Original Investigation

Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure
A Meta-analysis

Navdeep Tangri, MD, PhD, FRCPC; Morgan E. Grams, MD, PhD; Andrew S. Levey, MD; Josef Coresh, MD, PhD; Lawrence J. Appel, MD; Brad C. Astor, PhD, MPH; Gabriel Chodick, PhD; Allan J. Collins, MD; Ognjenka Djurdjev, MSc; C. Raina Elley, MBCHB, PhD; Marie Evans, MD, PhD; Amit X. Garg, MD, PhD; Stein I. Hallan, MD, PhD; Lesley A. Inker, MD, MS; Sadayoshi Ito, MD, PhD; Sun Ha Jee, PhD; Csaba P. Kovesdy, MD; Florian Kronenberg, MD; Hiddo J. L. Heerspink, PharmD, PhD; Angharad Marks, MBBCh, MRCP, MSc, PhD; Girish N. Nadkarni, MD, MPH; Sankar D. Navaneethan, MD, MPH; Robert G. Nelson, MD, PhD; Stephanie Titze, MD, MSc; Mark J. Sarnak, MD, MS; Benedicte Stengel, MD, PhD; Mark Woodward, PhD; Kunitoshi Iseki, MD, PhD; for the CKD Prognosis Consortium

IMPORTANCE Identifying patients at risk of chronic kidney disease (CKD) progression may facilitate more optimal nephrology care. Kidney failure risk equations were previously developed and validated in 2 Canadian cohorts. Validation in other regions and in CKD populations not under the care of a nephrologist is needed.

OBJECTIVE To evaluate the accuracy of the risk equations across different geographic regions and patient populations through individual participant data meta-analysis.

DATA SOURCES Thirty-one cohorts, including 721 357 participants with CKD stages 3 to 5 in more than 30 countries spanning 4 continents, were studied. These cohorts collected data from 1982 through 2014.

STUDY SELECTION Cohorts participating in the CKD Prognosis Consortium with data on end-stage renal disease.

DATA EXTRACTION AND SYNTHESIS Data were obtained and statistical analyses were performed between July 2012 and June 2015. Using the risk factors from the original risk equations, cohort-specific hazard ratios were estimated and combined in meta-analysis to form new pooled kidney failure risk equations. Original and pooled kidney failure risk equation performance was compared, and the need for regional calibration factors was assessed.

MAIN OUTCOMES AND MEASURES Kidney failure (treatment by dialysis or kidney transplant).

RESULTS During a median follow-up of 4 years, 23 829 cases of kidney failure were observed. The original risk equations achieved excellent discrimination (ability to differentiate those who developed kidney failure from those who did not) across all cohorts (overall *C* statistic, 0.90; 95% CI, 0.89-0.92 at 2 years; *C* statistic, 0.88; 95% CI, 0.86-0.90 at 5 years); discrimination in subgroups by age, race, and diabetes status was similar. There was no improvement with the pooled equations. Calibration (the difference between observed and predicted risk) was adequate in North American cohorts, but the original risk equations overestimated risk in some non-North American cohorts. Addition of a calibration factor that lowered the baseline risk by 32.9% at 2 years and 16.5% at 5 years improved the calibration in 12 of 15 and 10 of 13 non-North American cohorts at 2 and 5 years, respectively (P = .04 and P = .02).

CONCLUSIONS AND RELEVANCE Kidney failure risk equations developed in a Canadian population showed high discrimination and adequate calibration when validated in 31 multinational cohorts. However, in some regions the addition of a calibration factor may be necessary.

JAMA. 2016;315(2):164-174. doi:10.1001/jama.2015.18202
Corrected on January 25, 2016.

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: CKD Prognosis Consortium are listed at the end of the article.

Corresponding Author: Josef Coresh, MD, PhD, Chronic Kidney Disease Prognosis Consortium Data Coordinating Center, 2024 E. Monument St, Baltimore, MD 21287 (ckdpc@jhmi.edu).

Chronic kidney disease (CKD) is increasing in incidence and prevalence worldwide.[1] Rates of progression to kidney failure varies among individuals with CKD and depends on the severity of kidney disease, comorbid conditions, and risk of dying before kidney failure onset.[2,3] Interventions to slow CKD progression, planning for initiation of dialysis and transplant, and early creation of arteriovenous fistula have been advocated, but these strategies may be expensive and are associated with risks. Treatment would ideally be recommended only for patients at high risk of progression and for whom the benefit exceeds the harm.[4,5]

Tangri et al[6] previously developed kidney failure risk equations that use demographic and laboratory data to predict progression of CKD to kidney failure. The risk equations were developed in 3449 patients with stages 3 to 5 CKD who were referred for nephrology care in Ontario, Canada, and were validated in referred patients with CKD in British Columbia, Canada. The preferred risk equations (the 4-variable and 8-variable equations) are age-, sex-, and laboratory value–based, thereby enabling automated risk reporting whenever laboratory tests are performed.[7] The 4-variable equation requires age, sex, estimated glomerular filtration rate (eGFR), and urinary albumin to creatinine ratio (ACR), facilitating integration into clinical practice.

The kidney failure risk equations are widely used through electronic applications (eg, http://www.qxmd.com/calculate-online/nephrology/kidney-failure-risk-equation), with some initial validation in other countries and health care systems.[7-12] However, widespread adoption of the risk equations requires validation in additional populations including nonwhite ethnicities, patients not under nephrology care, and cohorts outside North America. Their accuracy in different geographic regions and patient populations is evaluated herein.

Methods

Participating Cohorts

Thirty-one cohorts participating in the Chronic Kidney Disease Prognosis Consortium (CKD-PC) were selected for validation based on data availability.[13] The CKD-PC is a collaborative research group integrating data from more than 50 cohorts spanning 40 countries and involving 2 million individuals.[13] The diverse cohorts include populations across a wide range of baseline risk of kidney failure. For the purpose of this analysis, cohorts were selected to include patients with stages 3 to 5 CKD with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 and an absence of kidney failure at baseline who had follow-up information on kidney failure, defined as treatment by dialysis or a kidney transplant. Data transfer and analysis took place between July 2012 and June 2015. Data in included cohorts were collected from September 1982 through October 2014. This study was approved for use of deidentified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, and the need for informed consent was waived.

Measurement of Variables in Cohorts

As in the original kidney failure risk equationss, GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation.[14] Serum creatinine concentrations were standardized to isotope dilution mass spectrometry–traceable methods where possible.[14] For studies in which creatinine measurements were not standardized to isotope dilution mass spectrometry, the creatinine levels were reduced by 5%, as previously reported.[15,16] Albuminuria was represented as a log-transformed urine ACR. Alternative measures of urine protein excretion (protein to creatinine ratio, 24-hour urine collection, urinary dipstick) were transformed to the ACR using previously developed equations.[6,17,18] When available, baseline values for serum albumin, phosphorous, calcium, and bicarbonate, as well as physical examination measures of weight, systolic and diastolic blood pressure, were derived from each cohort. Age, sex, and ethnicity (black or nonblack), as well as the presence of diabetes and hypertension, were also derived from the individual cohorts, with information on race collected as part of routine clinical care for the health systems and as demographic data for the study cohorts. Diabetes was defined as fasting glucose of at least 126.1 mg/dL (to convert glucose to mmol/L, multiply by 0.0555), nonfasting glucose of at least 200 mg/dL or glycated hemoglobin (HbA_{1c}) of at least 6.5%, use of glucose-lowering drugs, or self-reported diabetes. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive drugs for treatment of hypertension. Potential participants missing any baseline data were excluded from analysis. Information on individual cohorts is provided in eAppendix 1 in the Supplement.

Statistical Analysis

There were 4 kidney failure risk equations developed in the original cohorts: the 3-variable (age, sex, and eGFR), the 4-variable (3-variable + ACR), the 6-variable (4-variable + diabetes and hypertension), and the 8-variable equations (4-variable + calcium, phosphate, bicarbonate, and albumin). The 4-variable and 8-variable equations demonstrated the best performance in the original cohorts; thus, the focus of this validation effort centered on the 4-variable and 8-variable equations.

