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Grams, Morgan E.; Brunskill, Nigel J.; Ballew, Shoshana H.; Sang, Yingying; Coresh, Josef; Matsushita, Kunihiro

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Morgan E Grams, MD, PhD*, Nigel J Brunskill, MD, PhD*, Shoshana H Ballew, PhD, Yingying Sang, MSc, Josef Coresh, MD, PhD, Kunihiro Matsushita, MD, PhD, Aditya Surapaneni, PhD, Samira Bell, MD, Juan J Carrero, PharmD, PhD, Gabriel Chodick, PhD, Marie Evans, MD, PhD, Hiddo JL Heerspink, PhD, Lesley A Inker, MD, MS, Kunitoshi Iseki, MD, Philip A Kalra, MD, H Lester Kirchner, PhD, Brian J Lee, MD, Adeera Levin, MD, Rupert W Major, MD, PhD, James Medcalf, MD, PhD, Girish N Nadkarni, MD, MPH, David MJ Naimark, MD, MSc, Ana C Ricardo, MD, Simon Sawhney, MD, PhD, Manish M Sood, MD, MSc, Natalie Staplin, PhD, Nikita Stempniewicz, MSc, Benedicte Stengel, MD, PhD, Keiichi Sumida, MD, MPH, Jamie P Traynor, MD, Jan van den Brand, PhD, Chi-Pang Wen, MD, DrPH, Mark Woodward, PhD, Jae Won Yang, MD, Angela Yee-Moon Wang, MD, PhD†, Navdeep Tangri, MD, PhD†

For the CKD Prognosis Consortium

*Indicates co-first authors; †Indicates co-last authors

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (Grams, Ballew, Sang, Coresh, Matsushita, Surapaneni, Woodward)

Division of Precision of Medicine, Department of Medicine, New York University Grossman School of Medicine, New York, NY (Grams)

Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (Brunskill)

John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom (Brunskill, Major, Medcalf)

Renal Unit, Ninewells Hospital, Dundee, United Kingdom and Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, United Kingdom (Bell)

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Huddinge, Sweden (Carrero)

Medical Division, Maccabi Healthcare Services, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Chodick)

Department of Clinical Intervention, and Technology (CLINTEC), Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden (Evans)

Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center, Groningen, Netherlands (Heerspink)

Tufts Medical Center, Boston, MA (Inker)

Okinawa Heart and Renal Association, Okinawa, Japan (Iseki)

Department of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom (Kalra)

Geisinger Health System, Danville, PA (Kirchner)

Kaiser Permanente, Hawaii Region, and Moanalua Medical Center, Honolulu, Hawaii (Lee)

Division of Nephrology, University of British Columbia, Vancouver, Canada (Levin)

Department of Health Sciences, University of Leicester, Leicester, UK (Major)

UK Renal Registry, The Renal Association, Bristol, UK and Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (Medcalf)

Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, New York (Nadkarni)

Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada (Naimark)

Department of Medicine, University of Illinois, Chicago, Illinois (Ricardo)

University of Aberdeen, Aberdeen, Scotland, UK (Sawhney)

Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Canada, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada and Division of Nephrology, Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada (Sood)

MRC Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, Oxford, UK (Staplin)

AMGA (American Medical Group Association), Alexandria, Virginia and OptumLabs Visiting Fellow (Stempniewicz)

University Paris-Saclay, UVSQ, University Paris-Sud, Inserm, Clinical Epidemiology team, CESP, Villejuif, France (Stengel)

Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN (Sumida)

Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital Glasgow Scotland, UK (Traynor)

Department of Nephrology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands (van den Brand)

National Health Research Institutes, Miaoli, Taiwan and China Medical University Hospital, Taichung, Taiwan (Wen)

George Institute for Global Health, Australia, and George Institute for Global Health, Imperial College, London, United Kingdom (Woodward)

Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea (Yang)

Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong (Wang)

Division of Nephrology, Department of Medicine, University of Manitoba, Winnipeg, Canada (Tangri)

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Address for corresponding author: Chronic Kidney Disease Prognosis Consortium (Co-PIs: Drs. Josef Coresh and Morgan Grams), 2024 E. Monument Street, Baltimore, MD, 21287; email: ckdpc@jhmi.edu

Abstract:

Objective: To predict adverse kidney outcomes for use in optimizing medical management and clinical trial design.

Research Design and Methods: In this individual participant data meta-analysis, 43 cohorts (N=1,621,817) from research studies, electronic medical records, and clinical trials with global representation were separated into development and validation cohorts. Models were developed and validated within strata of diabetes mellitus (presence or absence) and eGFR (≥60 or <60 ml/min/1.73 m^2) to predict a composite of ≥40% decline in eGFR or kidney failure (receipt of kidney replacement therapy) over 2-3 years.

