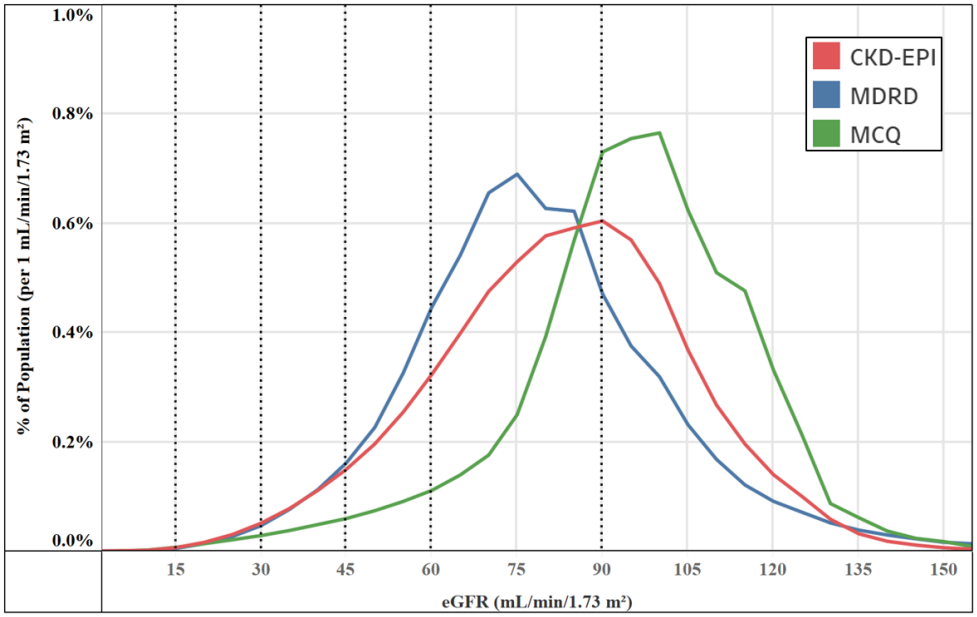
Abbreviations: ESRD, End Stage Renal Disease; SD, standard deviation; eGFR, estimated GFR; SCr, serum creatinine; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; CVD, Cardiovascular Disease; BP, Blood Pressure

3.2 eGFR Distribution and Classification

The average eGFR was considerably lower for CKD-EPI (82.7 ml/min/1.73m^2) and MDRD (79.7 ml/min/1.73m^2) compared to MCQ (94.9 ml/min/1.73m^2) equation. Accordingly, the prevalence of GFR category 3–5 (< 60 mL/min/1.73 m²) was 15.8% with CKD-EPI, 17.3% with MDRD, and 6.4% with MCQ. Prevalence for eGFR $_{MCQ}$ < 79 mL/min/1.73 m² was 15.9%. Average eGFR $_{CKD-EPI}$ for patients with eGFR $_{CKD-EPI}$ < 60 was 47.3 mL/min/1.73 m², while for patients with eGFR $_{MCQ}$ < 60 mL/min/1.73 m² average eGFR $_{CKD-EPI}$ was 37.6 mL/min/1.73 m². Comparing the distributions of eGFR from the three estimating equations in Figure 4, the MCQ

equation shifts the population to higher GFR estimates (category 1: CKD-EPI, 40.1%; MDRD, 28.8%; MCQ 66.1%).

Figure 4: Distribution of Estimated GFR using the CKD-EPI, MDRD, and MCQ Equations



	% of Population	# of Patients
G1 (≥ 90)	38.55%	1,745,533
	27.43%	1,242,117
	64.50%	2,920,357
G2 (60-89)	45.70%	2,069,131
	54.60%	2,472,398
	28.97%	1,311,555
G3a (45-59)	10.29%	465,780
	12.56%	568,767
	3.73%	168,719
G3b (30-44)	4.30%	194,772
	4.39%	198,674
	1.96%	88,566
G4 (15-29)	1.10%	49,711
	0.96%	43,580
	0.78%	35,295
G5 (<15)	0.07%	3,088
	0.05%	2,479
	0.08%	3,523

