

## Article

# Development of Risk Prediction Equations for Incident Chronic Kidney Disease

Nelson, Robert G, Grams, Morgan E, Ballew, Shoshana H, Sang, Yingying, Azizi, Fereidoun, Chadban, Steven J, Chaker, Layal, Dunning, Stephan C, Fox, Caroline, Hiraakawa, Yoshihisa, Iseki, Kunitoshi, Ix, Joachim, Jafar, Tazeen H, Köttgen, Anna, Naimark, David MJ, Ohkubo, Takayoshi, Prescott, Gordon, Rebholz, Casey M, Sabanayagam, Charumathi, Sairenchi, Toshimi, Schöttker, Ben, Shibagaki, Yugo, Tonelli, Marcello, Zhang, Luxia, Gansevoort, Ron T, Matsushita, Kunihiro, Woodward, Mark, Coresh, Josef, Shalev, Varda and for the CKD Prognosis Consortium, ;

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1 **Development of Risk Prediction Equations for Incident Chronic Kidney Disease**

2

3 **Running title:** Predicting Chronic Kidney Disease

4

5 Robert G. Nelson, MD, PhD<sup>1</sup>; Morgan E. Grams, MD, PhD<sup>2</sup>; Shoshana H. Ballew, PhD<sup>2</sup>; Yingying Sang,  
6 MS<sup>2,3</sup>; Fereidoun Azizi, MD<sup>4</sup>; Steven J. Chadban, MD, PhD<sup>5</sup>; Layal Chaker, MD, PhD<sup>6</sup>; Stephan C. Dunning,  
7 MBA<sup>7</sup>; Caroline Fox, MD<sup>8</sup>; Yoshihisa Hirakawa, MD<sup>9</sup>; Kunitoshi Iseki, MD, PhD<sup>10</sup>; Joachim Ix, MD, MAS<sup>11</sup>;  
8 Tazeen H. Jafar, MD, MPH<sup>12</sup>; Anna Köttgen, MD, MPH<sup>2,13</sup>; David M.J. Naimark, MD, MSc<sup>14</sup>; Takayoshi  
9 Ohkubo, MD, PhD<sup>15</sup>; Gordon J. Prescott, BSc, MSc, PhD, CStat<sup>16</sup>; Casey M. Rebholz, PhD<sup>2</sup>; Charumathi  
10 Sabanayagam, PhD<sup>17</sup>; Toshimi Sairenchi, PhD<sup>18</sup>; Ben Schöttker, PhD<sup>19</sup>; Yugo Shibagaki, MD<sup>20</sup>; Marcello  
11 Tonelli, MD, SM<sup>21</sup>; Luxia Zhang, MD<sup>22</sup>; Ron T. Gansevoort, MD, PhD<sup>23</sup>; Kunihiro Matsushita, MD, PhD<sup>2</sup>;  
12 Mark Woodward, PhD<sup>2,24</sup>; Josef Coresh, MD<sup>2</sup>, PhD; Varda Shalev, MD<sup>25</sup>; for the CKD Prognosis  
13 Consortium

14

15 1 Chronic Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases,  
16 National Institutes of Health, Phoenix, Arizona

17 2 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

18 3 OptumLabs Visiting Fellow, OptumLabs, Cambridge, MA

19 4 Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of  
20 Medical Sciences, Tehran, Iran

21 5 Charles Perkins Centre, University of Sydney, Sydney, Australia

- 22 6 Academic Center for Thyroid Diseases, Erasmus Medical Center, Rotterdam, Netherlands; Department  
23 of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands; Department of Epidemiology,  
24 Erasmus Medical Center, Rotterdam, Netherlands
- 25 7 OptumLabs, Cambridge, MA
- 26 8 Population Sciences Branch, National Heart, Lung, and Blood Institute, National Institutes of Health,  
27 Bethesda, MD, and the Framingham Heart Study, Framingham, MA
- 28 9 Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine,  
29 Nagoya, Japan
- 30 10 Nakamura Clinic & Okinawa Asia Clinical Investigation Synergy, Okinawa, Japan (K Iseki);
- 31 11 University of California, San Diego, La Jolla, and Veterans Affairs San Diego Healthcare System, San  
32 Diego, California
- 33 12 Program in Health Services and Systems Research, Duke-NUS Medical School, Singapore; Department  
34 of Medicine, Aga Khan University, Karachi, Pakistan; Duke Global Health Institute, Durham, Duke  
35 University, NC, USA
- 36 13 Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center - University of Freiburg,  
37 Freiburg, Germany
- 38 14 Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada
- 39 15 Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
- 40 16 Medical Statistics Team, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen,  
41 Aberdeen, UK

42 17 Singapore National Eye Centre, Singapore Eye Research Institute, Singapore, Singapore; Yong Loo Lin  
43 School of Medicine, National University of Singapore, Singapore; Duke-NUS Medical School, Singapore,  
44 Singapore

45 18 Department of Public Health, Dokkyo Medical University, Tochigi, Japan

46 19 Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg,  
47 Germany; Network Aging Research, University of Heidelberg, Heidelberg, Germany

48 20 Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University  
49 School of Medicine, Kawasaki, Japan

50 21 Department of Medicine, University of Calgary, Calgary, Alberta, Canada

51 22 Peking University Institute of Nephrology, Division of Nephrology, Peking University First Hospital,  
52 Beijing, China

53 23 Department of Nephrology, University Medical Center Groningen, University of Groningen,  
54 Groningen, the Netherlands

55 24 The George Institute for Global Health, University of Oxford, UK and The George Institute for Global  
56 Health, University of New South Wales, Australia

57 25 Medical Division, Maccabi Healthcare Services, and Sackler Faculty of Medicine, Tel Aviv University,  
58 Tel Aviv, Israel

59

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63 **Address for correspondence:** Chronic Kidney Disease Prognosis Consortium Data Coordinating Center  
64 (Co-Principal Investigators, Josef Coresh, MD, PhD, Morgan E. Grams, MD PhD), 2024 E. Monument  
65 Street, Baltimore, MD 21205; Tel: 410-955-9917, Fax: 410-955-8086, E-mail: [ckdpc@jhmi.edu](mailto:ckdpc@jhmi.edu)

66

67 Key Points:

68 Question: Can development of chronic kidney disease be predicted using readily available demographic,  
69 clinical, and laboratory variables?

70 Findings: In this analysis of 5,222,711 individuals in 34 multinational cohorts from 28 countries, 5-year  
71 risk prediction equations for CKD were developed and demonstrated high discrimination (median C-  
72 statistic for the equation for people without diabetes, 0.85; median C-statistic for the equation for  
73 people with diabetes, 0.80) and variable calibration (69% of the study populations had a slope of  
74 observed to predicted risk between 0.80 and 1.25). Discrimination and calibration were similar in 9  
75 external cohorts consisting of 2,253,540 people.

76 Meaning: Equations for predicting risk of incident chronic kidney disease were developed in over 5  
77 million people from 34 multinational cohorts and demonstrated high discrimination and variable  
78 calibration in diverse populations.

79 **ABSTRACT**

80 **IMPORTANCE** - Early identification of individuals at elevated risk of developing chronic kidney disease  
81 could improve clinical care through enhanced surveillance and better management of underlying health  
82 conditions.

83 **OBJECTIVE** – To develop assessment tools to identify individuals at increased risk of chronic kidney  
84 disease, defined by reduced estimated glomerular filtration rate (eGFR).

85 **DESIGN, SETTING, AND PARTICIPANTS** – Individual level data analysis of 34 multinational cohorts from  
86 the CKD Prognosis Consortium including 5,222,711 individuals from 28 countries. Data were collected  
87 from April, 1970 through January, 2017. A two-stage analysis was performed, with each study first  
88 analyzed individually and summarized overall using a weighted average. Since clinical variables were  
89 often differentially available by diabetes status, models were developed separately within participants  
90 with diabetes and without diabetes. Discrimination and calibration were also tested in 9 external  
91 cohorts (N=2,253,540).

92 **EXPOSURE** Demographic and clinical factors.