Results: There were 17,399 and 24,591 events in development and validation cohorts, respectively. Models predicting ≥40% eGFR decline or kidney failure incorporated age, sex, eGFR, albuminuria, systolic blood pressure, anti-hypertensive medication use, history of heart failure, coronary heart disease, atrial fibrillation, smoking status, and body-mass index (and hemoglobin A1c, insulin use, and oral diabetes medication use in those with diabetes). The median C-statistic was 0.774 (interquartile range [IQR]: 0.753, 0.782) in the diabetes/higher eGFR validation cohorts, 0.769 (IQR: 0.758, 0.808) in the diabetes/lower eGFR validation cohorts, 0.740 (interquartile range [IQR]: 0.717, 0.763) in the no diabetes/higher eGFR validation cohorts, and 0.750 (IQR: 0.731, 0.785) in the no diabetes/lower eGFR validation cohorts. Incorporating previous 2-year eGFR slope minimally improved model performance, and only in the higher eGFR cohorts.

Conclusions: Novel prediction equations for an eGFR decline of ≥40% eGFR can be applied successfully for use in the general population in persons with and without diabetes with higher or lower eGFR.

Introduction

Chronic kidney disease (CKD) afflicts nearly 10% of the world's population and 25% of the population with diabetes mellitus.(1; 2) Advanced CKD is largely irreversible; thus, early intervention is critical for reducing CKD progression and CKD-associated morbidity and mortality. The armamentarium of therapeutic options for preventing adverse kidney outcomes has greatly expanded over the past five years to include renin-angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2-I), glucagon-like peptide-1 (GLP1) agonists, and selective mineralocorticoid receptor antagonists.(3-8) When used early in the course of disease, these agents have the potential to prevent kidney failure, whereas in patients with advanced CKD, effective therapy may only function to delay the onset. As such, optimal medical management requires early identification of patients at high risk of decline in estimated glomerular filtration rate (eGFR).(9-13)

Accurate prediction of the risk of CKD progression can also inform clinical trial design and enrollment. For patients with eGFR <60 ml/min/1.73 m^2, Tangri et al. previously developed a kidney failure risk equation (KFRE) that uses demographic and laboratory data to predict the progression of CKD to kidney failure (receipt of kidney replacement therapy), the major outcome in clinical trials in advanced CKD.(14-19) In patients with eGFR ≥60 ml/min/1.73 m^2, the short-/intermediate-term risk of kidney failure is very low, and clinical trials often evaluate treatment effects on 40% decline in eGFR, the major surrogate outcome for kidney failure accepted by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).(6; 20) However, there are no widely-used prediction models for 40% decline in eGFR in the general population.

To inform risk prediction of early adverse kidney outcomes, we conducted a multinational observational study of >1 million patients in 43 cohorts. We focused on the general population, including but not limited to patients with early CKD (preserved eGFR ≥60 ml/min/1.73 m^2 but urine albumin-to-creatinine ratio (ACR) >30 mg/g) and high cardiovascular risk. Our goal was to develop and externally validate prediction models for the composite outcome of 40% decline in eGFR or kidney failure using variables that are readily available in the electronic medical record, with a focus on the population with diabetes.

Research Design and Methods

Study population

Included cohorts were drawn from the CKD Prognosis Consortium, a global consortium of cohorts with data on kidney function and outcomes and at least 1000 participants (www.ckdpc.org).(21) For the present study, cohorts were required to have measures of creatinine and albuminuria at baseline and at least two years of observation thereafter. In total, 43 cohorts had adequate data and all agreed to participate. The time period of observation ranged from 1990 and 2017 and data from 23 countries were included. For the purpose of equation development, we divided cohorts into development and validation subsets, with development occurring in cohorts able to send individual participant data to the Data Coordinating Center as well as a random selection of 50% of the cohorts from OptumLabs® Data Warehouse (OLDW), and validation occurring in the remaining cohorts. The OLDW is a longitudinal, real-world data asset with de- identified administrative claims and electronic health record (EHR) data.(22) This

study was approved for use of de-identified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. The need for informed consent was waived by the institutional review board.

Procedures

In all cohorts, eGFR was estimated using the CKD-EPI 2021 equation(23) and serum or plasma creatinine. Other key variables included demographics and urine ACR. For participants with measured urine protein-to-creatinine ratio (PCR) but not ACR, values were converted to ACR using the unadjusted conversion equation (**Appendix 1**).(24) For patients without diabetes, we also allowed urine dipstick protein categories and similarly converted these values to ACR. Other variables tested for inclusion were hypertension, systolic blood pressure, antihypertension medications, history of heart failure, history of coronary heart disease, history of atrial fibrillation, smoking status, body-mass index, as well as prior eGFR slope**.** Prior eGFR slope was estimated using all available creatinine measures and linear regression over the previous 2-years at the individual level and categorized as <-3 ml/min/1.73 m^2 per year, between -3 and -1 ml/min/1.73 m^2, -1 to 1 ml/min/1.73 m^2 per year (reference category), and >1 ml/min/1.73 m^2 per year. For patients with diabetes, we also considered hemoglobin A1c, insulin medication use, and oral diabetes medications.