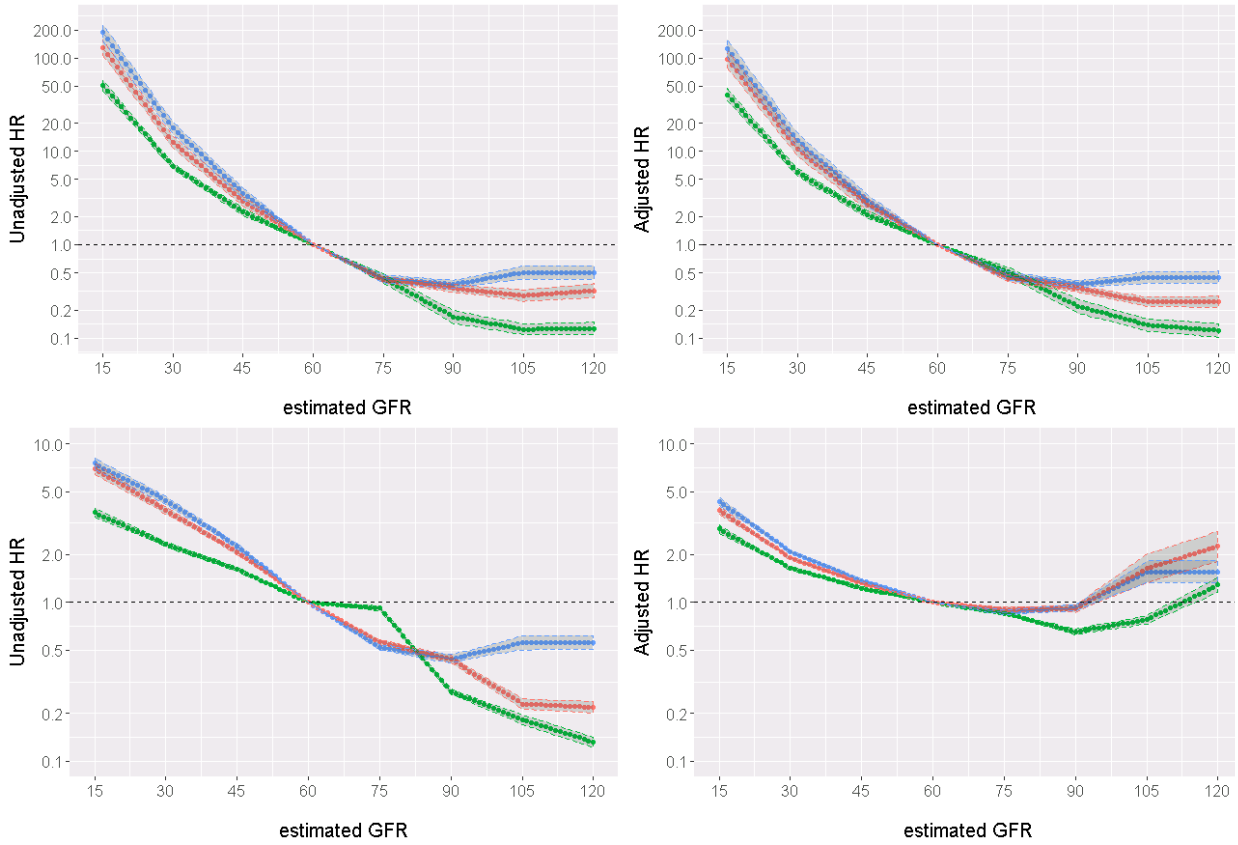
3.3 Continuous Risk Association

In Figure 5, the CKD-EPI and MDRD equations had a similar relationship with risk of ESRD and all-cause mortality when eGFR < 90 ml/min/1.73 m^2. For eGFR > 90 ml/min/1.73 m^2, hazard ratios were smaller (farther from the null, < 1.0) for estimates from the CKD-EPI compared to the MDRD equation. After adjusting for risk factors, the risk gradient at higher estimates of GFR was still steeper for CKD-EPI compared to MDRD, for ESRD but not all-cause mortality.

Comparing the CKD-EPI and MCQ equations, the risk gradient of estimated GFR with ESRD and all-cause mortality was steeper for CKD-EPI in GFR category 3–5 range (eGFR < 60 ml/min/1.73 m^2) and shallower when eGFR ≥ 75 ml/min/1.73 m^2, even after adjusting for risk

factors. For the adjusted models of both ESRD and all-cause mortality hazard ratios were similar for the equations when eGFR was between 60 and 75 ml/min/1.73 m^2.

Figure 5: Estimated GFR and Hazard Ratios (HR) of ESRD and All-Cause Mortality (ACM)



Error ribbons for each equation indicate 95% confidence intervals for estimated GFR. Reference value is estimated GFR of 60 mL/min/1.73m2. Adjusted hazard ratio adjusted for age, sex, race/ethnicity, smoking status, history of cardiovascular disease, diabetes, hypertension, systolic blood pressure. Hazard ratios below the dotted black line at 1.0 indicate a lower risk of ESRD or all-cause mortality, and above the line a higher risk.

Abbreviations: ESRD, End Stage Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; MCQ, Mayo Clinic Quadratic

In general, all three equations estimate patients with the highest risk of ESRD to the lowest estimates of GFR. For all-cause mortality each equation in the adjusted models had a J-shape risk relationship, where higher eGFR is associated with lower or similar risk of mortality, until eGFR $\geq$ 90 ml/min/1.73 m^2, with even higher estimates associated with higher risk.

3.4 Deciles of eGFR by Estimating Equation and Risk Association

Estimated GFR values for deciles were similar with the CKD-EPI and MDRD equations in the two highest (9 and 10) and lowest deciles (1 and 2), while in between (3–8), deciles for the CKD-EPI equation occurred at higher values of eGFR than the equivalent deciles for MDRD. The most noticeable differences in crude incidence rates of ESRD and all-cause mortality between the CKD-EPI and MDRD equations where in the 8-10th deciles, where incidence rates for the CKD-EPI equation continued to decline, while for the MDRD equation rates began to increase. Similarly, adjusted hazard ratios for risk of ESRD by deciles showed a consistent risk gradient for the CKD-EPI equation, with higher deciles corresponding to lower risk (except from the 7th to the 8th decile), while risk increased from the 8th to the 10th decile for MDRD. The largest relative differences in hazard ratios for risk of ESRD were in the 9th (AHR $_{CKD\text{-}EPI}$: 0.76 vs. AHR $_{MDRD}$: 0.91) and 10th deciles (AHR $_{CKD\text{-}EPI}$: 0.68 vs. AHR $_{MDRD}$: 1.08). In contrast, for all-cause mortality the CKD-EPI equation had a steeper positive risk gradient in the 8th through 10th deciles than the MDRD equation.

Table 2: eGFR Deciles, Crude Incidence Rates (CIR), and Adjusted Hazard Ratios (AHR)

eGFR Decile (~10%)	CKD-EPI			MDRD			MCQ		
	eGFR mL/min/1.73 m²	CIR ESRD; ACM	AHR ESRD; ACM	eGFR mL/min/1.73 m²	CIR ESRD; ACM	AHR ESRD; ACM	eGFR mL/min/1.73 m²	CIR ESRD; ACM	AHR ESRD; ACM
1	< 53	22.0; 64.5	17.6; 1.57	< 52	22.6; 59.9	16.1; 1.81	< 69	22.0; 63.0	17.8; 1.55
2	53 – 63	3.7; 28.3	3.32; 1.06	52 – 60	3.6; 28.5	3.05; 1.22	69 – 80	3.3; 36.2	3.39; 1.09
3	64 – 71	2.0; 18.5	1.90; 0.96	61 – 67	2.0; 16.7	1.86; 1.05	81 – 86	1.9; 21.2	2.11; 0.89
4	72 – 77	1.4; 14.2	1.38; 0.92	68 – 72	1.4; 14.9	1.37; 1.01	87 – 91	1.5; 13.1	1.66; 0.85
5	78 – 83	1.2; 13.9	1.18; 0.95	73 – 76	1.2; 10.2	1.14; 0.94	92 – 95	1.2; 10.7	1.35; 0.92
6	84 – 88	1.0; 11.9	1.01; 0.94	77 – 82	1.0; 11.8	0.99; 1.01	96 – 100	1.0; 9.1	1.14; 0.97
7	**89 – 94**	**1.1; 9.7**	**Reference**	**83 – 87**	**1.0; 9.2**	**Reference**	**101 – 105**	**1.0; 8.5**	**Reference**
8	95 – 100	1.0; 7.8	0.89; 1.20	88 – 95	0.9; 9.5	0.88; 1.14	106 – 111	1.0; 7.5	0.97; 1.04
9	101 – 110	0.9; 6.3	0.76; 1.55	96 – 107	1.0; 9.8	0.91; 1.27	112 – 118	1.0; 6.4	0.95; 1.30
10	≥ 111	0.9; 4.8	0.68; 2.65	≥ 108	1.3; 12.4	1.08; 1.92	≥ 119	0.9; 4.6	0.79; 1.96

Adjusted hazard ratio adjusted for age, sex, race, smoking status, history of cardiovascular disease, diabetes, hypertension, systolic blood pressure, with the 7th decile for the respective equations as the reference category.
Abbreviations: ESRD, End Stage Renal Disease; ACM, all-cause mortality;
Crude incidence rates calculated per 1,000 person years.