Participant-level data were analyzed for each individual cohort. Meta-analysis was performed across studies using a random-effects model. Risk relationships observed in the original cohorts were compared with those seen in the validation cohorts. Cox proportional hazards models were fit using the variables included in each of the original equations within each study, allowing both the regression coefficients and the baseline hazard to vary. All variables were centered (age, 70 years; 56% men, eGFR, 36 mL/min/1.73 m^2; ACR, 170 mg/g; phosphate, 3.9 mg/dL; albumin, 4.0 g/dL; bicarbonate, 25.6 mEq/L; and calcium, 9.4 mg/dL; to convert calcium to mmol/L, multiply by 0.25), as per the original study.[6] The refit coefficients were then pooled across studies using random-effects meta-analysis. Pooled and original coefficients were compared using the z test.[19]

Table 1. Baseline Characteristics of the Participating Cohorts[a]

Cohort	No. of Participants[b]	Follow-up Time, Median (IQI), y	Age, mean (SD), y	No. (%)		eGFR, mean (SD), mL/min/1.73 m^2	No. (%) of Participants With Albuminuria,[c]	No. of Kidney Failure Events[d]	Kidney Failure Incidence, per 1000 Patient-Years
				Men	Black Race				
North America									
AASK[e]	898	8 (4-10)	55 (11)	537 (60)	898 (100)	40 (12)	592 (66)	303	47.3
ARIC	722	12 (7-14)	67 (5)	332 (46)	171 (24)	50 (10)	192 (27)	112	15.0
BC CKD[e]	11 131	3 (2-5)	70 (13)	6042 (54)	44 (0.4)	31 (11)	7928 (71)	2091	52.5
CCF ACR[e]	4102	2 (1-4)	71 (11)	1950 (48)	747 (18)	48 (10)	1643 (40)	101	10.4
CCF DIP[e]	12 275	3 (1-4)	72 (13)	5457 (44)	1579 (13)	46 (11)	2835 (23)	300	10.3
CRIC[e]	3099	6 (4-7)	59 (11)	1720 (56)	1315 (42)	40 (11)	1866 (63)	796	49.4
Geisinger[e]	20 720	4 (2-6)	70 (10)	8605 (42)	211 (1)	51 (8)	1961 (44)	453	4.9
ICES-KDT[e]	100 569	4 (2-6)	73 (11)	46 883 (47)	0	46 (12)	39 611 (39)	3093	7.0
KEEP	16 425	4 (2-6)	69 (12)	5338 (32)	28 (2)	48 (10)	3961 (33)	500	7.0
KPNW[e]	1486	5 (3-6)	73 (10)	672 (45)	166 (11)	45 (11)	478 (32)	100	15.3
MDRD[e]	1459	6 (3-12)	52 (13)	891 (61)	921 (26)	33 (14)	921 (85)	1041	96.1
Mt Sinai BioMe[e]	3574	2 (1-5)	65 (13)	1620 (45)	0	42 (14)	970 (63)	525	47.7
Pima Indians	78	3 (1-5)	58 (14)	23 (29)	0	36 (15)	74 (95)	53	168.3
REGARDS	3158	7 (5-8)	72 (9)	1402 (44)	1308 (41)	47 (11)	1079 (36)	240	11.8
Sunnybrook[e]	3098	3 (2-5)	71 (14)	1758 (57)	0	37 (13)	1378 (75)	382	35.2
VA CKD	434 810	4 (3-4)	75 (9)	423 521 (97)	38 893 (9)	47 (11)	14 084 (41)	8836	5.0
Subtotal	617 604	4 (3-6)	74 (10)	506 751 (82)	50 251 (8)	46 (11)	79 573 (41)	18 926	7.5
Non-North America									
CRIB[e]	382	3 (1-7)	61 (14)	248 (65)	22 (6)	21 (11)	259 (84)	190	120.9
GCKD	3927	2 (2-3)	62 (11)	2412 (61)	0	42 (10)	2163 (56)	89	9.1
GLOMMS-1	1007	4 (1-6)	71 (13)	509 (51)	0	31 (9)	701 (70)	122	31.2
Gonryo	1088	3 (1-5)	66 (13)	652 (60)	0	32 (16)	343 (95)	345	100.9
HUNT	1060	13 (6-14)	75 (8)	393 (37)	0	49 (9)	313 (30)	55	5.3
Maccabi	58 630	5 (3-6)	73 (11)	25 820 (44)	0	49 (10)	10 938 (35)	1383	5.4
MASTERPLAN[e]	579	6 (4-6)	61 (12)	395 (68)	15 (3)	35 (12)	314 (54)	134	45.1
MMKD	140	4 (2-5)	49 (11)	89 (64)	0	30 (15)	133 (95)	70	131.3
NephroTest[e]	1317	3 (2-6)	61 (14)	919 (70)	151 (11)	35 (13)	857 (69)	292	55.4
NZDCS	8865	7 (4-8)	71 (11)	3903 (44)	6 (0.07)	43 (15)	1099 (15)	808	14.9
Okinawa 83	1698	17 (17-17)	69 (10)	419 (25)	0	51 (8)	599 (35)	55	1.9
Okinawa 93	15 162	7 (7-7)	70 (10)	4925 (32)	0	52 (7)	1090 (7)	131	1.2
RENAAL[e,f]	1434	3 (2-4)	60 (7)	890 (62)	199 (14)	37 (11)	1434 (100)	335	82.7
Severance	3173	10 (9-12)	60 (10)	1547 (49)	0	54 (7)	384 (12)	92	2.9
SRR CKD[e]	5291	2 (1-3)	69 (14)	3511 (66)	0	24 (9)	4335 (82)	802	75.8
Subtotal	103 753	4 (3-7)	71 (12)	46 632 (45)	393 (0.4)	47 (12)	24 962 (34)	4903	9.2
Overall total	721 357	4 (3-7)	74 (10)	55 3383 (77)	50 644 (7)	46 (11)	104 534 (40)	23829	7.8

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACR, urine albumen to creatinine ratio; ARIC, Atherosclerosis Risk in Communities; BC CKD, British Columbia Chronic Kidney Disease; CCF, Cleveland Clinic Foundation; CRIB, Chronic Renal Impairment in Birmingham; CRIC, Chronic Renal Insufficiency Cohort; DIP, dipstick protein; eGFR, estimated glomerular filtration rate; GCKD, German CKD; GLOMMS, Grampian Laboratory Outcomes, Morbidity and Mortality Studies; HUNT, Nord Trøndelag Health Study; ICES-KDT, Institute for Clinical Evaluative Sciences, Provincial Kidney, Dialysis, and Transplantation; IQI, interquartile interval; KEEP, Kidney Early Evaluation Program; KPNW, Kaiser Permanente Northwest; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients With the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease; NZDCS, New Zealand Diabetes Cohort Study; REGARDS, Reasons for Geographic and Racial Differences in Stroke Study; RENAAL, Reduction of Endpoints in Non–insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; SRR-CKD, Swedish Renal Registry CKD; VA CKD, Veterans Administration CKD.

[a] Representative references for each cohort are provided in eAppendix 3 in the Supplement.

[b] The number of participants represents the total number with data for the 3-variable equation.

[c] The proportion of participants with a urine albumin to creatinine ratio of 30 mg/g or higher, urine protein to creatinine ratio of 50 mg/g or higher, or a dipstick protein of 1+ or more. The proportion out of the total number of participants with data for the 4-variable equation is listed in eAppendix 1 in the Supplement.

[d] Kidney failure is defined as treatment by dialysis or a kidney transplant.

[e] Denotes cohorts that participated in the validation of the 8-variable equation.

[f] RENAAL contains participants from 28 countries, including the United States and Canada. However, because the majority of participants stemmed from non-North American countries, the cohort was classified as non-North American.

A set of pooled risk equations were developed to compare with the original risk equations. Pooled coefficients from the random-effects meta-analysis were combined with a pooled baseline hazard, defined as the average refit baseline hazard weighted by the number of kidney failure events.