Outcomes

The primary outcome was the composite of decline in eGFR ≥ 40% or kidney failure. This outcome was chosen because of its status as an accepted surrogate kidney endpoint by the EMA

and FDA.(12) In sensitivity analyses, we also evaluated a composite of decline in eGFR ≥30% or kidney failure and a composite of decline in eGFR ≥50% or kidney failure.

Predicting ≥40% decline in eGFR or kidney failure in the general population

We developed a new equation to predict the composite of ≥40% decline in eGFR or kidney failure over 2-3 years, the typical time-frame of a clinical trial. To incorporate research cohorts which had different time windows between repeat creatinine measurements, we allowed the follow-up to range from 1.5 years to 3.5 years. Our first model (Model 1) incorporated only the four variables that had previously been selected for use in the KFRE (age, sex, eGFR, ACR).(14) We then evaluated the addition of previously identified indicators associated with eGFR decline: systolic blood pressure, antihypertensive medication, their interaction term, history of heart failure, history of coronary heart disease, history of atrial fibrillation, smoking status, and body-mass index (Model 2). Finally, we tested the addition of prior eGFR slope (Model 3). Each model was developed by fitting logistic regression of the composite outcome on covariates in each development cohort and then summarizing via random-effects meta-analysis using the restricted maximum likelihood for estimation and inputs of point estimates for each cohort. To assess performance, we estimated discrimination in each validation cohort using Harrell's C-statistic(25) and then summarized as the median and 25^{th}-75^{th} percentile across cohorts. We assessed model improvement between Model 2 and Model 3 by 1) running each model in the subset of patients with non-missing previous 2-year eGFR slope, 2) estimating change in C-statistics between the two models, and 3) meta-analyzing change in C-statistic in the same manner. We evaluated calibration by plotting deciles of predicted vs. observed risk. We also evaluated risk gradients, estimating the relative risk of events in the top decile compared to those

in the lowest decile. In the case of <5 events in the lowest decile, it was iteratively combined with the adjacent decile until there were at least 5 events in the combined categories.(26) In sensitivity analyses, we also evaluated the risk relationships when modeled in multinomial logistic regression, capturing death as a competing outcome. We also evaluated more specific data inputs for anti-hypertension medication (separate indicators for RAAS blockers vs. other anti-hypertension medications) and oral hypoglycemic medications (separate indicators for SGLT2-I and GLP1RA vs. other oral hypoglycemic medications) in the OLDW cohorts. These modifications did not improve the overall c-statistic (data not shown). Thus, we maintained the simpler Model 2 and 3 for ease of implementation.

Analyses were done in Stata version 16 (StataCorp) using complete case analysis and the R package "mvmeta" for the multivariate meta-analysis of all odds ratios. Statistical significance was determined using a 2-sided test with a threshold P value of <0.05.

Role of the Funding Source

The funder of this study had no role in the study design, data collection, analysis, data interpretation, or writing of the report. MEG and JC had full access to all analyses and all authors had final responsibility for the decision to submit for publication, informed by discussions with collaborators.

Results

Baseline characteristics

In total, there were 707,929 participants in 20 development cohorts with 17,399 cases of ≥40% decline in eGFR or kidney failure over an average of 3 years (range 1.5 to 3.5), split into strata by presence of diabetes and baseline eGFR (**Table 1, Supplemental Tables S1-4**). Average age was 57 years, 58% were women, mean eGFR was 86 ml/min/1.73 m^2, and median urine ACR was 15 mg/g. There were 913,888 participants in 23 validation cohorts with 24,591 cases with ≥40% decline in eGFR or kidney failure. Average age, eGFR, and urine ACR was similar to the development cohorts, but the proportion of women was lower owing to the inclusion of the cohort from the Veterans Administration.

Development and validation of a model for the composite endpoint of ≥40% decline in eGFR or kidney failure in cohorts with eGFR ≥60 ml/min/1.73 m^2

The risk prediction models for ≥40% decline in eGFR or kidney failure developed in participants with eGFR ≥60 ml/min/1.73 m^2 with only four variables (Model 1: age, sex, eGFR and urine ACR) had a median (25^{th} -75^{th} percentile of cohorts) c-statistic of 0.704 (0.681-0.738) in the validation cohorts of participants without diabetes and 0.750 (0.719, 0.758) in the validation cohorts of participants with diabetes (**Table 2,** Model 1). Coefficients varied between those without and with diabetes: older age was strongly associated with ≥40% decline in eGFR or kidney failure in the population without diabetes, but less so in the population with diabetes, and female sex and lower eGFR were risk factors only among participants with diabetes. Higher urine ACR was a consistent risk factor across groups.