93 **MAIN OUTCOMES AND MEASURES** – Incident eGFR <60 ml/min/1.73 m<sup>2</sup>.

94 **RESULTS** – In 4,441,084 participants without diabetes (mean age, 54 years, 38% female), there were  
95 660,856 incident cases of reduced eGFR during a mean follow-up of 4.2 years. In 781,627 participants  
96 with diabetes (mean age, 62 years, 13% female), there were 313,646 incident cases during a mean  
97 follow-up of 3.9 years. Equations for the 5-year risk of reduced eGFR included age, sex, ethnicity, eGFR,  
98 history of cardiovascular disease, ever smoker, hypertension, BMI, and albuminuria. For participants  
99 with diabetes, the models also included diabetes medications, hemoglobin A1c, and the interaction  
100 between the two. The risk equations had a median C statistic for the 5-year predicted probability of  
101 0.845 (25<sup>th</sup> – 75<sup>th</sup> percentile, 0.789-0.890) in the cohorts without diabetes and 0.801 (25<sup>th</sup> – 75<sup>th</sup>  
102 percentile, 0.750-0.819) in the cohorts with diabetes. Calibration analysis showed that 9 out of 13 (69%)

103 study populations had a slope of observed to predicted risk between 0.80 and 1.25. Discrimination was  
104 similar in 18 study populations in 9 external validation cohorts; calibration showed that 16 out of 18  
105 (89%) had a slope of observed to predicted risk between 0.80 and 1.25.

106 CONCLUSIONS AND RELEVANCE – Equations for predicting risk of incident chronic kidney disease  
107 developed in over 5 million people from 34 multinational cohorts demonstrated high discrimination and  
108 variable calibration in diverse populations.

109



## 110 INTRODUCTION

111 Chronic kidney disease (CKD) is a global public health problem that is associated with major adverse  
112 health events, including kidney failure, cardiovascular disease, and death. The Global Burden of Disease  
113 study estimates that nearly 697 million persons worldwide had reduced estimated glomerular filtration  
114 rate (eGFR) or increased albuminuria in 2016, an increase of 70% since 1990.<sup>1</sup> Globally, years of life lost  
115 due to CKD increased by 53% in the same period.<sup>1</sup> CKD is the 16<sup>th</sup> most common cause of years of life  
116 lost.<sup>2</sup> Factors associated with the increased prevalence of CKD include the aging of the population and  
117 the increasing prevalence of diabetes, hypertension, and obesity. The ability to identify people at risk for  
118 CKD may prevent adverse health outcomes associated with CKD. Moreover, even in those who are  
119 diagnosed with CKD, proper management may be hindered by lack of awareness of CKD and its  
120 management among clinicians and uncertainties about the underlying risk of CKD progression.

121

122 A kidney failure risk equation may help improve care for patients with established CKD,<sup>3,4</sup> but relatively  
123 little work has been performed to develop predictive tools to identify those at increased risk for  
124 *developing* CKD, defined by reduced eGFR, despite the high lifetime risk of CKD, which is estimated to be  
125 59.1% in the United States.<sup>3</sup> A simple risk assessment tool that helps clinicians quickly identify patients  
126 at increased risk of reduced eGFR and provides an estimate of the magnitude of risk for reduced eGFR  
127 could lead to better and more targeted surveillance strategies and potentially to better management of  
128 the factors associated with reduced eGFR. In the present study, data from multinational cohorts were  
129 used to develop and evaluate risk prediction equations for CKD defined by reduced eGFR.

130

## 131 METHODS

132 This study was approved for use of deidentified data by the institutional review board at the Johns  
133 Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. The need for informed consent  
134 was waived by the institutional review board.

135

### 136 **Participating cohorts**

137 The Chronic Kidney Disease Prognosis Consortium (CKD-PC) includes study cohorts worldwide that were  
138 identified from the general population and from patients at high risk of cardiovascular disease  
139 (**eAppendix 1**).<sup>4-9</sup> Inclusion criteria required that cohorts included at least 1,000 participants, data on  
140 serum creatinine and albuminuria, and 50 or more events of the outcome of interest. Included cohorts  
141 consisted of prospective studies, clinical trials, and administrative healthcare datasets. Separate risk  
142 models were developed for those with and without diabetes mellitus. The analyses among participants  
143 without diabetes included 31 cohorts, and the analyses among participants with diabetes included 15  
144 cohorts. Within cohorts, eligible participants were aged  $\geq 18$  years old with an eGFR  $>60$  ml/min/1.73 m<sup>2</sup>  
145 at baseline. Eligible participants had no previous end-stage kidney disease and had at least one serum  
146 creatinine value during follow-up. Because the prevalence and incidence of CKD differ by race/ethnicity,  
147 data on race and ethnicity were analyzed from the participating cohorts. Methods used to determine  
148 race varied from cohort to cohort, but most cohorts used self-report to define race and ethnicity. Data  
149 were collected from April, 1970 through January, 2017.

150

### 151 **Procedures**

152 The CKD-EPI creatinine equation was used to calculate eGFR.<sup>10</sup> In cohorts where the creatinine  
153 measurement was not standardized to isotope dilution mass spectrometry (IDMS), values were  
154 multiplied by 0.95 before eGFR calculation.<sup>11</sup> We defined diabetes as fasting glucose  $\geq 7.0$  mmol/L (126  
155 mg/dL), non-fasting glucose  $\geq 11.1$  mmol/L (200 mg/dL), hemoglobin A1c  $\geq 6.5\%$ , use of glucose lowering

156 drugs, or self-reported diabetes. Hypertension was defined as blood pressure >140/90 mm Hg or the use  
157 of anti-hypertensive medications. Smoking was classified as ever smoking vs. never smoking.  
158 Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke  
159 were considered to have a history of cardiovascular disease. Measures of albuminuria were restricted to  
160 the urine albumin-to-creatinine ratio. Among participants with diabetes, hemoglobin A1c, oral diabetes  
161 medications, and insulin use at baseline were also recorded.

162

### 163 **Outcomes**

164 The outcome of interest was incident eGFR <60 ml/min/1.73 m<sup>2</sup>. Additional outcomes were eGFR <45  
165 ml/min/1.73 m<sup>2</sup>, eGFR <30 ml/min/1.73 m<sup>2</sup>, and 40% decline in eGFR. Participants who developed end-  
166 stage kidney disease, mostly identified by procedure codes or by linkage to national registries before a  
167 qualifying outpatient level of eGFR were also considered to have developed the outcome of interest. In  
168 secondary analyses, we evaluated the risk of confirmed outcomes. Outcomes were defined as confirmed  
169 if there were at least three measures of eGFR (one baseline, two during follow-up) and the first eGFR  
170 below the threshold was confirmed by a second qualifying eGFR between 90 days and 2 years later, or if  
171 the linear slope of eGFR decline crossed the threshold during follow-up (**eAppendix 1**). In both cases, the  
172 event date was considered the date of the first qualifying eGFR measurement.

173

### 174 **Prediction Model Development**

175 The prediction model was built from weighted-average hazard ratios estimated in all participating  
176 cohorts and an adjusted baseline risk estimated in cohorts with frequent outcome assessment. To  
177 estimate the hazard ratios, each study was first analyzed individually, then combined, weighting the  
178 study by the square-root of the number of events in each cohort and capped at 5-times the median  
179 study weight. This method was used to ensure that the largest studies did not dominate the analysis due

180 to small within-study variance compared to total variance. We performed complete case analysis,  
181 excluding variables which were missing more than 50% of the time in cohort-specific analyses. Since  
182 variables were often differentially available by diabetes status (e.g., albuminuria, hemoglobin A1c;  
183 missing data shown in **eTable 1A and B**), models were developed separately for participants with  
184 diabetes and without diabetes. The primary model included demographic variables (age, sex, ethnicity),  
185 eGFR (linear splines with knot at 90 ml/min/1.73 m<sup>2</sup>), history of cardiovascular disease, ever smoker,  
186 hypertension, BMI, and albuminuria. The primary model for participants with diabetes also included  
187 diabetes medications (insulin vs. only oral medications vs. none), hemoglobin A1c, and the interaction  
188 between the two.