Discrimination of the original and pooled kidney failure risk equations was assessed using the Harrell *C* statistic within each study, which was then meta-analyzed using random-effects models. Performance was also evaluated in predetermined subgroups of black or non-black race, presence or absence of diabetes mellitus, and age older or younger than 65 years. The discrimination of the original and pooled risk equations was compared by assessing the meta-analyzed difference in the *C* statistic within individual studies. Finally, within each set of original and pooled risk equations, the discrimination of the 4- vs 6- and 4- vs 8-variable risk equations was compared by meta-analyzing the difference in individual study *C* statistics (6-variable performance is reported in the supplementary materials).

Calibration (the difference between observed and predicted risk) was examined by plotting the observed 2-year and 5-year probability of kidney failure in individual cohorts and comparing it to the predicted risk using the original and pooled risk equations. This was done in 5 risk categories (for 2 years, 0% to <2%, 2% to <6%, 6% to <10%, 10% to <20%, and ≥20%; for 5 years, 0% to <5%, 5% to <15%, 15% to <25%, 25% to <50%, and ≥50%). In the absence of clinical practice guidelines that recommend risk cut-offs or strata for CKD progression, the risk categories used were adopted from the original development study and subsequent CKD-PC publications.[6] Calibration varied across cohorts; thus, factors that might explain heterogeneity in baseline risk were investigated by regressing cohort-specific baseline risk on cohort characteristics (eg, region of cohort, mean eGFR, proportion of the cohort with black race, diabetes mellitus, and hypertension). Baseline risk was estimated for each cohort using Cox proportional hazards models, holding the variable coefficients constant and equal to the original risk equations regression coefficients but allowing the intercept to vary. The only cohort characteristic associated with cohort-specific baseline hazard was region of cohort, with higher baseline risk in North American cohorts compared with non-North American cohorts.

Regional variation in baseline risk was addressed through the development of 2 regional calibration factors (North America and non-North America). The regional calibration factors were developed as the ratio of the event-weighted regional mean to the original baseline hazard. A Brier score, the squared difference between the observed vs predicted binary outcomes (observed minus predicted risk), was used to evaluate whether calibration improved with the "regional-calibrated original" risk equations, in each study.[20] The Wilcoxon sign-rank test was used to evaluate the differences in Brier score between original and regional-calibrated original risk equations. An overall Brier score was calculated using event-weighted means. The square root of this overall score was reported as the root-mean-squared error between observed and predicted risk. A *P* value <.05 was considered statistically significant. All tests were 2-sided. All analyses were performed using Stata MP 13 (StataCorp).

Table 2. Hazard Ratios for Kidney Failure of the Component Variables in the Original vs Pooled 4- and 8-Variable Equations

	Hazard Ratio (95% CI)	
	Original	Pooled
4-Variable Equation		
Age per 10 years older	0.80 (0.75-0.86)	0.80 (0.76-0.84)
Men	1.28 (1.04-1.58)	1.38 (1.29-1.48)
eGFR per 5 mL/min/1.73 m^2	0.57 (0.54-0.61)	0.63 (0.60-0.67)[a]
ACR per log increase	1.57 (1.44-1.71)	1.56 (1.47-1.67)
8-Variable Equation		
Age per 10 years older	0.82 (0.77-0.88)	0.83 (0.80-0.86)
Men	1.17 (0.95-1.46)	1.34 (1.24-1.44)
eGFR per 5 mL/min/1.73m^2	0.61 (0.58-0.65)	0.66 (0.62-0.70
ACR per log increase	1.40 (1.28-1.53)	1.42 (1.30-1.54)
Calcium per 1 mg/dL	0.80 (0.68-0.95)	0.85 (0.79-0.93)
Phosphate per 1 mg/dL	1.30 (1.18-1.43)	1.17 (1.11-1.24)
Bicarbonate per 1 mEq/L	0.93 (0.90-0.96)	0.99 (0.98-1.00)[b]
Albumin per 1 g/dL	0.71 (0.56-0.90)	0.70 (0.61-0.80)

Abbreviations: ACR, urine albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

SI conversion factors: to convert calcium from mg/dL to mmol/L, multiply by 0.25.

[a] *P*<.05.

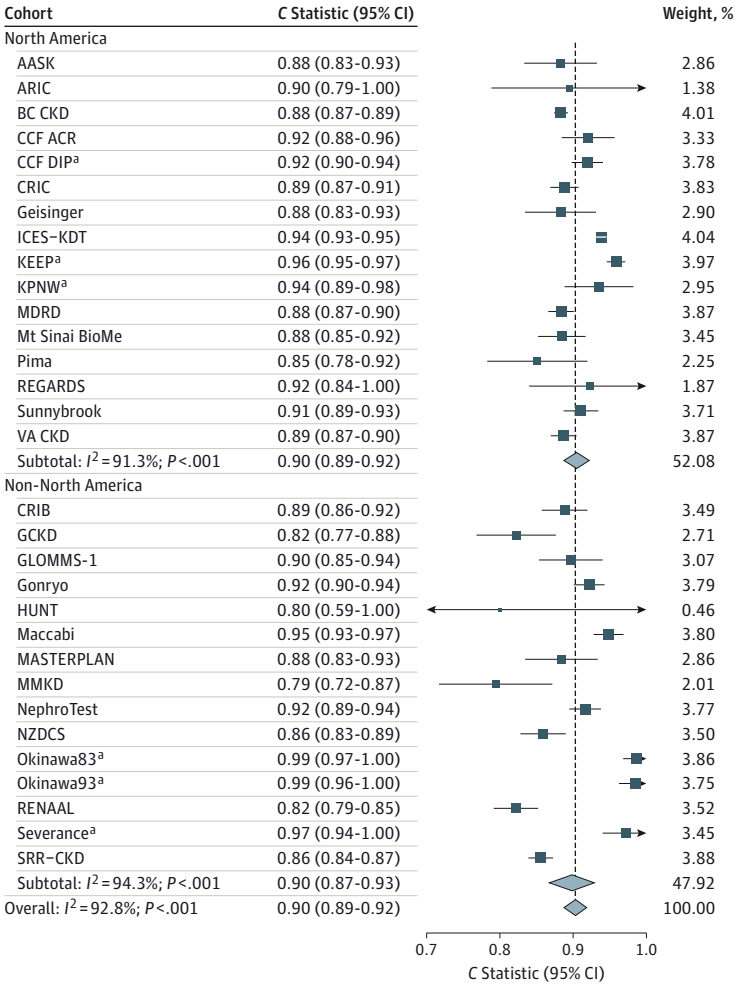
[b] *P*<.001.

Results

There were 721 357 CKD patients and 23 829 kidney failure events in 31 cohorts with an average follow-up time of 4.2 years (**Table 1**). A total of 16 cohorts (617 604 patients) were based in North America, and 15 cohorts (103 753 patients) were from Asia, Europe, and Australasia. Missing data varied by cohort (median of 0% for the 4-, 1% for the 6-, and 41% for the 8-variable equations; eAppendix 1 in the Supplement). The amount of missing data was higher in North American cohorts (median missing of 2% for the 4-, 3% for the 6-, and 79% for the 8-variableequations) than in non-North American cohorts (median missing of 0% for the 4-, 1% for the 6-, and 9% for the 8-variable equations). All 31 cohorts had the variables necessary to validate the 4-variable, 29 cohorts had the variables necessary to validate the 6-variable, and 16 cohorts had the variables necessary to validate the 8-variable equations.

The mean age of the study population was 74 years, and the mean baseline eGFR was 46 mL/min/1.73 m^2. Cohorts ranged from being predominantly men (Veterans Administration CKD, 97%) to majority women (Okinawa 83, 75%). Forty percent of the patients had diabetes, and 84% had hypertension (eTable 1 in the Supplement). Forty percent of the study participants had a baseline urinary ACR of 30 mg/g or greater. The observed incidence of kidney failure ranged from 1.2 events per 1000 person-years in Okinawa to 168.3 events per 1000

Figure 1. Discrimination Statistics (*C* Statistics) for Original 4-Variable Equation at 2 Years by Cohort



Due to a limited number of events, confidence intervals were wide in some studies and therefore capped at 1.00 (maximum value for *C* statistic). Size is proportional to the weight of the study in a random effects meta-analysis. Arrows indicate that the true values are beyond the range of the axis. The dotted line indicates the overall *C* statistic. Representative references and expanded acronyms for each cohort name are provided in eAppendix 3 in the Supplement.