Incorporating additional variables in the model (Model 2) revealed strong associations with 40% decline in eGFR or kidney failure, particularly for systolic blood pressure, a history of heart failure, and smoking status (**Table 2,** Model 2). Hemoglobin A1c and insulin use were also associated with the outcome in the population with diabetes. The median (25^{th} -75^{th} percentile of cohorts) C-statistic for Model 2 was 0.740 (0.717, 0.763) and 0.774 (0.753, 0.782) in the validation cohorts for people without and with diabetes, respectively (**Supplemental Table S5**). There was good calibration in the populations without and with diabetes (**Figure 1A-B**). The observed risk in the top vs. bottom decile was greater with Model 2 compared with Model 1 (median (IQR) cohort risk gradient: 17.4 (14.0-19.5) vs. 13.1 (10.6-14.4) in those without diabetes, 16.4 (14.3-21.3) vs. 13.2 (11.4-15.0) in those with diabetes). Adding prior eGFR slope improved discrimination by only a modest amount in the validation cohorts among participants without and with diabetes (**Table 2,** Model 3).

Development and validation of a model for the composite endpoint of ≥40% decline in eGFR or kidney failure in cohorts with eGFR <60 ml/min/1.73 m^2

The risk prediction models for ≥40% decline in eGFR or kidney failure developed in participants with eGFR <60 ml/min/1.73 m^2 with only four variables (Model 1: age, sex, eGFR and urine ACR) had a median (25^{th} -75^{th} percentile of cohorts) c-statistic of 0.712 (0.677, 0.772) in the validation cohorts of participants without diabetes and 0.760 (0.731, 0.799) in the validation cohorts of participants with diabetes (**Table 3,** Model 1). Coefficients varied between those without and with diabetes in eGFR <60 ml/min/1.73 m^2: older age was protective for ≥40% decline in eGFR or kidney failure in those with diabetes, but not in people without diabetes, and

male sex was a risk factor in patients without diabetes but protective in those with diabetes. Higher urine ACR was a consistent predictor of higher risk of adverse outcomes.

Systolic blood pressure, a history of heart failure, and smoking status were again strong risk factors in people with eGFR <60 ml/min/1.73 m^2 (**Table 3,** Model 2). The median (25^{th} -75^{th} percentile of cohorts) C-statistic for Model 2 was 0.750 (0.731, 0.785) and 0.769 (0.758,0.808) in the validation cohorts for people without and with diabetes, respectively. Calibration is shown in **Figure 1C and D**. The observed risk in the top vs. bottom decile was greater with Model 2 compared with Model 1 (median (IQR) cohort risk gradient: 11.6 (10.2-13.6) vs. 8.9 (8.3-10.5) in those without diabetes, 19.5 (16.2-19.6) vs. 17.3 (16.2-19.6) in those with diabetes). Adding prior eGFR slope did not significantly improve discrimination in the validation cohorts in either the population without or with diabetes (**Table 3,** Model 3).

Sensitivity analyses

Model performance was similar when estimated using hypertension as a categorical variable (instead of systolic blood pressure and anti-hypertension medications) in both eGFR <60 ml/min/1.73 m^2 and eGFR ≥60 ml/min/1.73 m^2 (**Supplemental Tables S6-7**). Risk factors were similar when modeling the outcome as 30% decline or kidney failure, and as 50% decline or kidney failure, although absolute risks were higher for the former and lower for the latter (**Supplemental Tables S8-11**). The C-statistics for the 50% decline were generally higher, consistent with the relative rarity of the event. Finally, when multinomial models were used to

capture the competing event of death, risk relationships were fairly consistent, with risk estimates on average 1.5%, 0.9%, 2.0%, 2.7% lower when using the competing risk model in eGFR ≥60 without diabetes, eGFR ≥60 with diabetes, eGFR <60 without diabetes, eGFR <60 with diabetes. (**Supplemental Figure S1**; **Supplemental Table S12**).

Conclusions

In this multinational collaborative meta-analysis including >1 million individuals across 43 cohorts, we developed new models that predict ≥40% decline in eGFR or kidney failure for use in the general population. The risk tools are publicly available and may be useful in medical management and in clinical trial design (**www.ckdpcrisk.org/gfrdecline40**).(9-13) We chose ≥40% decline in eGFR or kidney failure as an outcome since it is accepted as a valid surrogate endpoint by regulatory bodies, but there was consistency in risk relationships when eGFR declines of ≥30% or ≥50% decline were examined. These models, when used in primary care settings, can identify patients at high risk of CKD progression even when eGFR is preserved. Additional work should evaluate how these and other equations developed for this population, such as our models to predict incidence of eGFR <60 ml/min/1.73 m^2 and incidence of albuminuria in people with and without diabetes mellitus,(27) could inform clinical care and trial recruitment.

Equations predicting ≥40% decline in eGFR or kidney failure may be useful if implemented in clinical practice, before significant eGFR decline has occurred. Despite decades of research and health policy work, CKD remains largely unrecognized until advanced stages (eGFR <30

ml/min/1.73 m^2),(28) when the window for intervention and kidney failure prevention is lost. Even patients at high risk of kidney failure remain largely unaware of their diagnosis and prognosis, and they continue to receive suboptimal care.(29; 30) Multiple disease-modifying therapies are available for patients: both SGLT2I and newer mineralocorticoid receptor antagonists improve CKD progression outcomes when given with renin-angiotensin system inhibitors. Thus, the new equation can identify high-risk patients who would benefit from an early "triple therapy approach" to prevent kidney failure over their lifetime.(5-8) Conversely, the potential side effects of triple therapy may outweigh the potential benefit in some low-risk individuals with CKD Stage G1-G2, and emphasize the need for risk stratification in early disease. When combined with risk prediction tools for cardiovascular disease, prediction tools for kidney outcomes can help personalize treatment choices, nominating specific medication regimens over others that may be less useful in a given patient.