The CKD-EPI and MCQ equations had similar incidence rates of ESRD, and small differences in rates for all-cause mortality. Adjusted hazard ratios for ESRD were smaller in the 3 –6th (towards the null) and 8 –10th deciles (away from the null) for the CKD-EPI equation compared to MCQ. For all-cause mortality hazard ratios were similar for both equations except in the 10th decile (AHR $_{CKD-EPI}$: 2.65 vs. AHR $_{MCQ}$: 1.96).

3.5 Net Reclassification Improvement (NRI)

Overall Table 3 shows NRI favored the CKD-EPI to MDRD equation for ESRD (0.12) and all-cause mortality (0.19). For all-cause mortality, NRI favored the CKD-EPI equation for both events (0.05) and non-events (0.14), and for ESRD for non-events only (NRI $_{No\ ESRD}$: 0.13 vs. NRI $_{ESRD}$: – 0.02). The most notable differences across subgroups were between age < 65 and ≥ 65 years, i.e., NRI favored CKD-EPI for reclassification of non-events and MDRD for events among patients < 65 (NRI $_{No\ Event}$: 0.23 ESRD and 0.23 all-cause mortality , NRI $_{Event}$: – 0.14 ESRD and – 0.18 all-cause mortality), and favored CKD-EPI for reclassification of events and MDRD non-events among patients ≥ 65 years (NRI $_{Event}$: 0.05 ESRD and 0.11 all-cause mortality, NRI $_{No\ Event}$: – 0.03 ESRD, and – 0.03 all-cause mortality).

Net reclassification improvement favored the CKD-EPI equation for reclassification of events and MCQ for non-events of ESRD and all-cause mortality overall, and consistently across subgroups. Combining event and non-event NRI, NRI favors the CKD-EPI equation for all-cause mortality and MCQ for ESRD (0.06 and – 0.07). Across demographic subgroups, NRI was largest in favor of the CKD-EPI equation among females (compared to males) for ESRD, and Hispanic, Asian or White patients (compared to Black) for all-cause mortality. Using deciles to calculate reclassification improvement, NRI for events still favored the CKD-EPI equation (0.03 for ESRD and 0.02 for all-cause mortality) and NRI for non-events the MCQ (–0.13 for ESRD

and –0.14 for all-cause mortality), but both values were smaller than the equivalent NRI using absolute GFR categories.

Table 3: Net Reclassification Improvement (NRI) for ESRD and All-Cause Mortality (ACM)

Subgroup	Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) vs. Modification of Diet in Renal Disease (MDRD)						Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) vs. Mayo Clinic Quadratic (MCQ)					
	End stage renal disease			All-cause mortality (ACM)			End stage renal disease			All-cause mortality (ACM)		
	NRI_{All}	NRI_{ESRD}	$NRI_{No\ ESRD}$	NRI_{All}	NRI_{ACM}	$NRI_{No\ ACM}$	NRI_{All}	NRI_{ESRD}	$NRI_{No\ ESRD}$	NRI_{All}	NRI_{ACM}	$NRI_{No\ ACM}$
All	**0.12**	-0.02	0.13	**0.19**	0.05	0.14	**-0.07**	0.31	-0.38	**0.06**	0.44	-0.38
Age ≥ 65	**0.02**	0.05	-0.03	**0.08**	0.11	-0.03	**-0.09**	0.33	-0.42	**0.05**	0.46	-0.41
Age < 65	**0.09**	-0.14	0.23	**0.05**	-0.18	0.23	**-0.09**	0.27	-0.36	**-0.01**	0.35	-0.36
Female	**0.12**	-0.04	0.16	**0.19**	0.03	0.16	**0.03**	0.38	-0.35	**0.08**	0.42	-0.34
Male	**0.10**	0.01	0.10	**0.18**	0.08	0.10	**-0.19**	0.24	-0.43	**0.04**	0.46	-0.42
Race												
White	**0.11**	-0.02	0.14	**0.20**	0.05	0.15	**-0.04**	0.37	-0.41	**0.06**	0.47	-0.41
Black	**0.10**	0.04	0.06	**0.13**	0.07	0.06	**-0.12**	0.00	-0.12	**-0.03**	0.09	-0.12
Hispanic	**0.08**	-0.09	0.17	**0.20**	0.03	0.17	**0.00**	0.28	-0.28	**0.14**	0.42	-0.28
Asian	**0.09**	-0.07	0.16	**0.18**	0.02	0.16	**0.02**	0.28	-0.25	**0.17**	0.42	-0.25
CVD	**0.03**	0.02	0.02	**0.11**	0.08	0.03	**-0.14**	0.30	-0.44	**0.02**	0.46	-0.43
No CVD	**0.11**	-0.04	0.15	**0.19**	0.04	0.15	**-0.06**	0.31	-0.37	**0.06**	0.43	-0.37
Diabetes	**0.07**	-0.02	0.08	**0.13**	0.04	0.09	**-0.08**	0.30	-0.38	**0.05**	0.43	-0.37
No Diabetes	**0.13**	-0.01	0.15	**0.21**	0.06	0.15	**-0.06**	0.32	-0.38	**0.07**	0.44	-0.38
HTN	**0.08**	-0.01	0.09	**0.16**	0.06	0.10	**-0.10**	0.30	-0.41	**0.04**	0.45	-0.40
No HTN	**0.12**	-0.08	0.20	**0.19**	-0.01	0.20	**0.00**	0.34	-0.34	**0.05**	0.39	-0.34
Smoking												
Never	**0.12**	-0.02	0.14	**0.22**	0.07	0.15	**-0.06**	0.32	-0.38	**0.08**	0.45	-0.37
Previous	**0.10**	0.01	0.09	**0.17**	0.08	0.10	**-0.12**	0.30	-0.42	**0.04**	0.46	-0.41
Current	**0.11**	-0.06	0.16	**0.15**	-0.02	0.17	**-0.06**	0.29	-0.34	**0.04**	0.38	-0.34