[a] Cohort with dipstick proteinuria.

person-years in the Pima Indian cohort. According to the original 4-variable equation, the proportion of each cohort that had a more than 20% 2-year predicted probability of kidney failure ranged from 0.23% (Okinawa 93 cohort) to 50% (Chronic Renal Impairment in Birmingham cohort).

Variable Coefficients in the Original and Pooled Kidney Failure Risk Equation

In general, coefficients for the association between different characteristics (eg, age, sex, eGFR, ACR) and the risk of kidney failure were similar in the original and pooled equations (**Table 2**). Exceptions were eGFR in the 4-variable equations (original vs pooled: HR, 0.57 vs 0.63 per 5 mL/min/1.73 m^2 higher eGFR) and serum bicarbonate in the 8-variable equations (0.93 vs 0.99 per 1 mEq/L higher serum bicarbonate), both of which were stronger in the original kidney failure risk equation.

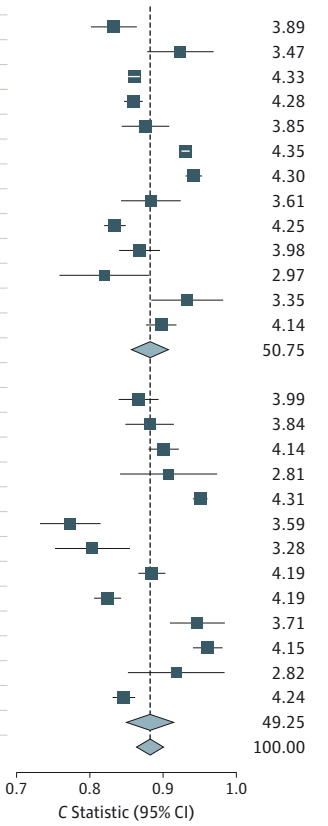
Discrimination

Measures of discrimination for the original 4-variable risk equation were excellent for the 2-year and 5-year predicted probability of kidney failure (**Figure 1** and **Figure 2**). Overall, the 4-variable equation had a pooled *C* statistic of 0.90 (95% CI, 0.89-0.92) at 2 years, and 0.88 (95% CI, 0.86-0.90) at 5 years. Within individual cohorts, discrimination was also excellent, with a *C* statistic of at least 0.80 in all but 2 cohorts; the MMKD (Mild to Moderate Kidney Disease) study 2-year *C* statistic was 0.79 (95% CI, 0.72-0.87) and the MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner) study 5-year *C* statistic was 0.77 (95% CI, 0.73-0.81). Discrimination for the original 8-variable risk equation was 0.89 (95% CI, 0.88-0.91) at 2 years and 0.86 (95% CI, 0.84-0.87) at 5 years (eFigure 1 in the Supplement). In prespecified subgroups of age, sex, race, region, and diabetes status, discrimination was qualitatively unchanged, with *C* statistics for the 4-variable equation ranging from 0.90 to 0.92 for 2 years and 0.87 to 0.89 for 5 years (**Figure 3**). Similar statistics for the 6-variable equation are shown in eFigure 2 in the Supplement.

In general, the pooled 4- and 8-variable equations resulted in similar discrimination to the original equations (eTables 2-7 in the Supplement). There was no significant difference in the overall *C* statistics of the pooled and the original kidney failure risk equations (eg, 4-variable risk equation over 2 years: −0.0006; 95% CI, −0.0020 to 0.0008). When

Figure 2. Discrimination Statistics (*C* Statistics) for Original 4-Variable Equation at 5 Years by Cohort

Cohort	*C* Statistic (95% CI)	Weight, %
North America		
AASK	0.83 (0.80-0.86)	3.89
ARIC	0.92 (0.88-0.97)	3.47
BC CKD	0.86 (0.85-0.87)	4.33
CRIC	0.86 (0.85-0.87)	4.28
Geisinger	0.88 (0.84-0.91)	3.85
ICES–KDT	0.93 (0.93-0.94)	4.35
KEEP[a]	0.94 (0.93-0.95)	4.30
KPNW[a]	0.88 (0.84-0.92)	3.61
MDRD	0.83 (0.82-0.85)	4.25
Mt Sinai BioMe	0.87 (0.84-0.90)	3.98
Pima	0.82 (0.76-0.88)	2.97
REGARDS	0.93 (0.88-0.98)	3.35
Sunnybrook	0.90 (0.88-0.92)	4.14
Subtotal: I^2 = 97.1%, *P* < .001	0.88 (0.86-0.91)	50.75
Non-North America		
CRIB	0.87 (0.84-0.89)	3.99
GLOMMS-1	0.88 (0.85-0.91)	3.84
Gonryo	0.90 (0.88-0.92)	4.14
HUNT	0.91 (0.84-0.97)	2.81
Maccabi	0.95 (0.94-0.96)	4.31
MASTERPLAN	0.77 (0.73-0.81)	3.59
MMKD	0.80 (0.75-0.85)	3.28
NephroTest	0.88 (0.87-0.90)	4.19
NZDCS	0.82 (0.81-0.84)	4.19
Okinawa83[a]	0.95 (0.91-0.98)	3.71
Okinawa93[a]	0.96 (0.94-0.98)	4.15
Severance[a]	0.92 (0.85-0.98)	2.82
SRR–CKD	0.85 (0.83-0.86)	4.24
Subtotal: I^2 = 96.1%, *P* < .001	0.88 (0.85-0.91)	49.25
Overall: I^2 = 96.5%, *P* < .001	0.88 (0.86-0.90)	100.00



Due to a limited number of events, confidence intervals were wide in some studies and therefore capped at 1.00 (maximum value for C statistic). Size is proportional to the weight of the study in a random effects meta-analysis. The dotted line indicates the overall *C* statistic. Representative references and expanded acronyms for each cohort name are provided in eAppendix 3 in the Supplement.

[a] Cohort with dipstick proteinuria.

2-year risk in all 31 cohorts was assessed individually, the pooled 4-variable equation performed significantly better than the original 4-variable equation in 5 cohorts, and in 5 cohorts it performed significantly worse (*P* < .05 for each comparison).

Discrimination of the 8-variable risk equation was slightly better than the 4-variable equation in cohorts that had the necessary components for both equations (eTables 8 and 9 in the Supplement). This was true using either the original or the pooled risk equations and in nearly all subgroups of interest.

Calibration

Plots of the observed vs predicted risk demonstrated differences in calibration, with suboptimal performance in some of the non-North American cohorts (eFigures 3-6 for the North American cohorts; eFigures 7-10 for the non-North American cohorts, both in the Supplement). Baseline risk varied by region, with higher levels in North America compared with non-North America using the 4-variable equation (**Figure 4**). There was slightly less variation in baseline risk by region using the 8-variable equation (eFigure 11 in the Supplement). In non-North American studies, use of a regional calibration factor that lowered the baseline risk by 32.9% at 2 years and 16.5% at 5 years decreased the root mean-squared distance of the observed to expected risk from 0.237 to 0.228 at 2 years and 0.299 to 0.287 at 5 years for the 4-variable equation and improved performance in 12 out of 15 studies at 2 years (*P* = .04) and 10 out of 13 studies at 5 years (*P* = .02) (eTable 10 in the Supplement). In contrast, use of a regional calibration factor in North American cohorts, the region where the kidney failure risk equations were developed, did not significantly improve performance. For example, the root mean-squared distance of the observed to expected risk at 2 years only minimally changed from 0.152 to 0.151 with the addition of the calibration factor and increased from 0.264 to 0.272 at 5 years for the 4-variable equation. eAppendix 2 in the Supplement shows all equations.