Predicting 40% decline in eGFR emphasizes the importance of risk factors for CKD progression over current eGFR. eGFR itself is critical but a poor treatment target since glomerular sclerosis is irreversible. In Tangri's KFRE for patients with eGFR <60 ml/min/1.73 m^2, eGFR is the dominant risk factor with a relative hazard of 0.57 per 5 ml/min/1.73m^2.(14) In our general population models to predict a 40% decline in eGFR, however, eGFR is only modestly or not associated with the outcome (relative hazard 0.83-1.03 per 5 ml/min/1.73 m^2). These differences – and the fact that the vast majority of patients with early CKD do not develop kidney failure(31) -- suggest that our models fill an important gap for use in general population.

Because we observed that many of the risk factor associations were different within groups categorized by the presence or absence of eGFR <60 ml/min/1.73 m^2 and diabetes mellitus, we developed separate risk equations for each. For example, older age was a risk factor for eGFR decline in eGFR ≥60 ml/min/1.73 m^2 but not among eGFR <60 ml/min/1.73 m^2. The most consistent risk factor across models was albuminuria, a potentially modifiable metric of disease activity. Vascular disease, particularly heart failure, and vascular risk factors, particularly higher systolic blood pressure, also consistently heralded a higher risk of 40% decline in eGFR. Interestingly, incorporating prior eGFR slope did not greatly improve any of the risk models' performance. Since eGFR slopes require additional calculation for use in risk tools, the logistical issues in implementation may not be worth the incremental benefit.

Strengths of this study include its large sample size and diversity in geography, ethnicity and health system design, providing strong evidence for generalizability. Our new equations use readily available inputs for accurate prediction of a 40% decline in eGFR. However, there are some limitations. First, we focused on patients who had measurements for eGFR and albuminuria (allowing quantitative and dipstick proteinuria measures among patients without diabetes). Thus, some results may be biased due to an informative measurement process or inaccurate when catalogued in the electronic medical record. However, we did not see any differences in accuracy in cohort studies where measurements were part of scheduled study visits. Second, we were unable to test biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM1), or tumor necrosis factor (TNF)-receptor superfamily members 1A and 1B. These tests are not available in most patients; models incorporating these tests would require a change from current practice. As cystatin C use

increases in clinical settings, inclusion or substitution of cystatin C-based eGFR for creatinine-based eGFR should also be tested. Finally, which cutoffs should define low, medium and high risk and how they best connect to clinical actions remains to be defined.

In conclusion, our new equations for predicting 40% decline in kidney function may inform clinical trial design as well as identify individuals at high-risk for CKD progression for effective intervention, early in the course of disease. Implementation studies of the new equations in health systems are needed.

Contributors: MEG and YS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MEG, NB, SHB, JC, KM, AYMW, and NT were responsible for the study concept and design. MEG, SHB, YS, JC, KM, and AS with the CKD-PC investigators/collaborators listed below were involved in the acquisition of data. MEG, NB, SHB, YS, JC, KM, AYMW, and NT drafted the manuscript. All the authors contributed to the analysis and interpretation of data and to the critical revision of the manuscript for important intellectual content as well as the final decision to submit for publication. MEG, and JC guarantee the integrity of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing: CKD-PC has agreed with collaborating cohorts not to share data outside the consortium. Each participating cohort has its own policy for data sharing.

Competing interests: All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author)

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CKD-PC investigators/collaborators (study acronyms/abbreviations are listed in **Appendix 2** in the Supplement

ADVANCE: John Chalmers, Mark Woodward; **CRIC:** Chi-yuan Hsu, Ana Ricardo, Amanda Anderson, Panduranga Rao, Harold Feldman; **Geisinger:** Alex R. Chang, Kevin Ho, Jamie Green, H. Lester Kirchner; **Go-DARTS:** Samira Bell, Moneeza Siddiqui, Colin Palmer; **Maccabi:** Varda Shalev, Gabriel Chodick; **NephroTest:** Benedicte Stengel, Marie Metzger, Martin Flamant, Pascal Houillier, Jean-Philippe Haymann; **OLDW:** Nikita Stempniewicz, John Cuddeback, Elizabeth Ciemins; **RCAV:** Csaba P. Kovesdy, Keiichi Sumida; **SCREAM:** Juan J Carrero, Marco Trevisan, Carl Gustaf Elinder, Björn Wettermark; **SKS:** Philip Kalra, Rajkumar Chinnadurai, James Tollitt, Darren Green