Abbreviations: CVD, Cardiovascular Disease; HTN, Hypertension
NRI calculated using eGFR categories: < 15, 15-29, 30-44, 45-59, 60-89, and ≥ 90 mL/min/1.73 m²
*Positive numbers in **orange** favor **CKD-EPI** for reclassification, negative numbers in **blue** in favor **MDRD***

3.6 Reclassification Matrix

3.6.1 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Compared to Modification of Diet in Renal Disease (MDRD)

Summing the percentages of the study population (top right of each box) in the diagonals from Tables 4, overall 81.7% of patients were classified into the same GFR category using the CKD-EPI and MDRD equations, 15.7% of patients were reclassified upward into categories of higher estimated GFR, and 2.6% downward to lower values of GFR. In general patients reclassified upward to higher categories of eGFR with the CKD-EPI compared to MDRD equation, were younger, less likely to be Black, male, or die, than those classified in the same category with

both equations, while patients reclassified downward, were older, more likely to be Black, female, and die (Appendix Table 1: Section D, E, I, and K).

Patients reclassified downward with the CKD-EPI compared to MDRD equation had a higher risk of ESRD and all-cause mortality (values below the diagonal), and patients reclassified upward a lower risk (values above the diagonal), except for reclassification to GFR 2 $_{\text{CKD-EPI}}$ from GFR 1 $_{\text{MDRD}}$ which had similar mortality risk to patients in GFR 1 with both equations. In the margins of the table, having GFR 1 $_{\text{CKD-EPI}}$ was associated with a 40% decreased risk of ESRD compared to GFR 2 $_{\text{CKD-EPI}}$, and GFR 1 $_{\text{MDRD}}$ (compared to GFR 2 $_{\text{MDRD}}$) only a 20% decreased risk. Adjusted hazard ratios for all-cause mortality for GFR category 3–5 were similar for both equations.

Table 4: Reclassification, Crude Incidence Rates (CIR), and Adjusted Hazard Ratios (AHR), CKD-EPI vs. MDRD

	eGFR Categories	Modification of Diet in Renal Disease (MDRD)						CKD-EPI
		G1 (≥ 90)	G2 (60 – 89)	G3a (45 – 59)	G3b (30 – 44)	G4 (15 – 29)	G5 (< 15)	Total
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	G1 (≥ 90)	1,170,793 (25.9%) 1.1; 0.7 (0.6 - 0.7) 8.4; 1.5 (1.3 - 1.7)	574,740 (12.7%) 0.7; 0.5 (0.5 - 0.6) 4.0; 1.0 (0.9 - 1.1)				number of patients (%) ESRD: CIR; AHR (95% CI) ACM: CIR; AHR (95% CI)	1,745,533 (38.5%) 1.0; 0.6 (0.5 - 0.6) 7.0; 1.3 (1.2 - 1.5)
	G2 (60 – 89)	71,324 (1.6%) 1.7; 1.1 (1.0 - 1.3) 47.8; 1.3 (1.3 - 1.4)	1,879,847 (41.5%) 1.5; 1.0 (Reference) 14.4; 1.0 (Reference)	117,960 (2.6%) 2.5; 1.8 (1.6 - 2.0) 9.2; 1.2 (1.2 - 1.2)				2,069,131 (45.7%) 1.5; 1.0 Reference 15.3; 1.0 Reference
	G3a (45 – 59)		17,811 (0.4%) 4.2; 2.3 (1.8 - 3.0) 75.2; 1.3 (1.2 - 1.3)	431,120 (9.5%) 5.1; 3.1 (2.7 - 3.5) 35.7; 1.3 (1.2 - 1.3)	16,849 (0.4%) 11.3; 6.7 (5.1 - 8.7) 21.0; 1.8 (1.7 - 2.0)			465,780 (10.3%) 5.3; 3.1 (2.7 - 3.6) 36.6; 1.2 (1.2 - 1.3)
	G3b (30 – 44)			19,687 (0.4%) 8.3; 4.7 (3.7 - 5.9) 97.5; 1.6 (1.5 - 1.6)	173,588 (3.8%) 18.6; 10.2 (8.2 - 12.6) 67.2; 1.8 (1.7 - 1.9)	1,497 (0.0%) 77.0; 37.4 (29.8 - 47.0) 41.4; 4.1 (3.5 - 4.7)		194,772 (4.3%) 18.0; 9.8 (7.9 - 12.1) 70.0; 1.7 (1.6 - 1.8)
	G4 (15 – 29)				8,237 (0.2%) 36.6; 20.6 (16.0 - 26.5) 138.1; 2.2 (2.1 - 2.3)	41,436 (0.9%) 106.4; 53.7 (41.9 - 68.8) 115.9; 2.9 (2.8 - 3.0)	38 (0.0%) 370.1; 241.3 (130.7 - 445.4) 30.1; 7.2 (2.2 - 23.7)	49,711 (1.1%) 94.5; 48.1 (37.7 - 61.4) 119.4; 2.6 (2.6 - 2.7)
	G5 (<15)	number of patients (%) ESRD: CIR; AHR (95% CI) ACM: CIR; AHR (95% CI)				647 (0.0%) 346.7; 197.9 (136.4 - 287.0) 204.0; 4.2 (3.6 - 4.9)	2,441 (0.1%) 373.4; 202.8 (158.2 - 259.9) 124.5; 5.2 (4.7 - 5.7)	3,088 (0.07%) 367.9; 195.7 (151.3 - 253.0) 140.8; 4.7 (4.4 - 5.0)
MDRD	Total	1,242,117 (27.4%) 1.1; 0.8 (0.7 - 0.9) 11.0; 1.4 (1.3 - 1.5)	2,472,398 (54.6%) 1.3; 1.0 Reference 12.5; 1.0 Reference	568,797 (12.6%) 4.7; 3.0 (2.7 - 3.5) 32.5; 1.3 (1.3 - 1.3)	198,674 (4.4%) 18.6; 10.4 (8.3 - 13.0) 65.9; 1.8 (1.8 - 1.9)	43,580 (1.0%) 107.7; 55.1 (43.0 - 70.6) 114.4; 2.9 (2.8 - 3.0)	2,479 (0.07%) 373.4; 213.6 (167.3-272.6) 122.7; 5.2 (4.7 - 5.7)	4,528,015 (100%) 3.5 per 1,000 person yrs 18.2 per 1,000 person yrs

Abbreviations: ESRD, End Stage Renal Disease; ACM, all-cause mortality;
Crude incidence rates calculated per 1,000 person years.
Adjusted hazard ratio adjusted for age, sex, race, smoking status, history of cardiovascular disease, diabetes, hypertension, systolic blood pressure, with the 7th decile for the respective equations as the reference category.