Discussion

In this collaborative meta-analysis involving 721 357 patients across 31 cohorts and over 30 countries, the kidney failure risk equations accurately predict the 2-year and 5-year probability of kidney failure in patients with CKD with a wide range of variation in age, sex, race, and in the presence or absence of diabetes.

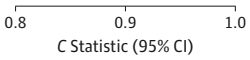
The original equations reported by Tangri et al[6] demonstrated excellent discrimination and appropriate calibration in the majority of the North American cohorts, and the addition of a recalibration factor optimized performance in non-North American populations. The 4-variable equation (age, sex, eGFR, and albuminuria) can be easily implemented in electronic

Figure 3. Discrimination Statistics (C Statistics) for Original 4-Variable and 8-Variable Equations at 2 and 5 Years by Subgroup

A 4-Variable equation

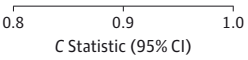
2-Year predicted probability of kidney failure

Cohort	No. of Patients	C Statistic (95% CI)
Diabetes		
Yes	140 947	0.897 (0.869-0.924)
No	126 536	0.918 (0.898-0.937)
Black		
Yes	13 125	0.910 (0.892-0.928)
No	236 463	0.896 (0.879-0.914)
Age, y		
≥65	196 626	0.903 (0.879-0.926)
<65	70 847	0.898 (0.874-0.922)



5-Year predicted probability of kidney failure

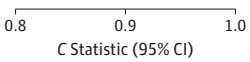
Cohort	No. of Patients	C Statistic (95% CI)
Diabetes		
Yes	105 343	0.881 (0.863-0.900)
No	118 543	0.893 (0.873-0.914)
Black		
Yes	8997	0.884 (0.856-0.912)
No	199 073	0.878 (0.857-0.899)
Age, y		
≥65	162 600	0.885 (0.857-0.913)
<65	61 276	0.874 (0.851-0.897)



B 8-Variable equation

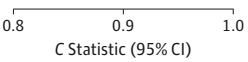
2-Year predicted probability of kidney failure

Cohort	No. of Patients	C Statistic (95% CI)
Diabetes		
Yes	17 770	0.890 (0.874-0.906)
No	22 223	0.902 (0.889-0.915)
Black		
Yes	3311	0.892 (0.874-0.909)
No	31 420	0.898 (0.886-0.911)
Age, y		
≥65	24 336	0.905 (0.882-0.927)
<65	15 678	0.891 (0.876-0.905)



5-Year predicted probability of kidney failure

Cohort	No. of Patients	C Statistic (95% CI)
Diabetes		
Yes	16 040	0.862 (0.848-0.875)
No	22 223	0.867 (0.847-0.887)
Black		
Yes	2991	0.851 (0.827-0.876)
No	30 307	0.867 (0.850-0.884)
Age, y		
≥65	23 527	0.874 (0.858-0.889)
<65	14 513	0.853 (0.834-0.871)



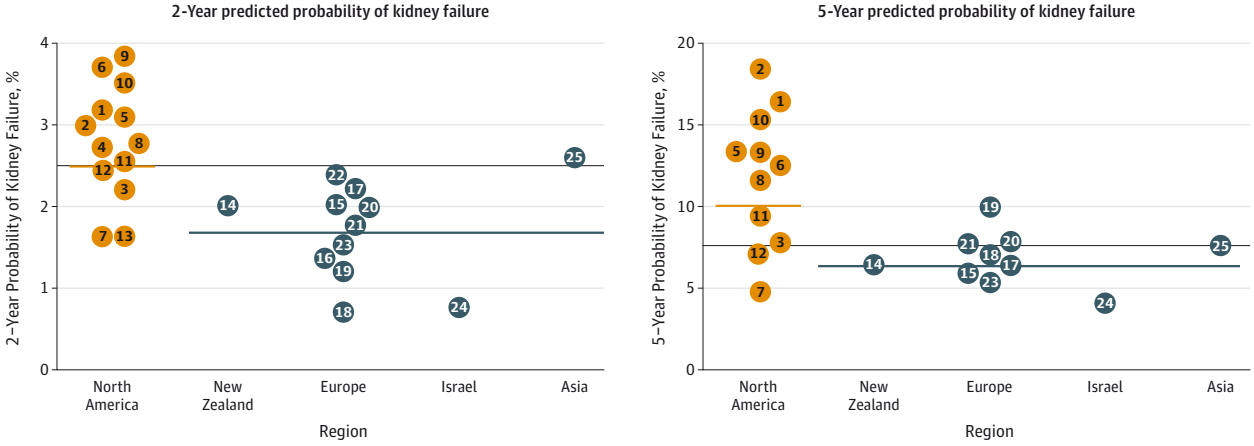
In the 4-variable equation analyses, 31 cohorts contributed to the 2-year analysis and 26 cohorts to the 5-year analysis. In the 8-variable equation analyses, 16 cohorts contributed to 2-year analysis and 11 cohorts contributed to the 5-year analysis.

medical records and laboratory information systems. The use of this equation is consistent with the Kidney Disease Improving Global Outcomes (KDIGO) guideline, which recommends integration of risk prediction in the evaluation and management of CKD[21] and is in agreement with a strong body of evidence demonstrating the importance of eGFR and albuminuria in predicting prognosis.[13,15,22-35]

Previous investigators developed alternative risk prediction models for progression of CKD to kidney failure,[36] but most have not been externally validated. The kidney failure risk equations developed by Tangri et al[6] were externally validated in a cohort of Canadian CKD patients referred for nephrology care, but their accuracy in nonreferred patients and regions outside Canada remained unknown. Thus, current clinical practice guidelines recommended the use of risk equations for predicting prognosis and planning dialysis access, but with appropriate caution regarding their external validity.[37] The current validation study addresses these concerns, and more widespread clinical assessment can now be recommended. Similar to previous work, an incremental improvement in performance was observed with an 8-variable risk equation, which additionally includes serum albumin, phosphate, bicarbonate, and calcium levels over the 4-variable equation. The magnitude of improvement was smaller than in the original study but may be meaningful for patients for whom data for both equations is readily available. These findings suggest that the 4-variable risk equation might be adopted more widely, but the 8-variable equation should be made available if the additional variables are obtained and increased precision is desired.

The risk associations observed in the pooled validation sample were similar to those in the original kidney failure risk equation. In particular, younger age, male sex, lower eGFR, and higher albuminuria were associated with a higher risk of kidney failure defined by treatment with dialysis or transplant. The finding of lower risk of kidney failure with older age is consistent with the previous literature[25] and is likely due to a combination of factors: 1) the same disease process (eg, diabetic nephropathy in a patient with type 1 diabetes with age of diagnosis at 15 years) is more likely to be indolent, if the patient has an eGFR of 30 mL/min/1.73 m^2 at age 75 years (60 years of exposure) vs age 45 years (30 years of exposure); 2) as patients age, they are more likely to die from a competing cause (malignancy, cardiovascular disease) than reach kidney failure; and 3) older patients may be more likely to choose conservative care for kidney failure rather than treatment with dialysis or transplant, our primary outcome.[38] It is important to note that in the original development of the risk equation,[6] competing risk models were evaluated and a threshold of eGFR of less than 10 mL/min/1.73 m^2 was tested as a secondary out-

Figure 4. Refit Baseline Hazard of Original 4-Variable Equation at 2 and 5 Years in Individual Cohorts Stratified by Region



North America													
Cohort No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Cohort Name	AASK	ARIC	BC CKD	CCF ACR	CRIC	Geisinger	ICES-KDT	MDRD	Mt Sinai BioMe	Pima	REGARDS	Sunnybrook	VA CKD

Non-North America												
Cohort No.	14	15	16	17	18	19	20	21	22	23	24	25
Cohort Name	NZDCS	CRIB	GCKD	GLOMMS-1	HUNT	MASTERPLAN	MMKD	NephroTest	RENAAL	SRR-CKD	Maccabi	Gonryo

Horizontal gray line represents the centered baseline hazard for the original 4-variable kidney failure risk equation (age 70 years; male, 56%; eGFR, 36 mL/min/1.73 m^2; urine albumin to creatinine ratio, 170 mg/g); the orange and blue horizontal lines represent the weighted mean refit baseline hazard within each region (North America and non-North America). The 25 cohorts included represent studies with available urine albumin to creatinine ratio. Studies with dipstick proteinuria were not included in the calculation. See Table 1 footnotes for expansion of cohort abbreviations.

come; no differences in the performance of the kidney failure risk equations was observed.