189  
190 The albuminuria variable was handled differently for those with vs. without diabetes. For the model  
191 among participants with diabetes, missing albuminuria was treated as a dummy variable with reference  
192 at a urine albumin-to-creatinine ratio of 10 mg/g. For the model among participants without diabetes,  
193 where albuminuria was available only in a minority of individuals, a patch approach was used.<sup>12</sup> Models  
194 were fit in all the cohorts using all variables except albuminuria, and data were combined as described  
195 above. The weighted average coefficients were then held constant in cohort-specific models among  
196 participants with measures of albuminuria to obtain a conditional coefficient for albuminuria, which was  
197 then combined for analyses using the weighting described above. This conditional, weighted average  
198 coefficient for albuminuria was applied to the observed level of albuminuria less the expected level of  
199 albuminuria (**eTable 2**) and combined with the weighted-average coefficients for the other variables in  
200 the final model.

201  
202 To obtain the adjusted baseline risk for use with the primary model, we held the weighted-average  
203 coefficients constant and fit a multivariable competing risk model in the studies with follow-up for

204 mortality and mean time between creatinine measures of less than one year. The adjusted sub-hazard  
205 was smoothed using a Weibull distribution and the mean was estimated using weights determined by  
206 the method described above. The prediction model then combined the mean adjusted baseline risk with  
207 the weighted-average coefficients.

208

### 209 **Evaluation of Model Performance**

210 To evaluate model discrimination, Harrell's C-statistic was estimated within each cohort and  
211 summarized as the median and interquartile range across studies. Model calibration was plotted using  
212 observed versus predicted risk per decile of predicted risk at 5 years in each cohort with frequent  
213 measures of creatinine (median time between two measurements was approximately 1 year or less and  
214 mean follow-up time was at least two years) and quantified using a regression of the deciles of mean  
215 observed risk on the mean predicted risk in a zero-intercept linear regression model. Calibration was  
216 assessed by visual inspection of the plots (dots showing deciles are close to identity line) and by the  
217 slope of observed to predicted risk being near to 1.<sup>13</sup> To summarize calibration, we determined the  
218 number of study populations with an observed risk within 1.25-fold that of the predicted risk (i.e., with a  
219 slope between 0.80 and 1.25 (1/0.8)). These metrics of discrimination and calibration were also  
220 calculated within 9 external validation cohorts selected from OptumLabs® Data Warehouse. **eAppendix**  
221 **1** describes the methods for selecting centers for the nine external validation cohorts. The OptumLabs  
222 Data Warehouse contains deidentified longitudinal health information on patients receiving care in  
223 health systems participating in the OptumLabs collaborative research and innovation center in the U.S.  
224 The database includes people ages 18 to 88 years, from diverse ethnicities and geographical regions  
225 across the United States (**eTable 3**). The electronic health record (EHR)-derived data include a subset of  
226 EHR data that have been normalized and standardized across health systems into a single database,  
227 including information on demographics, laboratory values, encounter and discharge codes.<sup>14</sup>

228  
229 To compare the newly developed models to existing equations, predicted risks using the newly  
230 developed models were compared with risks calculated using two published equations identified in a  
231 recent review<sup>15</sup> (herein referred to as the Chien equation<sup>16</sup> and the O'Seaghdha equation<sup>17</sup>, respectively  
232 **eAppendix 4**). The Chien equation was developed in 5,168 Chinese individuals who underwent baseline  
233 health examinations at the National Taiwan University Hospital<sup>16</sup> and annual follow-up examinations  
234 that included measurements of serum creatinine concentration for assessing the outcome of reduced  
235 eGFR. During a median follow-up of 2.2 years, 190 individuals developed CKD. We used the Chien clinical  
236 equation, which included age, body mass index, diastolic blood pressure, and history of type 2 diabetes  
237 and stroke. The O'Seaghdha prediction model was developed in the predominantly white population of  
238 Framingham, Massachusetts, using baseline serum creatinine and a subsequent measure 10 years later.  
239 Among the 2,490 individuals aged 45-64 years included in this study, 229 developed eGFR <60  
240 ml/min/1.73m<sup>2</sup> at 10 years. The O'Seaghdha model included age, hypertension, diabetes, eGFR  
241 category, and albuminuria.<sup>17</sup>

242  
243 The performance of the newly developed model, the Chien equation, and the O'Seaghdha equation  
244 were compared in the CKD-PC cohorts that provided individual-level participant data and had the  
245 required variables for all equations. Differences in C-statistics were estimated within all cohorts and  
246 then summarized using random-effects meta-analysis. Brier scores, the mean squared difference  
247 between the predicted risk vs observed binary outcomes, were used to evaluate which risk equation  
248 showed the best calibration within each cohort (**eAppendix 4**).<sup>18</sup> Brier scores were assessed only within  
249 the subset of cohorts with frequent assessments of creatinine. Comparisons of the discrimination and  
250 calibration were also performed within the 9 external validation cohorts from OptumLabs Data  
251 Warehouse.

252  
253 All analyses were performed in Stata 15 (StataCorp. 2017. College Station, TX: StataCorp LLC). Statistical  
254 significance was determined using a two-sided test with a threshold p-value of <0.05.

255

## 256 **RESULTS**

257 Overall, 5,222,711 participants were included (**eTable 4**), of whom 781,627 (15.0%) had diabetes.

258 Baseline characteristics of participants in the 34 individual cohorts are shown in **Table 1** according to the  
259 presence or absence of diabetes. The population without diabetes had a mean age of 54 years (SD, 16)  
260 and 38% were female. The population with diabetes had a mean age of 62 years (SD, 11) and 13% were  
261 female, owing primarily to the Veterans Administration cohort, which was 97% male.

262

263 Among the 4,441,084 participants without diabetes, there were 660,856 (14.9%) incident cases of eGFR  
264 <60 ml/min/1.73m<sup>2</sup> during a mean follow-up of 4.2 years, and 374,513 (56.7%) of them were confirmed  
265 by subsequent eGFR measurements. Among the 781,627 participants with diabetes, there were 313,646  
266 (40.1%) incident cases during a mean follow-up of 3.9 years, and 212,246 (67.7%) of them were  
267 confirmed by subsequent eGFR measurements. The number of participants and the total and confirmed  
268 number of events of incident reduced eGFR in the nondiabetic and diabetic cohorts are shown in **eTable**  
269 **5**.

270

### 271 **Risk factors for reduced eGFR**

272 Weighted-average sub-hazard ratios of major risk factors for incident eGFR <60 ml/min/1.73m<sup>2</sup> are  
273 shown in **Table 2** and for other eGFR thresholds in **eTable 6** according to the presence or absence of  
274 diabetes. Older age, female sex, black race, hypertension, history of cardiovascular disease, lower eGFR,  
275 and higher urine albumin-to-creatinine ratio were each significantly associated with incident eGFR <60

276 ml/min/1.73m<sup>2</sup> in both the diabetic and nondiabetic cohorts. Smoking was significantly associated with  
277 incident eGFR <60 ml/min/1.73m<sup>2</sup> only in the nondiabetic cohorts, and elevated hemoglobin A1c and  
278 presence and type of diabetes medicines were significantly associated with incident eGFR <60  
279 ml/min/1.73m<sup>2</sup> in the diabetic cohorts.

280

### 281 **Discrimination**

282 Measures of discrimination for the 5-year predicted probability of incident eGFR <60 ml/min/1.73m<sup>2</sup>,  
283 based on the predictive models, are shown separately for the nondiabetic and diabetic cohorts in **eTable**  
284 **7A**. The median C statistic for the 5-year predicted probability of all eGFR events <60 ml/min/1.73m<sup>2</sup>  
285 was 0.845 (25<sup>th</sup> – 75<sup>th</sup> percentile, 0.789-0.890) in the cohorts without diabetes and 0.801 (25<sup>th</sup> – 75<sup>th</sup>  
286 percentile, 0.750-0.819) in the cohorts with diabetes, reflecting good discrimination. For confirmed  
287 eGFR events <60 ml/min/1.73m<sup>2</sup>, the median C statistic was 0.869 (25<sup>th</sup> – 75<sup>th</sup> percentile, 0.823-0.897) in  
288 the cohorts without diabetes and 0.808 (25<sup>th</sup> – 75<sup>th</sup> percentile, 0.794-0.836) in the cohorts with diabetes.  
289 Measures of discrimination for the lower incident eGFR thresholds are shown in **eTable 7B**.