3.6.2 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Compared to Mayo Clinic Quadratic (MCQ)

Overall 59.5% of patients were classified into the same GFR category using the CKD-EPI and MCQ equations, 1.3% of patients were reclassified upward into categories of higher estimated

GFR, and 39.1% downward to lower values of GFR. In general patients reclassified downward with the CKD-EPI compared to MCQ equation are older, less likely to be male (except for reclassification to GFR 2 $_{\text{CKD-EPI}}$ from GFR 1 $_{\text{MCQ}}$) and Black (Appendix Table 2: Section D, E, I, and K).

Table 5: Reclassification, Crude Incidence Rates (CIR), and Adjusted Hazard Ratios (AHR), CKD-EPI vs. MDRD

	eGFR Categories	Mayo Clinic Quadratic (MCQ)						CKD-EPI
		G1 (≥ 90)	G2 (60 – 89)	G3a (45 – 59)	G3b (30 – 44)	G4 (15 – 29)	G5 (<15)	Total
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	G1 (≥ 90)	1,689,318 (37.3%) 1.0; 0.4 (0.4 - 0.4) 6.4; 1.3 (1.2 - 1.4)	56,215 (1.2%) 1.4; 0.7 (0.6 - 0.8) 22.4; 1.2 (1.0 - 1.3)				number of patients (%) ESRD: CIR; AHR (95% CI) ACM: CIR; AHR (95% CI)	1,745,533 (38.5%) 1.0; 0.6 (0.5 - 0.6) 7.0; 1.3 (1.2 - 1.5)
	G2 (60 – 89)	1,231,039 (27.2%) 1.2; 0.5 (0.5 - 0.6) 10.2; 0.9 (0.9 - 1.0)	837,970 (18.5%) 2.1; 1.0 (Reference) 22.3; 1.0 (Reference)	122 (0.0%) 12.1; 2.3 (0.9 - 6.4) 27.6; 9.3 (4.5 - 19.1)				2,069,131 (45.7%) 1.5; 1.0 Reference 15.3; 1.0 Reference
	G3a (45 – 59)		406,570 (9.0%) 4.4; 2.1 (1.9 - 2.3) 35.4; 1.2 (1.2 - 1.2)	58,159 (1.3%) 11.1; 3.3 (2.8 - 3.9) 45.6; 1.3 (1.3 - 1.3)	1,051 (0.0%) 38.7; 6.6 (4.9 - 9.0) 38.3; 1.7 (1.3 - 2.3)			465,780 (10.3%) 5.3; 3.1 (2.7 - 3.6) 36.6; 1.2 (1.2 - 1.3)
	G3b (30 – 44)		10,800 (0.2%) 5.8; 3.4 (2.7 - 4.3) 63.5; 1.4 (1.3 - 1.5)	110,438 (2.4%) 11.5; 5.1 (4.2 - 6.0) 63.5; 1.5 (1.5 - 1.6)	72,347 (1.6%) 28.9; 9.8 (8.0 - 11.9) 81.2; 1.8 (1.8 - 1.9)	1,187 (0.0%) 114.8; 19.7 (16.0 - 24.3) 64.3; 2.3 (2.0 - 2.6)		194,772 (4.3%) 18.0; 9.8 (7.9 - 12.1) 70.0; 1.7 (1.6 - 1.8)
	G4 (15 – 29)				15,168 (0.3%) 36.0; 17.1 (13.9 - 21.0) 106.8; 2.2 (2.1 - 2.3)	33,947 (0.7%) 120.1; 41.3 (33.1 - 51.5) 124.9; 2.8 (2.7 - 2.8)	596 (0.0%) 437.0; 112.9 (88.7 - 143.7) 134.6; 3.5 (3.0 - 4.1)	49,711 (1.1%) 94.5; 48.1 (37.7 - 61.4) 119.4; 2.6 (2.6 - 2.7)
	G5 (<15)	number of patients (%) ESRD: CIR; AHR (95% CI) ACM: CIR; AHR (95% CI)				161 (0.0%) 236.6; 116.9 (76.7 - 178.2) 204.4; 5.0 (4.2 - 6.0)	2,927 (0.1%) 375.9; 148.6 (115.8 - 190.7) 137.4; 4.5 (4.2 - 4.9)	3,088 (0.07%) 367.9; 195.7 (151.3 - 253.0) 140.8; 4.7 (4.4 - 5.0)
MCQ	Total	2,920,357 (64.5%) 1.0; 0.4 (0.3 - 0.4) 8.1; 1.0 (0.9 - 1.0)	1,311,555 (29.0%) 2.8; 1.0 Reference 26.7; 1.0 Reference	168,719 (3.7%) 11.4; 2.2 (1.9 - 2.5) 57.3; 1.2 (1.2 - 1.3)	88,566 (2.0%) 30.2; 5.6 (4.7 - 6.6) 85.0; 1.6 (1.6 - 1.6)	35,295 (0.7%) 120.3; 28.7 (23.7 - 34.7) 123.1; 2.6 (2.5 - 2.6)	3,523 (0.07%) 386.1; 108.5 (88.3 - 133.4) 137.0; 4.5 (4.1 - 4.9)	4,528,015 (100%) 3.5 per 1,000 person yrs 18.2 per 1,000 person yrs

Abbreviations: ESRD, End Stage Renal Disease; ACM, all-cause mortality;
Crude incidence rates calculated per 1,000 person years.
Adjusted hazard ratio adjusted for age, sex, race, smoking status, history of cardiovascular disease, diabetes, hypertension, systolic blood pressure, with the 7th decile for the respective equations as the reference category.