Although recalibration was not needed in most North American cohorts, adding a regional calibration factor in non-North American cohorts improved calibration and would allow the risk equations to be used clinically in countries with different levels of baseline risk. This is similar to the Framingham Heart Study equation, which is used for estimating cardiovascular risk and has been recalibrated for use in multiple different populations.[19] Differences in baseline risk between cohorts and regions may reflect different cohort inclusion criteria or treatment preferences for kidney failure rather than physiological differences in disease progression because risk relationships between the risk factors and kidney failure were fairly uniform across settings. Further studies examining additional causes of heterogeneity in higher- vs lower-risk populations are needed.

There are important clinical and research implications to this study's findings. Clinicians can now use the 4- or 8-variable kidney failure risk equations, with the recalibration factor where applicable, that can inform patient-clinician communication and treatment decisions regarding the absolute risk of kidney failure, rather than the CKD stage alone. Decisions regarding access placement or transplant referral could be made once kidney failure risk thresholds are exceeded. Some kidney failure risk thresholds have been proposed on the basis of physician surveys and decision analyses (>3% or 5% risk for 5 years for nephrology referral, >20% or 40% risk over 2 years for vascular access planning), and should be evaluated further in cluster randomized trials or time series analyses. Routine reporting and clinical implementation is already under way in several centers, and its effect on patient care and health services is being studied. From a research perspective, the risk equation can be used to estimate event rates and statistical power for kidney failure outcomes in clinical trials and may be useful in selecting higher-risk patients for trial inclusion and identifying risk-treatment interactions.[39,40]

This study has limitations. First, the risk equation does not assess kidney failure risk in patients with CKD stages G1 (GFR ≥90 mL/min/1.73m^2) and G2 (GFR 60-89 mL/min/1.73m^2). Previous studies have shown that patients with stages G1 to G2 and high levels of albuminuria should be considered as high risk. Second, due to the variables required, validation of the 8-variable equation was not possible in all cohorts. Therefore, nested comparisons between equations are limited to a subset. In some cohorts, proteinuria was converted to albuminuria. Although no meaningful differences in discrimination were observed in these populations, it is possible that risk relationships may differ slightly for the 2 measures. Furthermore, even with the inclusion of more than 700 000 participants in more than 30 countries, there was not significant representation from countries where there is limited access to renal replacement therapy. Validation in these countries with a combined end point of treated and untreated kidney failure should be performed. Third, there were missing data, particularly in the North American health systems. Missing data reduce the generalizability of our findings to North American health sys-

tems. However, results reflect data available in clinical health systems. Fourth, the risk equations provide the risk of kidney failure over 2 and 5 years. These time frames are important for decisions regarding nephrology referral, dialysis access planning, and preemptive transplant (ie, kidney transplant prior to receiving dialysis), but they do not capture longer-term risk of kidney failure, which may affect other clinical decisions such as lifestyle modification.[41] Fifth, the kidney failure risk equation incorporates routinely collected laboratory data. Accuracy of risk predictions may be enhanced in specific subpopulations by novel biomarkers of CKD; however, the incremental gain in predictive accuracy may not be justified by the cost of these newer assays for the entire CKD population.[42] Sixth, there is no evidence that using the equation will improve outcomes. Well-designed pragmatic randomized trials are needed to definitively establish the evidence for efficacy.

Strengths of this study include the large patient population and accompanying diversity in age, sex, race, and etiology of kidney disease. In North America, the 4-variable original risk equation appears generalizable and highly accurate in most cohorts and can be easily implemented across multiple health care systems. Elsewhere, the recalibrated risk equation appears more accurate and can also be integrated into health care platforms. Partnerships with mobile technology developers and health care systems may ensure that knowledge translation occurs without long delays, which are common in biomedical research.

Conclusions

Kidney failure risk equations developed in a Canadian population showed high discrimination and adequate calibration when validated in 31 multinational cohorts. However, in some regions the addition of a calibration factor may be necessary.

ARTICLE INFORMATION

Correction: The wrong version of the article that was published has been corrected on January 25, 2016.

Author Affiliations: Department of Medicine, Seven Oaks General Hospital, University of Manitoba, Winnipeg, Canada (Tangri); Department of Community Health Sciences, Seven Oaks General Hospital, University of Manitoba, Winnipeg, Canada (Tangri); Johns Hopkins Medical Institutions, Baltimore, Maryland (Grams, Appel); Division of Nephrology at Tufts Medical Center, Boston, Massachusetts (Levey, Inker, Sarnak); Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Coresh, Appel, Woodward); Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison (Astor); Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison (Astor); Medical Division, Maccabi Healthcare Services, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Chodick); Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, Minnesota (Collins); Department of Medicine, University of Minnesota, Minneapolis (Collins); Department of Measurement & Reporting, Provincial Health Service Authority, Vancouver, British Columbia, Canada (Djurdjev); Department of General Practice and Primary Health Care, School of Population Health, University of Auckland, Auckland, New Zealand (Elley); Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden (Evans); Departments of Medicine and Epidemiology and Biostatistics, Western University, and Institute for Clinical Evaluative Sciences, Ontario, Canada (Garg); Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science Technology, Trondheim (Hallan); Division of Nephrology, Department of Medicine, St Olav University Hospital, Trondheim, Norway (Hallan); Division of Nephrology, Endocrinology and Vascular Medicine, Department of Medicine, Tohoku University School of Medicine, Sendai, Japan (Ito); Department of Epidemiology and Health Promotion, Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea (Jee); Memphis Veterans Affairs Medical Center, Memphis, Tennessee (Kovesdy); University of Tennessee Health Science Center, Memphis, Tennessee (Kovesdy); Department of Medical Genetics, Molecular and Clinical Pharmacology, Division of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria (Kronenberg); Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, the Netherlands (Heerspink); Division of Applied Health Sciences, University of Aberdeen, and NHS Grampian, Foresterhill, Aberdeen, Scotland (Marks); Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York (Nadkarni); Division of Nephrology and Hypertension, Cleveland Clinic, Cleveland, Ohio (Navaneethan); National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona (Nelson); Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany (Titze); CESP, INSERM, Villejuif, France (Stengel); Université Paris-Saclay, Université Paris-Sud, UVSQ, Villejuif, France (Stengel); The George Institute for Global Health, Nuffield Department of Population Health, University of Oxford, Oxford, England (Woodward); The George Institute for Global Health, University of Sydney, Sydney, Australia (Woodward); Dialysis Unit, University Hospital of the Ryukyus, Nishihara, Okinawa, Japan (Iseki).

Author Contributions: Dr Coresh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tangri, Grams, Levey, Coresh,Sarnak, Stengel, Woodward, Iseki.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tangri, Grams, Levey, Coresh, Woodward, Iseki.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Grams, Coresh,Woodward.
Obtained funding: Coresh.
Administrative, technical, or material support: Grams, Coresh.
Study supervision: Tangri, Grams, Levey, Coresh, Sarnak, Stengel, Woodward, Iseki.

CKD-PC investigators/collaborators: (Study acronyms/abbreviations are listed in eAppendix 3 in the Supplement.)