290

### 291 **Predicted absolute risk**

292 Adjusted baseline sub-hazards for eGFR <60 ml/min/1.73m<sup>2</sup> were computed over time in nondiabetic  
293 and diabetic cohorts with frequent measures of creatinine using baseline covariates from the cohorts  
294 and weighted-average coefficients from the models (**Figure 1**). The figure illustrates the variability in the  
295 adjusted absolute risk across the cohorts that was unexplained by the covariates included in the models.  
296 Similar findings are shown for the lower incident eGFR thresholds in **eFigure 1** for the nondiabetic  
297 cohorts and **eFigure 2** for the diabetic cohorts.

298



299 Equations for the 5-year predicted risk of incident eGFR<60 ml/min/1.73m<sup>2</sup>, based on the predictive  
300 models and the mean baseline sub-hazards, are shown separately for individuals with or without  
301 diabetes in **eTable 8** and are available online at <http://ckdpcrisk.org/ckdrisk>. The predicted 5-year  
302 absolute risk of incident eGFR<60 ml/min/1.73m<sup>2</sup> in individuals without and with diabetes at three ages  
303 and for various combinations of risk factors are shown in **Figure 2** and in greater detail for all three  
304 incident eGFR thresholds in **eTables 9** and **10**. A wide range of risk was seen, and the level of risk was  
305 strongly associated with the demographic features and co-morbid conditions. The absolute risk was  
306 generally higher in persons with diabetes than in those without and increased with age regardless of the  
307 presence or absence of diabetes. Elevated albuminuria was also significantly associated with the  
308 absolute risk regardless of the presence or absence of diabetes. The 5-year absolute risk for confirmed  
309 eGFR reduction followed the same pattern as for the unconfirmed endpoint, with lower absolute risk for  
310 the confirmed endpoints (**eTables 9** and **10**). Equations for the 5-year predicted risk of other outcomes  
311 are shown in **eTables 11** and **12**.

312

### 313 **Calibration**

314 Model calibration was assessed visually by plotting observed versus predicted risk per decile of  
315 predicted risk at 5 years in the cohorts with frequent measures of creatinine. Plots for the eGFR <60  
316 ml/min/1.73m<sup>2</sup> endpoint are shown in **eFigure 3** and for the lower eGFR endpoints in **eFigures 4** and **5**.  
317 The plots reflected the performance of the equations for the primary endpoint in the cohorts, with 9 of  
318 the 13 (69%) study populations showing a slope of observed to predicted risk between 0.80 and 1.25  
319 (**eTable 13**). Calibration was generally better for the eGFR <60 ml/min/1.73m<sup>2</sup> endpoint compared to  
320 the lower eGFR endpoints, where it was poor in some cohorts (**eTables 14-15**). For example, for eGFR  
321 <45 ml/min/1.73 m<sup>2</sup>, just 5 of 13 (38%) study populations showed a slope between 0.80 and 1.25. For

322 eGFR <30 ml/min/1.73 m<sup>2</sup>, just 4 out of 11 (36%) study populations showed a slope between 0.80 and  
323 1.25. Calibration, by design, was best in the development cohorts with the highest number of events.

324

### 325 **External validation**

326 Model discrimination was tested in 18 study populations in 9 external validation cohorts (N=2,253,540,  
327 **eTable 16**). There were 288,462 events over 4.1 years of follow-up in the population without diabetes  
328 and 78,697 events over 3.5 years of follow-up in the population with diabetes. Discrimination was  
329 similar to that observed in the development cohorts. The median C statistic for the 5-year predicted  
330 probability of all eGFR events <60 ml/min/1.73m<sup>2</sup> was 0.84 (25<sup>th</sup> – 75<sup>th</sup> percentile, 0.83-0.87) in the  
331 population without diabetes and 0.81 (25<sup>th</sup> – 75<sup>th</sup> percentile, 0.80-0.82) in the population with diabetes  
332 (**eTable 17**). Calibration analysis showed that 16 out of 18 (89%) study populations with a slope between  
333 0.80 and 1.25 (**eFigure 6, eTable 18**). Discrimination and calibration for the lower eGFR endpoints are  
334 shown in **eFigures 7-8** and **eTables 17-18**. For example, for eGFR <45 ml/min/1.73 m<sup>2</sup>, 15 out of 18  
335 (83%) of study populations showed a slope between 0.80 and 1.25. For eGFR <30 ml/min/1.73 m<sup>2</sup>, 11  
336 out of 18 (61%) study populations showed a slope between 0.80 and 1.25. Differences in calibration  
337 could not be explained by differences in mean baseline characteristics in the underlying study  
338 populations.

339

### 340 **Comparison to existing equations**

341 The newly developed model for eGFR <60 ml/min/1.73m<sup>2</sup> in the absence of diabetes had better  
342 discrimination than the Chien equation (random-effects meta-analyzed difference in C statistic, 0.094,  
343 95% CI: 0.071-0.117) and the O'Seaghda equation (random-effects meta-analyzed difference in C  
344 statistics, 0.020, 95% CI: 0.015-0.025) when compared in the CKD-PC cohorts. Similarly, the Brier score  
345 was lower using the newly developed equation in the cohorts with frequent measures of creatinine,

346 indicating superior calibration for the newly developed equation (**eTable 19**). In the presence of  
347 diabetes, the newly developed model had better discrimination than the Chien equation (random-  
348 effects meta-analyzed difference in C statistic, 0.107, 95% CI: 0.087-0.128) and the O'Seaghdha equation  
349 (random-effects meta-analyzed difference in C statistics, 0.037, 95% CI: 0.030-0.044) and lower Brier  
350 scores in two out of three cohorts with frequent measures of creatinine. When evaluated in the 9  
351 external validation cohorts, model discrimination and calibration were also better using the newly  
352 developed equations compared to the Chien and O'Seaghdha equations (**eTable 20**).

353

## 354 **DISCUSSION**

355 Risk prediction models were developed that facilitated prediction of the 5-year probability of reduced  
356 eGFR in diverse populations of men and women with variable ages and ethnicity. Models were  
357 developed separately for people with vs. without diabetes. Readily available demographic, clinical, and  
358 laboratory variables were used in these risk models, so that risk calculators from these models could  
359 conceivably be added to electronic health records to identify patients at increased risk for developing  
360 reduced eGFR. Further study is needed to determine whether these risk equations can improve care. For  
361 example, future study could assess whether focusing resources on patients at highest risk of developing  
362 chronic kidney disease improves blood pressure control and/or weight loss. Future study might also  
363 determine whether prescribing medications to improve albuminuria or control diabetes might prevent  
364 occurrence of reduced eGFR in those at risk.

365

366 Several prediction models of CKD exist for use in the general population.<sup>16,17,19,20</sup> Equations previously  
367 developed to identify people at risk for incident eGFR <60 ml/min/1.73m<sup>2</sup> included the Chien equation  
368 and the O'Seaghdha equation, both of which have been externally validated.<sup>15-17</sup> External validation of  
369 the Chien clinical model was previously done in 3,205 Chinese adults from the Chin-Shan Community

370 Cardiovascular Cohort. Moderate discrimination was observed for the clinical prediction model in the  
371 development cohort (c-statistic = 0.77), but the discriminatory power of the model was greatly reduced  
372 in the external validation cohort (c-statistic = 0.67).<sup>16</sup> The O'Seaghdha risk score was validated in 1,777  
373 individuals from the ARIC study (c-statistic = 0.79 in Framingham and 0.74 in ARIC).<sup>17</sup> These prior studies  
374 did not develop separate equations for those with vs. without diabetes. The present study, which  
375 developed scores separately for people with vs. without diabetes, demonstrated higher C-statistics and  
376 better calibration than both the clinical Chien and the O'Seaghdha equations. This was true in the CKD-  
377 PC cohorts used in development of the equations as well as in the 9 external validation cohorts.