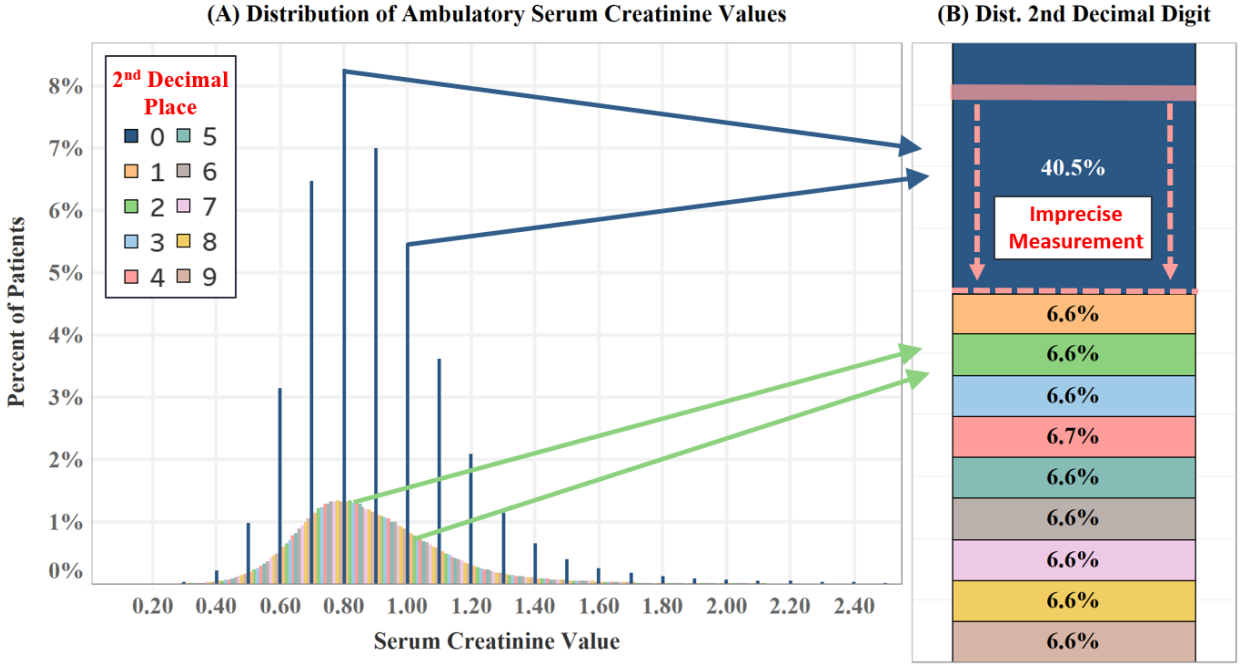
Patients reclassified downward with the CKD-EPI compared to MCQ equation had a higher risk of ESRD and all-cause mortality (adjusted hazard ratios below the diagonal), and patients reclassified upward a lower risk (adjusted hazard ratios above the diagonal), except for reclassification to GFR 2 $_{\text{CKD-EPI}}$ from GFR 1 $_{\text{MCQ}}$ which had lower mortality risk relative to patients in GFR 1 with both equations (AHR 0.9 vs. 1.3), and to GFR 2 $_{\text{CKD-EPI}}$ from GFR 3a $_{\text{MCQ}}$ which had higher mortality risk (AHR 9.3 vs. 1.3). In the margins of Table 5, crude incidence rates for GFR 2 were 1.5 (CKD-EPI) vs. 2.8 (MCQ) ESRD events per 1,000 person years, and 15.3 (CKD-EPI) vs. 26.7 (MCQ) mortality events per 1,000 person years. Differences in risk

gradients with eGFR categories from the CKD-EPI and MCQ equations were similar to those from the continuous distributions in Figure 5.

3.7 Precision of Serum Creatinine Measurements

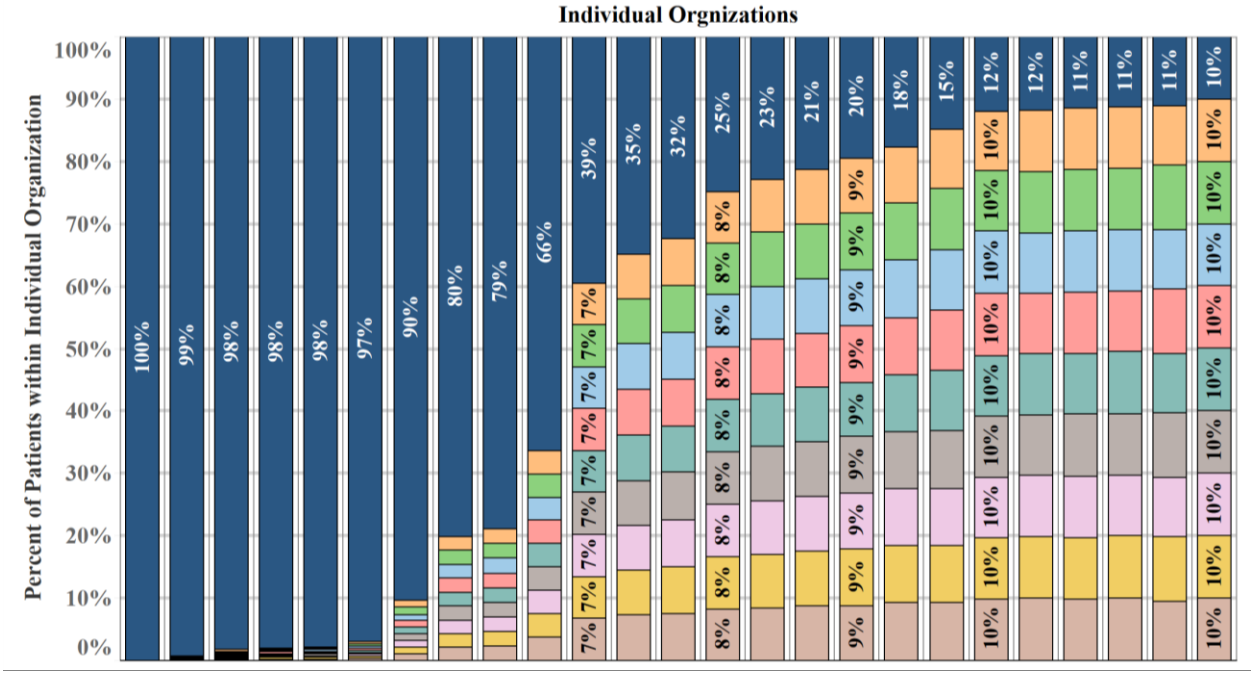
The spikes in the serum creatinine distribution in Figure 6 occur every 0.1 mg/dL, e.g., at 0.30, 0.40, 0.50, 0.60 mg/dL, etc... In our study population, 40.5% of patients had a 0 in the second decimal place of their serum creatinine measurement (dark blue). Figure 7 shows across individual health care organizations, 6 organizations have serum creatinine measurements almost exclusively recorded to the nearest 0.1 mg/dL (97%+ of patients with a 0 as the 2nd decimal), and 6 organizations have serum creatinine measurements almost exclusively recorded to the nearest 0.01 mg/dL (10–12% with a 0), the level of precision currently recommended by guidelines for clinical laboratories to report serum creatinine.[7]

Figure 6: Precision of Serum Creatinine Measurements from Clinical Laboratories



Precision of serum creatinine measurements was quantified using the proportion of values with a 0 in the second place after the decimal (e.g., 0.90, 1.00 mg/dL). Each color represents a different digit for the second place after the decimal (i.e., 0 through 9). The distribution on the left shows the proportion of the study population for the study population, and the column on the right is the distribution of digits in the 2nd decimal place.