AASK: Jackson T. Wright, Jr, MD, PhD, Case Western Reserve University; Lawrence J. Appel, MD, MPH, Johns Hopkins University; Tom Greene, PhD, University of Utah; and Brad C. Astor, PhD, MPH, University of Wisconsin. **ARIC:** Josef Coresh, MD, PhD, Kunihiro Matsushita, MD, PhD, Morgan E. Grams, MD, PhD, and Yingying Sang, MS, Johns Hopkins University. **British Columbia CKD:** Adeera Levin, MD, FRCPC, BC Provincial Renal Agency and University of British Columbia and Ognjenka Djurdjev, MSc, BC Provincial Renal Agency and Provincial Health Services Authority. **CCF:** Sankar D Navaneethan, MD, MPH, Joseph V. Nally, Jr, MD, and Jesse D. Schold, PhD, Cleveland Clinic. **CRIB:** David C. Wheeler, MD, FRCP, University College London; Jonathan Emberson, PhD, University of Oxford; Jonathan N. Townend, MD, FRCP, Queen Elizabeth Hospital Birmingham; and Martin J. Landray, PhD, FRCP, University of Oxford. **CRIC:** Lawrence J. Appel, MD, MPH, Johns Hopkins University; Harold Feldman, MD, MsCE, University of Pennsylvania; Chi-yuan Hsu, MD, MSc, University of California-San Francisco. **GCKD:** Kai-Uwe Eckardt, MD, University of Erlangen-Nürnberg; Anna Kottgen, MD, MPH, University of Freiburg; Florian Kronenberg, MD, Medical University of Innsbruck; and Stephanie Titze, MD, MSc, University of Erlangen-Nürnberg. **Geisinger:** Jamie Green, MD, MS, H. Lester Kirchner, PhD, and Robert Perkins, MD, and Alex R. Chang, MD, MS, Geisinger Medical Center, Danville, Pennsylvania. **GLOMMS-1 Study:** Corri Black, MBChB, MRCP, MSc, MFPH, FFPH, University of Aberdeen; Angharad Marks, MBBCh, MRCP, MSc, PhD, University of Aberdeen; Nick Fluck, BSc, MBBC, DPhil, FRCP, NHS Grampian, Aberdeen; Dr Laura Clark, MBChB, MD, MRCP, NHS Grampian, Aberdeen; and Gordon J. Prescott, BSc, MSc, PhD, CStat, University of Aberdeen. **Gonryo:** Sadayoshi Ito, MD, PhD, Tohoku University School of Medicine, Japan; Mariko Miyazaki, MD, Tohoku University School of Medicine; Masaaki Nakayama, MD, Fukushima Medical University and Tohoku University School of Medicine; and Gen Yamada, MD, Tohoku University School of Medicine. **HUNT:** Stein Hallan, MD, PhD, Norwegian University of

Science and Technology and St Olav University; Knut Aasarød, MD, PhD, Norwegian University of Science and Technology and St Olav University Hospital; and Solfrid Romundstad, MD, PhD, Norwegian University of Science and Technology. **ICES-KDT:** Amit X. Garg, MD, PhD, Western University and Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program; Eric McArthur, MSc, Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program; Gihad Nesrallah, MD, MSc, Humber Regional Hospital, Keenan Research Centre, St Michael's Hospital, and Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program; and S Joseph Kim, MD, PhD, Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program. **Pima Indian:** Robert G. Nelson, MD, PhD, and William C. Knowler, MD, DrPH, US National Institute of Diabetes and Digestive and Kidney Diseases. **REGARDS:** David G. Warnock, MD, University of Alabama at Birmingham; Paul Muntner, PhD, University of Alabama at Birmingham; Suzanne Judd, PhD, University of Alabama at Birmingham; William McClellan, MD, MPH, Emory University; and Orlando Gutierrez, MD, MMSc, University of Alabama at Birmingham. **Kaiser Permanente NW:** David H. Smith, RPh, PhD, Micah L Thorp, DO, MPH, and Eric S Johnson, PhD, Kaiser Permanente Northwest. **KEEP:** Allan J. Collins, MD, University of Minnesota and Minneapolis Medical Research Foundation, Shu-Cheng Chen, MS, MPH, and Suying Li, PhD, Minneapolis Medical Research Foundation. **Maccabi:** Gabriel Chodick, PhD, Maccabi Healthcare Services and Tel Aviv University, Israel; Varda Shalev, MD, Maccabi Healthcare Services and Tel Aviv University; Nachman Ash, MD, Maccabi Healthcare Services; and Bracha Shainberg, PhD, Maccabi Healthcare Services. **MASTERPLAN:** Jack F. M. Wetzels, MD, PhD, Radboud University Medical Centre, Nijmegen; Peter J. Blankestijn, MD, PhD, University Medical Center Utrecht; and Arjan D. van Zuilen, MD, PhD University Medical Center Utrecht. **MDRD:** Mark J. Sarnak, MD, MS, Andrew S. Levey, MD, Lesley A. Inker, MD, MS, and Vandana Menon, MD, PhD, Tufts Medical Center. **MMKD:** Florian Kronenberg, MD, Medical University of Innsbruck; Barbara Kollerits, PhD, MPH, Medical University of Innsbruck; and Eberhard Ritz, MD, Ruprecht-Karls-University. **Mt Sinai BioMe:** Girish N. Nadkarni, MD, MPH, Erwin P. Bottinger, MD, Stephen B. Ellis, and Rajiv Nadukuru, Icahn School of Medicine at Mount Sinai. **NephroTest:** Marc Froissart, MD, PhD, Inserm U1018; Benedicte Stengel, MD, PhD, Inserm U1018 and University of Paris Sud-11; Marie Metzger, PhD, Inserm U1018 and University of Paris Sud-11; Jean-Philippe Haymann, MD, PhD, Sorbonne Universités, UPMC Univ Paris 06, Assistance Publique-Hôpitaux de Paris; Pascal Houillier, MD, PhD, Assistance Publique-Hôpitaux de Paris, Paris Descartes University, France; and Martin Flamant, MD, PhD, Assistance Publique-Hôpitaux de Paris. **NZDCS:** C. Raina Elley, MBCHB, PhD, Timothy Kenealy, MBCHB, PhD, and Simon A. Moyes, MSc, University of Auckland; and John F. Collins, MBCHB, and Paul L. Drury, MA, MB, BCHIR, Auckland District Health Board. **Okinawa 83/93:** Kunitoshi Iseki, MD, University Hospital of the Ryukyus. **RENAAL:** Hiddo J. L. Lambers Heerspink, PharmD, PhD, University of Groningen; Barry E. Brenner, MD, PhD, Brigham and Women's Hospital and Harvard School of Medicine; and Dick de Zeeuw, MD, PhD, University of Groningen. **Severance:** Sun Ha Jee, PhD, Heejin Kimm, MD, PhD, and Yejin Mok, MPH, Yonsei University. **SRR-CKD:** Marie Evans, MD, PhD, Karolinska Institutet and Swedish Renal Registry and Maria Stendahl, MD, PhD, Swedish Renal Registry and Hospital of Ryhov. **Sunnybrook:** Navdeep Tangri, MD, PhD, FRCPC, University of Manitoba; Maneesh Sud, MD, University of Toronto; David Naimark, MD, MSc, FRCPC, University of Toronto. **VA CKD:** Csaba P. Kovesdy, MD, Memphis Veterans Affairs Medical Center and University of Tennessee Health Science Center; and Kamyar Kalantar-Zadeh, MD, MPH, PhD, University of California Irvine Medical Center.

CKD-PC Steering Committee: Josef Coresh, MD, PhD (chair), Johns Hopkins University; Ron T. Gansevoort, MD, PhD, University Medical Center Groningen; Morgan E. Grams, MD, PhD, Johns Hopkins University; Paul E. de Jong, MD, PhD, University Medical Center Groningen; Kunitoshi Iseki, MD, University Hospital of the Ryukyus; Andrew S. Levey, MD, Tufts Medical Center; Kunihiro Matsushita, MD, PhD, Johns Hopkins University; Mark J. Sarnak, MD, MS, Tufts Medical Center; Benedicte Stengel, MD, PhD, Inserm U1018 and University of Paris Sud; David Warnock, MD, University of Alabama at Birmingham; and Mark Woodward, PhD, George Institute and Johns Hopkins University.