378

379 Risk prediction models that estimate the absolute risk of specific adverse health outcomes have become  
380 increasingly popular clinical decision-making tools in recent years, and novel approaches to analyzing  
381 existing data are emerging that may enhance prediction.<sup>21</sup> Several models have been developed for  
382 estimating the risk of prevalent and incident CKD and end-stage kidney disease,<sup>4,16,17,19,20,22-24</sup> but even  
383 those with good discriminative performance have not always performed well in cohorts of people  
384 outside the original derivation cohort.<sup>15</sup> In our study, we show that the incidence of low eGFR varies  
385 across settings, even after adjustment for variable distribution of risk factors, providing an explanation  
386 for differences in calibration in prior studies.

387

388 Calibration is an essential aspect of risk prediction, particularly when absolute risk thresholds are used  
389 to drive clinical care. A tool that overestimates risk may result in unnecessary treatment, whereas one  
390 that underestimates risk may delay optimal management. By design, calibration in the development  
391 cohorts in our study was set to the overall weighted risk. Hence, we focused on calibration on external  
392 cohorts for an unbiased assessment. Surprisingly, in external validation in over 2 million people, model  
393 calibration was even better than that in the development cohorts, suggesting that it may generalize well

394 to US electronic health systems like those represented in OptumLabs Data Warehouse. Other strengths  
395 of this study include the large sample sizes of the nondiabetic and diabetic cohorts, and the broad  
396 clinical, geographic, and ethnic diversity of the individuals in those cohorts. However, we note that  
397 calibration of the developed risk equations may be poor in populations that differ substantially in the  
398 adjusted incidence of reduced eGFR or in which ascertainment of reduced eGFR is more or less sensitive.  
399

#### 400 **Limitations**

401 This study has several limitations. First, the absence of albuminuria data in most nondiabetic cohorts  
402 included in this study required that a statistical patch derived from nondiabetic cohorts with  
403 albuminuria data be applied to the remaining cohorts in order to estimate how inclusion of albuminuria  
404 altered the models. This approach allows valid estimation of risk even in the absence of albuminuria,  
405 although clinical assessment of albuminuria improved risk estimation and detection of early stage CKD  
406 defined by elevated albuminuria (A-stages) in the absence of reduced kidney function (G stages 1-2).<sup>25</sup>  
407 Second, the risk equations developed in this study incorporated routinely collected demographic,  
408 clinical, and laboratory data and their predictive accuracy might be enhanced by incorporating other  
409 variables, including genotype data or newly identified biomarkers of early CKD.<sup>26</sup> Third, the risk  
410 prediction equations developed in this study were intended to identify persons at increased risk of an  
411 intermediate health outcome. The risks of progression from CKD to kidney failure, cardiovascular  
412 disease, or death were not assessed by these equations. Fourth, no minimum change in eGFR was  
413 required in the primary predictive model to become a case of CKD, so someone with a baseline eGFR of  
414 61 ml/min/1.73m<sup>2</sup> and a follow-up eGFR of 59 ml/min/1.73m<sup>2</sup> would be considered to have the  
415 outcome of interest. Fifth, calibration varied across setting, with particularly poor performance in some  
416 of the research cohorts. The models for eGFR <45 and eGFR<30 ml/min/1.73 m<sup>2</sup> were poorly calibrated

417 in many of the development cohorts, which may be due in part to the low number of events and  
418 relatively short follow-up time.

419

420 **Conclusions**

421 Equations for predicting risk of incident chronic kidney disease were developed in over 5 million people  
422 from 34 multinational cohorts and demonstrated high discrimination and variable calibration in diverse  
423 populations.

424

425 **Contributors:** MEG and JC had full access to all the data in the study and take responsibility for the  
426 integrity of the data and the accuracy of the data analysis. RGN, JC, RG, MEG, KM, MW, and VS were  
427 responsible for the study concept and design. JC, SHB, YS, MEG, and KM with the CKD-PC  
428 investigators/collaborators listed below were involved in the acquisition of data. All the authors  
429 contributed to the analysis and interpretation of data and to the critical revision of the manuscript for  
430 important intellectual content. RGN, JC, MEG, and VS drafted the manuscript. MEG guarantees the  
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449 that might have an interest in the submitted work in the previous three years; no other relationships or  
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451

452 **Data sharing:** CKD-PC has agreed with collaborating cohorts not to share data outside the consortium.

453 Each participating cohort has its own policy for data sharing.

454

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

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458 preparation, no compensation was provided to any individuals listed for manuscript review):

459

460 **ADVANCE:** John Chalmers MD, PhD, George Institute, Australia; Mark Woodward, PhD, George Institute,

461 Australia, Oxford University, UK, and Johns Hopkins University, United States; Hisatomi Arima, MD, PhD,

462 George Institute, Australia; Vlado Perkovic, MBBS, PhD, George Institute, Australia; **ARIC:** Josef Coresh,

463 MD, PhD, Johns Hopkins University, United States; Kunihiro Matsushita, MD, PhD, Johns Hopkins

464 University, United States; Morgan Grams, MD, PhD, Johns Hopkins University, United States; Yingying

465 Sang, MSc Johns Hopkins University, United States; **AusDiab:** Kevan Polkinghorne, FRACP, MClInEpi,

466 PhD, Monash University, Australia; Steven Chadban, FRACP, PhD, University of Sydney, Australia; Robert

467 Atkins, FRACP, DSc, Monash University, Australia; **Beijing:** Luxia Zhang, MD, MPH, Peking University First

468 Hospital and Peking University, China; Lisheng Liu, MD, Beijing Hypertension League Institute, China;

469 Minghui Zhao, MD, Peking University First Hospital and Peking-Tsinghua Center for Life Sciences, China;

470 Fang Wang, MD, Peking University First Hospital and Peking University Health Science Center, China;

471 Jinwei Wang, PhD, Peking University First Hospital, China; **CARE:** Marcello Tonelli, MD, SM, University of

472 Alberta, Canada; Frank M. Sacks, MD, Harvard School of Public Health, United States; Gary C. Curhan,



473 MD, ScD, FASN, Channing Division or Network Medicine/Renal Division, Brigham and Women's Hospital,  
474 Harvard Medical School, Harvard School of Public Health, United States; **CHS:** Michael Shlipak, MD,  
475 MPH, University of California, San Francisco and San Francisco VA Medical Center, United States; Mark J  
476 Sarnak, Tufts Medical Center, United States; Ronit Katz, DPhil, University of Washington, United States;  
477 Jade Hiramoto, MD, University of California, San Francisco, United States; **CIRCS:** Hiroyasu Iso, MD, PhD,  
478 MPH, University of Tsukuba, Osaka Center for Cancer and Cardiovascular Disease Prevention, and Osaka  
479 University Graduate School of Medicine, Japan; Kazumasa Yamagishi, MD, PhD, University of Tsukuba  
480 and Osaka Center for Cancer and Cardiovascular Disease Prevention, Japan; Mitsumasa Umesawa, MD,  
481 PhD, University of Tsukuba, Osaka Center for Cancer and Cardiovascular Disease Prevention, and Dokkyo  
482 Medical University, Japan; Isao Muraki, MD, PhD, Osaka Center for Cancer and Cardiovascular Disease  
483 Prevention and Osaka University Graduate School of Medicine, Japan; **ESTHER:** Hermann Brenner, MD,  
484 MPH, German Cancer Research Center, Germany; Ben Schöttker, PhD, German Cancer Research Center,  
485 Germany; Kai-Uwe Saum, MPH, PhD, German Cancer Research Center, Germany; Dietrich Rothenbacher,  
486 MD, MPH, German Cancer Research Center and University of Ulm, Germany; **Framingham:** Caroline S.  
487 Fox, MD, MPH, National Heart, Lung, and Blood Institute, and Merck Research Laboratories, United  
488 States; Shih-Jen Hwang, PhD, National Heart, Lung, and Blood Institute, United States; **Geisinger:** Jamie  
489 Green, MD, MS, Geisinger Medical Center, United States; H Lester Kirchner, PhD, Geisinger Medical  
490 Center, United States; Gurmukteshwar Singh, Geisinger Medical Center, United States; Alex R Chang,  
491 MD, MS, Geisinger Medical Center, United States; **GLOMMS 2:** Corri Black, MBChB, MRCP, MSc, MFPH,  
492 FFPH, University of Aberdeen, United Kingdom; Angharad Marks, MBBCh, MRCP, MSc, PhD, University of  
493 Aberdeen, United Kingdom; Gordon J Prescott, BSc, MSc, PhD, CStat, University of Central Lancashire,  
494 United Kingdom; Laura Clark, MBChB, MD, MRCP, NHS Grampian, Aberdeen, United Kingdom; Nick  
495 Fluck, BSc, MBBC, DPhil, FRCP, NHS Grampian, United Kingdom; **Gubbio:** Massimo Cirillo, MD, University  
496 of Naples "Federico II", Italy; **HUNT:** Stein Hallan, MD, PhD, Norwegian University of Science and