CKD-PC Steering Committee: Josef Coresh (Chair), Shoshana H Ballew, Alex R. Chang, Ron T Gansevoort, Morgan E. Grams, Orlando Gutierrez, Tsuneo Konta, Anna Köttgen, Andrew S Levey, Kunihiro Matsushita, Kevan Polkinghorne, Elke Schäffner, Mark Woodward, Luxia Zhang

CKD-PC Data Coordinating Center: Shoshana H Ballew (Assistant Project Director), Jingsha Chen (Programmer), Josef Coresh (Co-Principal Investigator), Morgan E Grams (Co-Principal Investigator; Director of Nephrology Initiatives), Kunihiro Matsushita (Director), Yingying Sang (Lead Programmer), Aditya Surapeneni (Programmer), Mark Woodward (Senior Statistician)

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Table 1. Summary characteristics of cohorts used in model development and validation for prediction of the composite outcome of ≥40% decline in eGFR or kidney failure

	Population with eGFR ≥60 ml/min/1.73 m²				*Population with eGFR <60 ml/min/1.73 m²*			
	Population without diabetes		**Population with diabetes**		**Population without diabetes**		**Population with diabetes**	
	Development	**Validation**	**Development**	**Validation**	**Development**	**Validation**	**Development**	**Validation**
Number of cohorts	19	18	20	20	19	21	20	21
Number of participants	492669	556014	126638	244476	58094	64183	30530	49215
eGFR 30% decline, n (%)	14997 (3%)	17389 (3%)	9249 (7%)	19012 (8%)	6413 (11%)	6947 (11%)	5693 (19%)	9176 (19%)
eGFR 40% decline, n (%)	6355 (1%)	6643 (1%)	4183 (3%)	8642 (4%)	3516 (6%)	3815 (6%)	3345 (11%)	5491 (11%)
eGFR 50% decline, n (%)	2923 (1%)	2866 (1%)	2038 (2%)	4139 (2%)	1967 (3%)	2166 (3%)	2015 (7%)	3428 (7%)
Age, year	54 (15)	55 (15)	59 (13)	61 (12)	71 (12)	72 (11)	70 (10)	71 (10)
Female, %	60	60	48	36	62	62	55	46
eGFR, ml/min/1.73m²	92 (16)	92 (17)	90 (16)	89 (16)	47 (11)	47 (10)	46 (11)	47 (11)
ACR/PCR available?*	7.2	9.1	100	100	20	19	100	100
ACR, median (IQI)	9 (5-21)	9 (5-20)	12 (6-31)	12 (6-31)	19 (9-98)	23 (8-104)	27 (10-109)	28 (10-124)
Dipstick proteinuria + or higher, %	6.9	9.1	NA	NA	17	18	NA	NA
Hypertension, %	42	48	78	81	76	84	93	95
Systolic blood pressure (SD), mmHg	125 (16)	126 (17)	130 (16)	131 (16)	130 (18)	130 (18)	132 (18)	132 (18)
Anti-hypertensive medication use, %	27	28	47	38	53	54	65	59
Heart failure, %	2.2	2.8	5.4	6.2	12	14	18	19

Coronary heart disease, %	9.2	12	19	25	26	31	38	42
Atrial fibrillation, %	3.8	4.6	5.8	6.3	14	16	15	16
Current smoker, %	5.6	9.3	8.1	16	5.2	7.8	6.3	11
Former smoker, %	13	15	20	23	20	22	26	27
Body mass index (SD), kg/m^2	29 (7)	30 (17)	34 (8)	33 (7)	29 (6)	29 (6)	33 (7)	33 (7)
Hemoglobin A1c (SD), %	NA	NA	7.5 (1.7)	7.4 (1.6)	NA	NA	7.2 (1.5)	7.3 (1.4)
Oral glucose lowering medication use, %	NA	NA	48	49	NA	NA	39	40
Insulin use, %	NA	NA	21	19	NA	NA	27	25
Prior 2-year eGFR slope < -3 ml, %	29.8	29.4	31.7	31.1	52.0	49.4	53.9	55.8
Prior 2-year eGFR slope between -3 and -1 ml, %	16.4	15.3	17.8	18.8	16.6	17.1	15.9	15.5
Prior 2-year eGFR slope between -1 and 1 ml, %	22.5	22.5	20.4	20.9	14.6	15.5	13.8	13.4
Prior 2-year eGFR slope ≥ 1 ml, %	31.2	32.9	30.1	29.1	16.9	17.9	16.4	15.4

Mean (SD) are shown except where noted otherwise

* PCR was converted to ACR; dipstick was only converted to ACR in population without diabetes

NA – not applicable as the risk factor was not included in risk models.