CKD-PC Data Coordinating Center (Johns Hopkins University): Shoshana H. Ballew, PhD (assistant project director), Josef Coresh, MD, PhD, (principal investigator), Morgan E. Grams, MD, PhD (director of nephrology initiatives); Kunihiro Matsushita, MD, PhD (director); Yingying Sang, MS (lead programmer); and Mark Woodward, PhD (senior statistician) (also at George Institute).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Tangri reports receiving honoraria from Takeda Inc and serving on the advisory boards Takeda Inc and Otsuka. Dr Levey reports having a patent application pending for GFR estimation and serves as the principal investigator for CKD-EPI, and served as the chair for the Kidney Disease Outcomes Quality Initiative (KDOQI) Guideline 2012. Dr Coresh reports receiving grants from the National Kidney Foundation and Kidney Disease Improving Global Outcomes and having a patent pending for GFR estimation. Dr Chodick reports receiving grants from Amgen, Merck, Astra Zeneca, ZS Pharma, serving as a consultant for Hospira, NxStage, and Relypsa, and as a data safety and monitoring committee member for Bayer. Dr Elley reports receiving grants from the New Zealand Society for the Study of Diabetes. Dr Evans reports receiving payments for lectures from Amgen. Dr Garg reports receiving grants from Astellas. Dr Inker reports receiving grants from Pharmalink AB, Otsuka, and Gilead Sciences and has a patent pending on GFR estimation. Dr Kovesdy reports receiving personal fees from Abbott, Amgen, NPS, sanofi-aventis, ZS Pharma, and Relypsa, grants from the National Institutes of Health; grant support from Abbvie, Amgen, OPKO, Shire; and royalties for being an author of 2 chapters in *UpToDate*. Dr Heerspink reports receiving grants support Astra Zeneca and institutional honoraria, from Astellas, Boehringer Ingelheim, Janssen, Abbvie, and ZS-Pharma. Dr Marks reports receiving grants from the Chief Scientist Office, Scotland, the National Health Service Grampian Endowments, and from Wellcome Trust. Dr Navaneethan reports receiving personal fees for serving on the adjudication committees of Boehringer-Ingelheim and Abbvi.

Funding/Support: The CKD-PC Data Coordinating Center is funded in part by a program grant from the US National Kidney Foundation (NKF funding sources include AbbVie, Amgen, and Merck) and grant R01DK100446-01 from the National Institute of Diabetes and Digestive and Kidney Diseases. Dr Grams is supported by grant K08DK092287 from the National Institute of Diabetes and Digestive and Kidney Diseases. A variety of sources have supported enrollment and data collection including laboratory measurements, and follow-up in the collaborating cohorts of the CKD-PC. These funding sources include government agencies such as national institutes of health and medical research councils as well as foundations and industry sponsors listed in eAppendix 4 in the Supplement.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Some of the data reported herein have been supplied by the US Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

REFERENCES

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047.

2. O'Hare AM, Batten A, Burrows NR, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. *Am J Kidney Dis*. 2012;59(4):513-522.

3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.

4. O'Hare AM, Bertenthal D, Walter LC, et al. When to refer patients with chronic kidney disease for vascular access surgery: should age be a consideration? *Kidney Int*. 2007;71(6):555-561.

5. Tobe SW, Clase CM, Gao P, et al; ONTARGET and TRANSCEND Investigators. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: results from the ONTARGET and TRANSCEND studies. *Circulation*. 2011;123(10):1098-1107.

6. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305(15):1553-1559.

7. Tonelli M, Manns B. Supplementing creatinine-based estimates of risk in chronic kidney disease: is it time? *JAMA*. 2011;305(15):1593-1595.

8. Drawz PE, Goswami P, Azem R, Babineau DC, Rahman M. A simple tool to predict end-stage renal disease within 1 year in elderly adults with advanced chronic kidney disease. *J Am Geriatr Soc*. 2013;61(5):762-768.

9. Peeters MJ, van Zuilen AD, van den Brand JA, Bots ML, Blankestijn PJ, Wetzels JF; MASTERPLAN Study Group. Validation of the kidney failure risk equation in European CKD patients. *Nephrol Dial Transplant*. 2013;28(7):1773-1779.

10. Acedillo RR, Tangri N, Garg AX. The kidney failure risk equation: on the road to being clinically useful? *Nephrol Dial Transplant*. 2013;28(7):1623-1624.

11. Marks A, Fluck N, Prescott GJ, et al. Looking to the future: predicting renal replacement outcomes in a large community cohort with chronic kidney disease. *Nephrol Dial Transplant*. 2015;30(9):1507-1517.

12. Elley CR, Robinson T, Moyes SA, et al. Derivation and validation of a renal risk score for people with type 2 diabetes. *Diabetes Care*. 2013;36(10):3113-3120.

13. Matsushita K, van der Velde M, Astor BC, et al; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-2081.

14. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

15. Matsushita K, Mahmoodi BK, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012;307(18):1941-1951.

16. Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53(4):766-772.

17. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345(12):870-878.

18. Grams ME, Li L, Greene TH, et al. Estimating time to ESRD using kidney failure risk equations: results from the African American Study of Kidney Disease and Hypertension (AASK). *Am J Kidney Dis*. 2015;65(3):394-402.

19. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2):180-187.

20. Brier G. Verification of forecasts expressed in terms of probability. *Mon Weather Rev*. 1950;78:1-3. http://docs.lib.noaa.gov/rescue/mwr/078/mwr-078-01-0001.pdf. Accessed December 15, 2015.

21. Kidney Disease Improving Global Outcomes (KDIGO) Work Group. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Chapter 5: Referral to specialists and models of care. *Kidney Int Suppl*. 2013;3(1):112-119. doi:10.1038/kisup.2012.68.

22. Astor BC, Matsushita K, Gansevoort RT, et al; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. *Kidney Int*. 2011;79(12):1331-1340.

23. van der Velde M, Matsushita K, Coresh J, et al; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. *Kidney Int*. 2011;79(12):1341-1352.

24. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. *Kidney Int*. 2011;80(1):93-104.

25. Hallan SI, Matsushita K, Sang Y, et al; Chronic Kidney Disease Prognosis Consortium. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308(22):2349-2360.

26. Mahmoodi BK, Matsushita K, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet*. 2012;380(9854):1649-1661.

27. Fox CS, Matsushita K, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380(9854):1662-1673.

28. Nitsch D, Grams M, Sang Y, et al; Chronic Kidney Disease Prognosis Consortium. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ*. 2013;346:f324.

29. Shlipak MG, Matsushita K, Ärnlöv J, et al; CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369(10):932-943.

30. Wen CP, Matsushita K, Coresh J, et al; Chronic Kidney Disease Prognosis Consortium. Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar. *Kidney Int*. 2014;86(4):819-827.

31. Coresh J, Turin TC, Matsushita K, et al; CKD Prognosis Consortium. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311(24):2518-2531.

32. Grams ME, Sang Y, Ballew SH, et al; CKD Prognosis Consortium.. A Meta-analysis of the Association of Estimated GFR, albuminuria, age, race, and sex with acute kidney injury. *Am J Kidney Dis*. 2015;66(4):591-601.

33. James MT, Grams ME, Woodward M, et al; CKD Prognosis Consortium. A Meta-analysis of the Association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis*. 2015;66(4):602-612.

34. Matsushita K, Coresh J, Sang Y, et al; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3(7):514-525.

35. Grams ME, Sang Y, Levey AS, et al; Chronic Kidney Disease Prognosis Consortium. Kidney-failure risk projection for the living kidney-donor candidate [published online November 6, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1510491.

36. Tangri N, Kitsios GD, Inker LA, et al. Risk prediction models for patients with chronic kidney disease: a systematic review. *Ann Intern Med*. 2013;158(8):596-603.

37. Kidney Disease; Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3(1):1-150.

38. Hemmelgarn BR, James MT, Manns BJ, et al; Alberta Kidney Disease Network. Rates of treated and untreated kidney failure in older vs younger adults. *JAMA*. 2012;307(23):2507-2515.

39. Fried LF, Emanuele N, Zhang JH, et al; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903.

40. de Zeeuw D, Akizawa T, Audhya P, et al; BEACON Trial Investigators. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013;369(26):2492-2503.

41. Turin TC, Tonelli M, Manns BJ, et al. Lifetime risk of ESRD. *J Am Soc Nephrol*. 2012;23(9):1569-1578.

42. Isakova T, Xie H, Yang W, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA*. 2011;305(23):2432-2439.