497 Technology and St Olav University, Norway; Solfrid Romundstad, MD, PhD, Norwegian University of  
498 Science and Technology, Norway; Marius Øvrehus, PhD, Norwegian University of Science and  
499 Technology and St Olav University, Norway; Knut Asbjørn Langlo, MD, PhD, Norwegian University of  
500 Science and Technology and St Olav University Hospital, Norway; **IPHS:** Fujiko Irie, MD, PhD, Ibaraki  
501 Prefectural Office, Japan; Toshimi Sairenchi, PhD, Dokkyo Medical University School of Medicine, Japan;  
502 **JHS:** Adolfo Correa, MD, PhD, University of Mississippi Medical Center, United States; Casey M Rebholz,  
503 PhD, Johns Hopkins University, United States; Bessie A Young, MD, MPH, University of Washington and  
504 VA Puget Sound Health Care System, United States; L Ebony Boulware, MD, Duke School of Medicine,  
505 United States; Stanford Mwasongwe, MPH, Jackson State University, United States; **JSHC:** Tsuyoshi  
506 Watanabe, MD, PhD, Fukushima Medical University, Japan; Kunihiro Yamagata, MD, PhD, University of  
507 Tsukuba and Osaka Center for Cancer and Cardiovascular Disease Prevention, Japan; Kunitoshi Iseki,  
508 MD, Okinawa Heart and Renal Association, Japan; Kouichi Asahi, MD, PhD, Fukushima Medical  
509 University, Japan; **Maccabi:** Gabriel Chodick, PhD, Maccabi Healthcare Services, Israel; Varda Shalev,  
510 MD, Maccabi Healthcare Services and Tel Aviv University, Israel; **MESA:** Michael Shlipak, MD, MPH,  
511 University of California, San Francisco and San Francisco VA Medical Center, United States; Mark Sarnak,  
512 MD, MS, Tufts Medical Center, United States; Ronit Katz, DPhil, University of Washington, United States;  
513 Carmen Peralta, MD, MAS, University of California, San Francisco, San Francisco VA Medical Center, and  
514 Cricket Health, Inc, United States; **Mt Sinai BioMe:** Erwin Bottinger, MD, Icahn School of Medicine at  
515 Mount Sinai, United States; Girish N Nadkarni, MD, MPH, Icahn School of Medicine at Mount Sinai,  
516 United States; Stephen B Ellis, MS, Icahn School of Medicine at Mount Sinai, United States; Rajiv  
517 Nadukuru, MS, Icahn School of Medicine at Mount Sinai, United States; **NZDCS:** Timothy Kenealy,  
518 MBChB, PhD, University of Auckland, New Zealand; C Raina Elley, MBChB, PhD, University of Auckland,  
519 New Zealand; John F Collins, MBChB, FRACP, Auckland District Health Board, New Zealand; Paul L Drury,  
520 MA, MB, BCHIR, Auckland District Health Board, New Zealand; **Ohasama:** Takayoshi Ohkubo, MD, PhD,

521 Teikyo University, Japan; Kei Asayama, MD, PhD, Teikyo University, Japan; Hirohito Metoki, MD, PhD,  
522 Tohoku Medical and Pharmaceutical University, Japan; Masahiro Kikuya, MD, PhD, Teikyo University,  
523 Japan; Masaaki Nakayama, MD, PhD, St. Luke's International Hospital, Japan; **Okinawa83/93:** Kunitoshi  
524 Iseki, MD, Okinawa Heart and Renal Association, Japan; Chiho Iseki, PhD, Okinawa Heart and Renal  
525 Association, Japan; **Pima:** Robert G Nelson, MD, PhD, National Institute of Diabetes and Digestive and  
526 Kidney Diseases, United States; Helen C Looker, MBBS, National Institute of Diabetes and Digestive and  
527 Kidney Diseases, United States; William C Knowler, MD, DrPH, National Institute of Diabetes and  
528 Digestive and Kidney Diseases, United States; **PREVEND:** Ron T Gansevoort, MD, PhD, University Medical  
529 Center Groningen, The Netherlands; Stephan JL Bakker, MD, PhD, University Medical Center Groningen,  
530 The Netherlands; Hiddo JL Heerspink, PharmD, PhD, University of Groningen, The Netherlands; **Rancho**  
531 **Bernardo:** Simerjot K Jassal, MD, MAS, University of California San Diego and VA San Diego Healthcare,  
532 United States; Jaclyn Bergstrom, MS, University of California San Diego, United States; Joachim H Ix, MD,  
533 MAS, University of California San Diego and VA San Diego Healthcare, United States; Elizabeth Barrett-  
534 Connor MD, University of California San Diego, United States; **RCAV:** Csaba P Kovcsy, MD, Memphis  
535 Veterans Affairs Medical Center and University of Tennessee Health Science Center, United States;  
536 Kamyar Kalantar-Zadeh, MD, MPH, PhD, University of California Irvine Medical Center, United States;  
537 Keiichi Sumida, MD, PhD, University of Tennessee Health Science Center, United States; **RSIII:** Sanaz  
538 Sedaghat, PhD, Erasmus University Medical Center, The Netherlands; Layal Chaker, MD, PhD, Erasmus  
539 University Medical Center, The Netherlands; M Arfan Ikram, MD, PhD, Erasmus University Medical  
540 Center, The Netherlands; Ewout J Hoorn, MD, PhD, Erasmus University Medical Center, The  
541 Netherlands; Abbas Dehghan, MD, PhD, Imperial College London, United Kingdom; **SCREAM:** Juan J  
542 Carrero, PharmD, PhD, Karolinska Institutet, Sweden; Marie Evans, MD, PhD, Karolinska Institutet,  
543 Sweden; Björn Wettermark, PharmD, PhD, Karolinska Institutet, Sweden; Carl-Gustaf Elinder, MD, PhD,  
544 Karolinska Institutet, Sweden; **SEED:** Tien Yin Wong, MD, PhD, Duke-NUS Medical School, Singapore;