Figure 7: Precision of Serum Creatinine Measurements by Health Care Organization



Each column is a different health care organization. Each color represents a different digit for the second place after the decimal (i.e., 0 through 9), and percentages reflect the proportion of patients within each health care organization whose serum creatinine had a second decimal place for that given digit.

4 Discussion

In our study population of 4.5 million patients receiving ambulatory health care in the United States, overall the CKD-EPI equation estimated slightly higher GFR values than MDRD, and much lower values than the MCQ equation. Patients characteristics were similar among eGFR subgroups using the CKD-EPI and MDRD equations, while comparatively for GFR category 3–5 using the MCQ equation, patients were more likely to be male, Black, and sicker. The CKD-EPI equation had a similarly steep risk gradient to the MDRD equation in GFR category 3–5, both steeper than the risk gradient for the MCQ equation. Overall, reclassification improvement favored the CKD-EPI to MDRD equation for ESRD and all-cause mortality. GFR estimates from

the CKD-EPI equation substantially improved reclassification of events compared to estimates from the MCQ equation, with almost equally negative reclassification for non-events.

Our results confirm using "real world" data from diverse patient populations, that while staging CKD and determining contraindications for nephrotoxic medications is based on GFR estimates, the equation used to estimate GFR should impact the interpretation of values. The CKD-EPI and MDRD equations produce similar prevalence for eGFR < 60 ml/min/1.73 m^2, facilitating a move from the older MDRD equation to the currently recommended CKD-EPI equation. The MCQ equation has been shown to overestimate kidney function relative to measured GFR in many populations,[14-17] and markedly raises the mean level of estimated GFR. This complicates comparison and interpretation of values relative to those from measured GFR, or more accurate estimates, e.g., from the CKD-EPI equation.

Results from our models with eGFR as a continuous and categorical variable were internally consistent and showed the relationship of estimated GFR with risk of ESRD and all-cause mortality was similar with estimates from the CKD-EPI and MDRD equation at lower estimate of kidney function, and both stronger compared to the MCQ. At higher estimates of kidney function the risk relationship was stronger for the CKD-EPI equation relative to MDRD, but not quite as strong as the MCQ. Thus, if one focuses on risk gradients in GFR 3–5 range, the KDIGO recommended CKD-EPI equation has a similarly steep risk gradient to the MDRD equation, both steeper than the risk gradient with the MCQ equation. These results are consistent with previous research which have found the CKD-EPI equation more accurately categorizes risk of adverse events than the MDRD equation.[20-25] We add to the literature comparing the CKD-EPI and MCQ equations by including ESRD risk. In addition, we show by accounting for the shift in GFR estimates between equations, i.e., by using eGFR deciles instead of categories with

the same absolute thresholds, the relative risk gradient at higher GFR estimates is steeper and in favor of the CKD-EPI compared to MCQ.

The CKD-EPI equation had positive reclassification for both events and non-events with all-cause mortality compared to MDRD. For ESRD the gain for events with MDRD (–0.02) was small compared to the loss for non-events (0.13). Compared to the largest study, we showed slightly less reclassification, but similar NRI overall and by age group.[20] The reclassification comparison of the CKD-EPI and MCQ equation is more complicated since the MCQ markedly raises the mean level of estimated GFR. As a result, the CKD-EPI showed substantial favorable (> 0.3) reclassification for both ESRD and mortality events but the opposite for non-events (< –0.3). While previous literature has found similar improvements in NRI by event for all-cause mortality,[28] in this situation the NRI is difficult to interpret since it places an arbitrarily equal weight on their two large and opposite reclassification proportions. Arithmetically, the result is a positive NRI for mortality (favoring CKD-EPI) and negative NRI for ESRD (MCQ). However, quantitatively combining opposite reclassification should include a cost-benefit analysis with utilities to classifying individuals who will and will not develop ESRD at different GFR stages.

The J-shape risk association between estimated GFR for all three equations and risk of mortality is present in the adjusted models but not the unadjusted ones and can be primarily accounted for with adjustment for age. This is something that has been studied in the past and may be caused by a loss of muscle mass secondary to ill-health, corresponding to lower values of serum creatinine and better estimates of kidney function.[23] This is a limitation to estimating equations based on filtration markers related to muscle mass, e.g., serum creatinine.

One limitation of this study is data collection for serum creatinine was a part of clinical care, with variability in precision of measurements reported by clinical laboratories. While KDIGO

guidelines recommend labs report serum creatinine to the nearest 0.01 mg/dL, almost a quarter of health care organizations had measurements recorded exclusively by to the nearest 0.1 mg/dL. While there is evidence serum creatinine measurements are imprecise, this does not give any indication towards the accuracy of these measurements. No information was provided on standardization of serum creatinine calibration measurements to isotope dilution mass spectrometry, but prior research suggest by 2011, a year before the start of our dataset, standardization was in large part achieved by clinical laboratories.[10]

Another limitation was ascertainment of outcomes, i.e., ESRD using diagnosis and procedure codes, and all-cause mortality using date of death in the patients' electronic health record. These methods might be considered suboptimal to other methods, e.g., linking to the United States Renal Data System, or social security death index. Finally, our study included short follow-up which could impact generalizability of our results to longer term risk of ESRD and mortality.

Strengths of this study include the size of the study population and number of events, as well as the availability of data on risk factors. This "real-world" from diverse patient populations, allowed us to compare the equations among lesser studied subgroups. Another strength is its generalizability to patients receiving ambulatory care in the United States health care system, providing valuable information to health care providers and organizations on the implications of switching to the CKD-EPI equation from the MDRD or MCQ.

5 Conclusions

Our conclusion is that based on these risk data alone, the recommended CKD-EPI equation is superior to MDRD in classifying risk of ESRD and all-cause mortality. Similar estimates of GFR

from the two equations, especially in CKD range (GFR category 3–5), facilitate transitioning to the CKD-EPI equation from MDRD.