Table 2. Models predicting the composite outcome of ≥40% decline in eGFR or kidney failure in the population with eGFR ≥60 ml/min/1.73 m^2 and performance in the development and validation cohorts

	No Diabetes			Diabetes		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Age, 10y	1.59 (1.50, 1.69)	1.45 (1.36, 1.54)	1.40 (1.29, 1.52)	1.15 (1.11, 1.20)	1.16 (1.10, 1.22)	1.13 (1.06, 1.22)
Male	0.97 (0.88, 1.07)	0.87 (0.79, 0.95)	0.79 (0.69, 0.89)	0.80 (0.74, 0.87)	0.78 (0.71, 0.86)	0.77 (0.68, 0.86)
eGFR, 5ml	1.02 (1.00, 1.05)	1.03 (1.02, 1.05)	1.02 (1.00, 1.05)	0.93 (0.91, 0.95)	0.95 (0.92, 0.97)	0.95 (0.93, 0.98)
lnACR*	1.59 (1.50, 1.68)	1.52 (1.44, 1.61)	1.46 (1.36, 1.56)	1.64 (1.60, 1.68)	1.51 (1.45, 1.56)	1.48 (1.42, 1.54)
Systolic blood pressure, 20mmHg		1.36 (1.28, 1.44)	1.33 (1.21, 1.46)		1.16 (1.04, 1.30)	1.17 (1.02, 1.34)
Anti-hypertensive medication use		1.30 (1.12, 1.51)	1.39 (1.19, 1.64)		1.33 (1.21, 1.46)	1.32 (1.17, 1.49)
SBPxHTN meds		0.89 (0.83, 0.96)	0.88 (0.77, 1.00)		0.97 (0.86, 1.09)	0.90 (0.77, 1.05)
History of HF		2.87 (2.48, 3.32)	2.78 (2.32, 3.33)		2.52 (2.17, 2.92)	2.66 (2.22, 3.18)
History of CHD		1.51 (1.36, 1.67)	1.59 (1.37, 1.83)		1.24 (1.10, 1.41)	1.14 (0.98, 1.33)
History of Afib		1.12 (0.91, 1.38)	1.12 (0.89, 1.43)		1.36 (1.04, 1.79)	1.51 (1.15, 2.00)
Current smoker		1.46 (1.20, 1.79)	1.46 (1.15, 1.84)		1.13 (0.98, 1.30)	1.19 (1.00, 1.41)
Former smoker		1.20 (1.10, 1.31)	1.21 (1.06, 1.37)		1.08 (0.96, 1.22)	1.05 (0.92, 1.20)
BMI, 5 kg/m^2		1.04 (1.01, 1.08)	1.04 (1.00, 1.09)		1.03 (1.00, 1.06)	1.02 (0.98, 1.06)
HbA1c, mmol					1.10 (1.07, 1.14)	1.25 (1.04, 1.51)
Oral antiDM medication					0.94 (0.83, 1.06)	1.03 (0.82, 1.29)
Insulin					1.27 (1.08, 1.49)	1.47 (1.24, 1.73)
Slope† <-3 ml			1.25 (1.03, 1.53)			1.09 (1.05, 1.13)
-3ml ≤ Slope† < -1 ml			1.13 (0.93, 1.38)			0.93 (0.80, 1.08)
Slope† ≥ 1 ml			1.69 (1.45, 1.98)			1.21 (0.99, 1.49)
Development population, N	456,129	456,129	181,619	123,201	123,201	78,285
Median C-statistic (IQR)	0.715 (0.679, 0.741)	0.740 (0.702, 0.776)	0.739 (0.703, 0.761)	0.730 (0.698, 0.737)	0.759 (0.738, 0.780)	0.751 (0.717, 0.766)
Change in c-statistic from previous model/column (using same N) ‡		0.029 (0.021, 0.038)	0.007 (0.003, 0.010)	NA	0.035 (0.029, 0.041)	0.004 (0.002, 0.006)
Validation population, N	550,179	550,179	236,284	238,440	238,440	142,673
Median C-statistic (IQR)	0.704 (0.681, 0.738)	0.740 (0.717, 0.763)	0.743 (0.708, 0.758)	0.750 (0.719, 0.758)	0.774 (0.753, 0.782)	0.766 (0.747, 0.796)
Change in c-statistic from previous model/column (using same N) ‡		0.031 (0.026, 0.036)	0.008 (0.004, 0.012)		0.028 (0.022, 0.034)	0.003 (0.001, 0.005)

*lnACR was converted by urine dipstick protein using published equation as: lnACR = 2.4732 + 0.7537 × (if trace) + 1.7346 × (if +) + 3.3624 × (if ++) + 4.6676 × (if more than ++)

†Reference: -1 ml/min/1.73 m^2/year ≤ Slope < 1 ml/min/1.73 m^2/year

‡Change in Model 2 c-statistic is from Model 1, run with the same sample size. Change in Model 3 c-statistic is from Model 2, re-run with the smaller sample size of Model 3.