545 Charumathi Sabanayagam, MD, PhD, Singapore Eye Research Institute, Singapore; Ching-Yu Cheng, MD,  
546 PhD, Duke-NUS Medical School, Singapore; Riswana Banu Binte Mohamed Abdul Sokor, Singapore Eye  
547 Research Institute, Singapore; **Taiwan MJ:** Chi-Pang Wen, MD, DrPH, China Medical University Hospital,  
548 Taiwan; Chwen-Keng Tsao, BS, MJ Health Management Institution, Taiwan; Min-Kuang Tsai, MS,  
549 National Health Research Institutes, Taiwan; Chien-Hua Chen, MD, MPH, Show-Chwan Memorial  
550 Hospital, Taiwan; **TLGS:** Farhad Hosseinpanah, MD, Shahid Beheshti University of Medical Sciences, Iran;  
551 Farzad Hadaegh, MD, Shahid Beheshti University of Medical Sciences, Iran; Mohammadhassan  
552 Mirbolouk, MD, Johns Hopkins Ciccarone Center for Prevention of Heart Disease, United States;  
553 Fereidoun Azizi, MD, Shahid Beheshti University of Medical Sciences, Iran; **Tromso:** Marit Dahl Solbu,  
554 MD, PhD, UiT the Arctic University of Norway and University Hospital of North Norway, Norway; Trond  
555 Geir Jenssen, MD, PhD, UiT the Arctic University of Norway and Oslo University Hospital, Norway; Bjørn  
556 Odvar Eriksen, MD, PhD, UiT the Arctic University of Norway and University Hospital of North Norway,  
557 Norway; Anne Elise Eggen, PhD, UiT the Arctic University of Norway, Norway; **ULSAM:** Lars Lannfelt, MD,  
558 PhD, Uppsala University Hospital, Sweden; Anders Larsson, MD, PhD, Uppsala University, Sweden; Johan  
559 Ärnlov MD, PhD, Karolinska Institutet, Sweden; **ZODIAC:** Henk JG Bilo, MD, PhD, University of Groningen  
560 and University Medical Center Groningen, The Netherlands; Gijs WD Landman, MD, Gelre Ziekenhuizen,  
561 The Netherlands; Kornelis JJ van Hateren, MD, Langerhans Medical Research Group, The Netherlands;  
562 Nanne Kleefstra, MD, PhD, Langerhans Medical Research Group and University Medical Centre  
563 Groningen, The Netherlands.

564

565 **External validation cohort – OLDW:** Stephan C. Dunning, MBA, OptumLabs, United States; Nikita  
566 Stempniewicz, MSc, AMGA Alexandria, United States; John Cuddeback, MD, PhD, AMGA Alexandria,  
567 United States; Elizabeth Ciemins, PhD, MPH, MA, AMGA Alexandria, United States.

568

569 **CKD-PC Steering Committee:** Josef Coresh (Chair), MD, PhD, Johns Hopkins University, United States;  
570 Ron T Gansevoort, MD, PhD, University Medical Center Groningen, The Netherlands; Shoshana H Ballew,  
571 PhD, Johns Hopkins University, United States; Alex R. Chang, MD, MS, Geisinger Medical Center, United  
572 States; Morgan E. Grams, MD, PhD, Johns Hopkins University, United States; Stein Hallan, MD, PhD,  
573 Norwegian University of Science and Technology and St Olav University, Norway; Anna Köttgen, MD,  
574 MPH, University of Freiburg, Germany; Csaba P Kovcsdy, MD, Memphis Veterans Affairs Medical Center  
575 and University of Tennessee Health Science Center, United States; Andrew S Levey, MD, Tufts Medical  
576 Center, United States; Kunihiro Matsushita, MD, PhD, Johns Hopkins University, United States; Varda  
577 Shalev, MD, Maccabi Healthcare Services and Tel Aviv University, Israel; Mark Woodward, PhD, George  
578 Institute, Australia, Oxford University, UK, and Johns Hopkins University, United States; Luxia Zhang, MD,  
579 MPH, Peking University First Hospital and Peking University, China.

580

581 **CKD-PC Data Coordinating Center:** Shoshana H Ballew (Assistant Project Director), PhD, Johns Hopkins  
582 University, United States; Jingsha Chen (Programmer), MSc, Johns Hopkins University, United States;  
583 Josef Coresh (Principal Investigator), MD, PhD, Johns Hopkins University, United States; Morgan E Grams  
584 (Director of Nephrology Initiatives), MD, PhD, Johns Hopkins University, United States; Lucia Kwak  
585 (Programmer), MSc, Johns Hopkins University, United States; Kunihiro Matsushita (Director), MD, PhD,  
586 Johns Hopkins University, United States; Yingying Sang (Lead Programmer), MSc, Johns Hopkins  
587 University, United States; Aditya Surapneni (Programmer), PhD, Johns Hopkins University, United  
588 States; Mark Woodward (Senior Statistician), PhD, George Institute, Australia, Oxford University, UK, and  
589 Johns Hopkins University, United States.

590

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**Table 1.** Baseline characteristics of the participants in the 31 nondiabetic and 15 diabetic cohorts.

Study	Country	N	Age	Female	eGFR (ml/min/1.73m <sup>2</sup> )	History of CVD	Hypertension	Smoking	BMI
Nondiabetic cohorts									
ARIC	USA	12757	54 (6)	7082 (56%)	103 (14)	980 (8%)	4437 (35%)	7367 (58%)	27 (5)
AusDiab	Australia	6281	50 (12)	3471 (55%)	88 (14)	306 (5%)	1580 (25%)	2528 (41%)	27 (5)
Beijing	China	948	59 (9)	496 (52%)	85 (12)	127 (13%)	363 (38%)	321 (34%)	25 (3)
CARE	Canada	2923	57 (9)	343 (12%)	80 (13)	2923 (100%)	2432 (83%)	2332 (80%)	28 (7)
CHS	USA	2170	73 (4)	1341 (62%)	77 (11)	409 (19%)	1280 (59%)	1122 (53%)	27 (5)
CIRCS	Japan	10022	54 (9)	6275 (63%)	90 (14)	97 (1%)	3353 (33%)	3507 (35%)	23 (3)
ESTHER	Germany	3394	61 (6)	1885 (56%)	92 (15)	458 (13%)	2213 (65%)	1548 (47%)	27 (4)
Framingham	USA	2353	58 (9)	1290 (55%)	91 (16)	180 (8%)	828 (35%)	368 (16%)	28 (5)
Geisinger	USA	229448	50 (16)	132677 (58%)	95 (18)	23403 (10%)	113953 (50%)	110640 (49%)	30 (7)
GLOMMS 2	UK	24321	61 (14)	13598 (56%)	81 (15)	1962 (8%)	910 (4%)	NA	NA
Gubbio	Italy	1249	54 (6)	714 (57%)	85 (11)	44 (4%)	443 (35%)	688 (55%)	28 (4)
HUNT	Norway	34430	46 (13)	19114 (56%)	102 (15)	1170 (3%)	12377 (36%)	17992 (53%)	26 (4)
IPHS	Japan	70557	60 (10)	47934 (68%)	86 (12)	3603 (5%)	33626 (48%)	19565 (28%)	23 (3)
JHS	USA	2164	48 (11)	1312 (61%)	102 (17)	94 (4%)	885 (41%)	596 (28%)	31 (7)
JSHC	China	461797	63 (8)	279934 (61%)	94 (11)	34567 (9%)	193996 (42%)	62947 (14%)	23 (3)
Maccabi	Israel	939309	43 (15)	546440 (58%)	104 (17)	55138 (6%)	213398 (23%)	231695 (25%)	27 (5)
MESA	USA	4954	61 (10)	2623 (53%)	86 (13)	1 (0%)	2051 (41%)	2600 (53%)	28 (5)
Mt Sinai BioMe	USA	14590	48 (14)	8998 (62%)	93 (19)	722 (5%)	6385 (44%)	3910 (28%)	29 (7)
Ohasama	Japan	2346	60 (10)	1483 (63%)	98 (11)	91 (4%)	832 (35%)	349 (19%)	24 (3)
Okinawa8393	Japan	1624	50 (10)	957 (59%)	100 (13)	0 (0%)	NA	NA	24 (3)
Pima	USA	2733	28 (11)	1626 (59%)	125 (13)	NA	272 (10%)	793 (47%)	33 (8)
PREVEND	Netherlands	5977	49 (12)	3057 (51%)	97 (14)	247 (4%)	1773 (30%)	4160 (70%)	26 (4)