MCQ largely shifted the distribution of eGFR and eGFR-risk relationship to higher levels of eGFR. The markedly different absolute values reported with each equation, make it difficult for health care providers to translate recommendations based on one equation to another. While risk classification with the CKD-EPI equation, which is currently recommended by clinical guidelines to stage CKD with known risk relationships, is not superior to the MCQ equation, using the MCQ equation in an ambulatory setting would require significant considerations and adjustments for bias of GFR estimates, potentially introducing unnecessary risks of adverse events to patients, e.g., dosing errors of nephrotoxic medications.

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6 Appendices

Appendix Table 1: Patient Characteristics by Reclassification- CKD-EPI vs. MDRD

Appendix Table 2: Patient Characteristics by Reclassification- CKD-EPI vs. MCQ

Appendix Table 3: Appendix Table 1: Patient Characteristics Overall and by Estimated GFR ≥ 60 with each Equation

		All Patients		eGFR $_{CKD-EPI}$ ≥ 60		eGFR $_{MDRD}$ ≥ 60		eGFR $_{MCQ}$ ≥ 60	
Patients		4,528,015		3,836,609 (84.7%)		3,745,930 (84.7%)		4,238,993 (93.6)	
Outcomes	All-cause mortality	4.3%	195,262	2.7%	105,358	2.8%	106,377	3.4%	142,712
	ESRD	0.8%	37,152	0.3%	11,610	0.3%	11,173	0.4%	16,159
SCr (mg/dL)	Mean (SD)	0.9	(0.3)	0.8	(0.2)	0.8	(0.2)	0.9	(0.2)
eGFR mL/min/1.73 m²: Mean (SD)	CKD-EPI	82.7	(22.5)	89.2	(17.5)	89.8	(17.1)	85.8	(19.7)
	MDRD	79.7	(26.8)	85.7	(24.5)	86.4	(24.4)	82.5	(25.3)
	MCQ	94.9	(21.0)	101.2	(14.5)	101.6	(14.4)	98.3	(16.6)
Age (years)	Mean (SD)	58.4	(16.3)	55.6	(15.5)	55.7	(15.7)	57.2	(15.9)
Sex	Female	58.4%	2,642,646	58.1%	2,228,387	57.7%	2,159,780	58.9%	2,497,874
Race/Ethnicity	Asian	1.3%	60,876	1.5%	56,017	1.5%	55,313	1.4%	58,742
	Black	8.5%	385,826	8.9%	341,620	9.2%	343,087	8.3%	353,532
	Hispanic	1.5%	68,505	1.6%	63,011	1.7%	61,934	1.6%	66,204
	Other	0.3%	14,965	0.3%	12,978	0.3%	12,670	0.3%	14,070
	White	84.8%	3,841,874	84.0%	3,221,442	83.7%	3,134,246	84.8%	3,596,313
	Unknown/Missing	3.4%	155,969	3.7%	141,541	3.7%	138,680	3.5%	150,132
Comorbid Conditions	CVD	12.0%	545,062	9.2%	352,944	9.3%	348,484	10.5%	444,321
	Diabetes	22.9%	1,035,221	20.4%	782,221	20.4%	764,911	21.4%	906,131
	Hypertension	61.6%	2,791,076	57.0%	2,185,975	57.0%	2,134,281	59.5%	2,523,175
Smoking	Never	48.6%	2,198,551	49.3%	1,892,019	45.2%	1,844,757	49.1%	2,079,746
	Previous	24.4%	1,103,534	22.9%	880,490	30.8%	863,030	23.7%	1,003,159
	Current	19.8%	894,997	20.6%	791,013	15.8%	771,520	20.0%	849,164
	No measurement	7.3%	330,933	7.1%	273,087	8.2%	266,623	7.2%	306,924
Systolic BP	Mean (SD)	125.9	(16.1)	125.4	(15.8)	125.4	(15.9)	125.7	(16.0)
	No measurement	3.9%	178,933	3.9%	150,840	4.1%	146,993	4.0%	167,975
Follow-up (yr)	Mean (SD)	2.4	(1.1)	2.3	(1.1)	2.3	(1.1)	2.3	(1.1)

Abbreviations: ESRD, End Stage Renal Disease; SD, standard deviation; eGFR, estimated GFR; SCr, serum creatinine; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; CVD, Cardiovascular Disease; BP, Blood Pressure

Appendix Table 4: Alternative Net Reclassification Improvement Using Deciles and in eGFR Subgroups

Alternative NRI Calculcations	Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) vs. Modification of Diet in Renal Disease (MDRD)						Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) vs. Mayo Clinic Quadratic (MCQ)					
	End stage renal disease			All-cause mortality			End stage renal disease			All-cause mortality		
	NRI $_{All}$	NRI $_{ESRD}$	NRI $_{No\ ESRD}$	NRI $_{All}$	NRI $_{ACM}$	NRI $_{No\ ACM}$	NRI $_{All}$	NRI $_{ESRD}$	NRI $_{No\ ESRD}$	NRI $_{All}$	NRI $_{ACM}$	NRI $_{No\ ACM}$
Reclassification w/ deciles	**0.10**	0.08	0.02	**0.36**	0.33	0.03	**-0.10**	0.03	-0.13	**-0.11**	0.02	-0.14
eGFR $_{CKD-EPI}$ < 60 mL/min/1.73 m²	**0.06**	0.01	0.05	**0.14**	0.07	0.07	**-0.12**	0.22	-0.34	**0.05**	0.38	-0.34
eGFR $_{CKD-EPI}$ ≥ 60 mL/min/1.73 m²	**0.07**	-0.08	0.15	**0.18**	0.03	0.15	**0.08**	0.44	-0.36	**0.05**	0.41	-0.36

Net reclassification improvement was evaluated by comparing eGFR deciles between equations.
eGFR $_{CKD-EPI}$ < 60 and ≥ 60 mL/min/1.73 m² was evaluated using bias corrected NRI, which adjusts for the expected reclassification under the null hypothesis, i.e., symmetric reclassification on either side of the diagonal, and allows us to compare NRI in subgroups determined by one of the two equations being compared.
*Positive numbers in **orange** favor **CKD-EPI**, negative numbers in **blue** in favor of **MDRD** or **MCQ**.*

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Presentations

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Stempniewicz, N., Ballew, S., Ciemins, E., Grams, M., Matsushita, K., Penso, J., Coresh, J. (2017) A comparison of different equations for estimating GFR in 29 US health care organizations. American Society of Nephrology Kidney Week, New Orleans November 2017

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