Bold indicates statistically significant result

Table 3. Models predicting the composite outcome of ≥40% decline in eGFR or kidney failure in cohorts with eGFR <60 ml/min/1.73 m^2

	No Diabetes			Diabetes		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Age, 10y	0.97 (0.93, 1.01)	0.92 (0.87, 0.98)	0.86 (0.79, 0.93)	0.86 (0.80, 0.92)	0.84 (0.78, 0.91)	0.84 (0.77, 0.92)
Male	1.11 (1.02, 1.20)	1.06 (0.96, 1.18)	1.04 (0.91, 1.19)	0.89 (0.79, 0.99)	0.86 (0.77, 0.97)	0.88 (0.76, 1.01)
eGFR, 5ml	0.83 (0.80, 0.86)	0.85 (0.82, 0.87)	0.83 (0.80, 0.86)	0.91 (0.88, 0.94)	0.93 (0.89, 0.96)	0.92 (0.88, 0.96)
lnACR*	1.51 (1.46, 1.56)	1.48 (1.43, 1.53)	1.45 (1.39, 1.51)	1.67 (1.59, 1.74)	1.59 (1.51, 1.68)	1.56 (1.48, 1.65)
Systolic blood pressure, 20mmHg		1.27 (1.18, 1.37)	1.34 (1.18, 1.52)		1.23 (1.12, 1.35)	1.24 (1.11, 1.40)
Anti-hypertensive medication use		1.08 (0.95, 1.24)	1.21 (1.05, 1.40)		1.18 (1.02, 1.36)	1.23 (1.03, 1.47)
SBPxHTN meds		0.98 (0.89, 1.07)	0.99 (0.84, 1.16)		0.95 (0.85, 1.05)	0.95 (0.83, 1.08)
History of HF		1.63 (1.43, 1.86)	1.70 (1.45, 1.99)		1.52 (1.33, 1.75)	1.62 (1.38, 1.91)
History of CHD		1.26 (1.13, 1.41)	1.27 (1.10, 1.46)		1.24 (1.09, 1.42)	1.15 (0.98, 1.36)
History of Afib		1.08 (0.88, 1.31)	1.15 (0.89, 1.47)		1.05 (0.86, 1.27)	0.96 (0.77, 1.19)
Current smoker		1.34 (1.08, 1.66)	1.27 (0.93, 1.74)		0.97 (0.76, 1.23)	0.97 (0.73, 1.29)
Former smoker		1.19 (1.06, 1.34)	1.17 (1.00, 1.37)		1.15 (1.02, 1.30)	1.15 (1.01, 1.31)
BMI, 5 kg/m^2		0.98 (0.93, 1.02)	0.95 (0.90, 1.00)		1.03 (0.99, 1.06)	1.05 (1.01, 1.10)
HbA1c, mmol					1.00 (0.96, 1.04)	0.99 (0.79, 1.25)
Oral antiDM medication					0.88 (0.76, 1.02)	1.08 (0.82, 1.41)
Insulin					1.10 (0.95, 1.28)	1.24 (0.93, 1.64)
Slope† <-3 ml			0.93 (0.75, 1.15)			0.98 (0.93, 1.03)
-3ml ≤ Slope† < -1 ml			0.97 (0.77, 1.22)			0.95 (0.80, 1.13)
Slope† ≥ 1 ml			1.42 (1.12, 1.79)			1.17 (0.97, 1.41)
Development population, N	50567	50567	29595	29145	29145	21591
Median C-statistic (IQR)	0.702 (0.692, 0.725)	0.735 (0.717, 0.764)	0.739 (0.716, 0.762)	0.763 (0.720, 0.788)	0.787 (0.738, 0.805)	0.775 (0.731, 0.787)
Change in c-statistic from previous model/column (using same N) ‡		0.024 (0.018, 0.030)	0.004 (0.001, 0.007)		0.017 (0.013, 0.021)	0.002 (0.001, 0.003)
Validation population, N	63717	63717	39015	48041	48041	34350
Median C-statistic (IQR)	0.712 (0.677, 0.772)	0.750 (0.731, 0.785)	0.743 (0.706, 0.793)	0.760 (0.731, 0.799)	0.769 (0.758, 0.808)	0.766 (0.756, 0.808)
Change in c-statistic from previous model/column (using same N) ‡		0.025 (0.015, 0.036)	0.002 (-0.002, 0.006)	0.760 (0.731, 0.799)	0.012 (0.007, 0.018)	0.001 (-0.000, 0.002)

*lnACR was converted by urine dipstick protein using published equation as: lnACR = 2.4732 + 0.7537 × (if trace) + 1.7346 × (if +) + 3.3624 × (if ++) + 4.6676 × (if more than ++)

†Reference: -1 ml/min/1.73 m^2/year ≤ Slope < 1 ml/min/1.73 m^2/year

‡Change in Model 2 c-statistic is from Model 1, run with the same sample size. Change in Model 3 c-statistic is from Model 2, re-run with the smaller sample size of Model 3.

Bold indicates statistically significant result

Figure 1. Calibration of the new equations to predict 40% decline in eGFR over 2-3 years in validation cohorts (A) with eGFR ≥60 ml/min/1.73 m^2 and no diabetes; (B) with eGFR ≥60 ml/min/1.73 m^2 and diabetes; (C) with eGFR <60 ml/min/1.73 m^2 and no diabetes; and (D) with eGFR <60 ml/min/1.73 m^2 and diabetes

Figure legend: light gray --- <100 events; gray --- 100 ~ 199 events; dark gray --- 200 ~ 399 events; black --- 400+ events