Rancho Bernardo	USA	639	64 (10)	369 (58%)	75 (11)	49 (8%)	232 (36%)	354 (56%)	26 (4)
RCAV	USA	1765629	59 (13)	133822 (8%)	85 (15)	256353 (15%)	1196576 (68%)	NA	29 (6)
RSIII	Netherlands	2292	56 (6)	1333 (58%)	87 (12)	126 (5%)	1375 (60%)	1572 (69%)	27 (4)
SCREAM	Sweden	716952	52 (17)	392827 (55%)	95 (17)	40554 (6%)	177249 (25%)	NA	NA
SEED	Singapore	2358	54 (9)	1246 (53%)	88 (14)	156 (7%)	1164 (50%)	700 (30%)	26 (4)
Taiwan MJ	Taiwan	101216	41 (12)	52658 (52%)	91 (15)	2474 (2%)	16560 (16%)	26037 (28%)	23 (3)
TLGS	Iran	8502	37 (13)	4753 (56%)	81 (13)	171 (2%)	1404 (17%)	1839 (22%)	26 (5)
Tromso	Norway	6007	58 (10)	3522 (59%)	95 (12)	283 (5%)	3183 (53%)	3877 (65%)	26 (4)
ULSAM	Sweden	1142	50 (1)	0 (0%)	98 (10)	5 (0%)	416 (36%)	NA	25 (3)
		4441084	54 (16)	1673180 (38%)	93 (17)	426693 (10%)	1996070 (45%)	509588 (26%)	27 (6)
Diabetic cohorts									
ADVANCE	Multiple*	9339	66 (6)	3774 (40%)	83 (13)	2235 (24%)	8003 (86%)	4024 (43%)	28 (5)
AusDiab	Australia	427	59 (11)	189 (44%)	84 (13)	70 (16%)	287 (67%)	205 (48%)	30 (6)
Beijing	China	343	62 (9)	168 (49%)	85 (12)	80 (23%)	184 (54%)	127 (37%)	25 (4)
Geisinger	USA	34463	58 (15)	16842 (49%)	93 (18)	8606 (25%)	27251 (79%)	17563 (52%)	34 (8)
HUNT	Norway	1564	54 (12)	709 (45%)	95 (14)	130 (8%)	932 (60%)	892 (57%)	28 (5)
JHS	USA	390	54 (10)	241 (62%)	101 (18)	46 (12%)	310 (79%)	131 (34%)	35 (8)
Maccabi	Israel	72480	60 (13)	32972 (45%)	92 (15)	18147 (25%)	54586 (75%)	21733 (30%)	31 (6)
MESA	USA	659	63 (9)	304 (46%)	90 (15)	0 (0%)	455 (69%)	343 (52%)	31 (6)
Mt Sinai BioMe	USA	2652	54 (13)	1598 (60%)	91 (19)	511 (19%)	2013 (76%)	923 (37%)	32 (8)
NZDCS	New Zealand	14819	58 (13)	7152 (48%)	86 (16)	2260 (15%)	10197 (82%)	6469 (44%)	32 (7)
Pima	USA	933	43 (14)	577 (62%)	114 (17)	NA	335 (36%)	291 (40%)	34 (8)
RCAV	USA	607132	63 (10)	20241 (3%)	83 (15)	157611 (26%)	551356 (91%)	NA	32 (6)
SCREAM	Sweden	34307	60 (16)	14224 (41%)	91 (17)	8041 (23%)	20408 (59%)	NA	NA
SEED	Singapore	1029	58 (9)	508 (49%)	88 (15)	151 (15%)	742 (72%)	311 (30%)	28 (5)

ZODIAC	Netherlands	1090	63 (11)	522 (48%)	77 (12)	310 (28%)	794 (73%)	249 (23%)	29 (5)
		781627	62 (11)	100021 (13%)	85 (15)	198198 (25%)	677853 (87%)	53261 (38%)	32 (6)

Values are mean (SD) or percent of total N. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NA, not available. Racial distributions of the cohorts are available in **eTable 4** and the citations for each study are available in **eAppendix 2**.

\* Participants are from Australia, Canada, China, Czech Republic, Estonia, France, Germany, Hungary, India, Ireland, Italy, Lithuania, Malaysia, Netherlands, New Zealand, Philippines, Poland, Russia, Slovakia, and United Kingdom.

**Table 2.** Weighted-average sub-hazard ratios of major risk factors for incident eGFR<60 ml/min/1.73m<sup>2</sup> in the nondiabetic and diabetic cohorts.

Risk factors	Sub-Hazard Ratios (95% CI) for Incident eGFR<60ml/min/1.73m <sup>2</sup>	
	Non-diabetic model	Diabetic model
Age, per 5y	1.29 (1.27, 1.32)	1.14 (1.13, 1.15)
Female	1.20 (1.18, 1.22)	1.15 (1.11, 1.18)
Black	1.20 (1.13, 1.27)	1.10 (1.02, 1.18)
eGFR 60-90, per -5 ml	1.58 (1.57, 1.59)	1.43 (1.41, 1.44)
eGFR 90+, per -5 ml	1.37 (1.34, 1.41)	1.16 (1.14, 1.19)
History of CVD	1.22 (1.18, 1.26)	1.21 (1.17, 1.24)
Ever smoker	1.13 (1.10, 1.16)	1.00 (0.96, 1.04)
Hypertension	1.43 (1.40, 1.46)	1.44 (1.39, 1.50)
BMI, per 5 kg/m <sup>2</sup>	1.07 (1.05, 1.08)	1.05 (1.04, 1.07)
ACR, per 10-fold increase	1.42 (1.37, 1.48) <sup>†</sup>	1.45 (1.42, 1.49)
HbA1c (for oral DM meds), per 1%		1.06 (1.05, 1.07)
Insulin vs. oral DM meds (at 7% hba1c)		1.11 (1.05, 1.19)
No meds vs. oral DM meds (at 7% hba1c)		0.86 (0.83, 0.89)
Interaction: HbA1c * insulin vs. oral DM meds, per 1%		1.02 (1.00, 1.05)
Interaction: HbA1c * No meds vs. oral DM meds, per 1%		1.04 (1.02, 1.06)
ACR missing indicator (set ACR=10)		0.96 (0.93, 1.00)

<sup>†</sup>ACR was modeled using a patch in the non-diabetes model in which the coefficient for ACR was estimated in the population with available ACR with the other coefficients fixed. The model allows for prediction when ACR is missing.

**eTables 9 and 10** provide absolute risk and risk difference scenarios.

Abbreviations: ACR, urine albumin-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.

**Figure 1.** Variation in baseline adjusted competing risk of incident eGFR<60 ml/min/1.73m<sup>2</sup> in nondiabetic (A and C) and diabetic (B and D) cohorts with frequent measures of serum creatinine concentration. All events (confirmed and unconfirmed) are shown in Panels A and B and confirmed events are shown in Panels C and D.

Numbers after the cohort name in the key indicate the mean follow-up time in years. Each line represents the adjusted baseline risk in an individual cohort. The risk was determined by holding the weighted-average coefficients constant and fitting a multivariable competing risk model in each study. The adjusted sub-hazard was smoothed using a Weibull distribution. The pooled line represents the weighted mean which is used in the prediction equation.

**Figure 2.** Predicted 5-year absolute risk of incident eGFR <60 ml/min/1.73m<sup>2</sup> is shown for various scenarios in three ages and albuminuria categories in nondiabetic and diabetic individuals. All 5-year risks were computed for hypothetical individuals with a baseline eGFR of 90 ml/min/1.73m<sup>2</sup>. For the 5-year predicted risk in a hypothetical individual with diabetes, the hemoglobin A1c was also set to 7.7% and the individual was assumed to be receiving an oral diabetes medicine. Scenarios: Sex: male/female, Ethnicity: non-black/black, History of CVD: yes/no, Smoker: yes/no, Hypertension: yes/no, BMI: 25/35 kg/m<sup>2</sup>, ACR: not available (N/A; equation without ACR)/50/500 mg/g (non-DM); 5/50/500 mg/g (DM). Abbreviations: ACR, urine albumin-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus.

\*Each column contains 64 dots representing 64 hypothetical scenarios. The dots are shaded from light to dark based on the number of risk factors present, scaled from 0 to 4 based on the presence or absence of CVD, smoking, hypertension, and BMI 35 kg/m<sup>2</sup>.