

SUPPLEMENTAL MATERIAL

Title: Risk of progression and costs of care for patients with type 2 diabetes and chronic kidney disease

Authors: Navdeep Tangri, MD, PhD^{1*}, Rakesh Singh, PhD², Keith A. Betts, PhD³, Yuxian Du, PhD², Sophie Gao, MS³, Arvind Katta, PharmD, MS², Youssef M.K. Farag, MD, PhD, MPH², Samuel T. Fatoba, PhD², Hongjiao Liu, PhD³, Jingyi Chen, MS⁴, Thomas Ferguson, MS¹, Reid Whitlock, MS¹, Silvia J. Leon, MD¹, Ajay K. Singh, FRCP, MBA⁵

Affiliations:

¹ Department of Community Health Services, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

² Bayer U.S. LLC, Whippany, NJ, USA

³ Analysis Group, Inc., Los Angeles, CA, USA

⁴ Analysis Group, Inc., Boston, MA, USA

⁵ Harvard Medical School, Boston, MA, USA

***Corresponding author:**

Navdeep Tangri, MD, PhD

Email: ntangri@sogh.mb.ca

Supplementary Table S1. Diagnosis and procedure codes for chronic dialysis and kidney transplantation

Procedure	Coding classification system	Codes
Chronic dialysis	ICD-9-CM, Vol. 1 or 2 (diagnosis codes)	585.6, V45.11, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8
	ICD-10-CM codes	N18.6, Z99.2, Z49.31, Z49.01, Z49.02, Z49.31, Z49.32, Y84.1
	CPT4	90918, 90919, 90920, 90921, 90922, 90923, 90924, 90925, 90935, 90937, 90940, 90945, 90947, 90951, 90952, 90953, 90954, 90955, 90956, 90957, 90958, 90959, 90960, 90961, 90962, 90963, 90964, 90965, 90966, 90967, 90968, 90969, 90970, 90989, 90993, 90997, 90999
	HCPCS	G0257, G8081, G8082, G8085, G8714, G8715, G8956, G9264, G9265, G9266, S9335, S9339, G0491, G0492
		<i>Codes used in claims before 1/1/2009:</i> G0317, G0318, G0319, G0320, G0321, G0322, G0323, G0324, G0325, G0326, G0327
	ICD-9-CM, Vol 3 (procedure codes)	38.95, 39.27, 39.42, 39.95, 54.98
Kidney transplantation	ICD-10-PCS	5A1D00Z, 5A1D60Z, 3E1M39Z, 5A1D70Z, 5A1D80Z, 5A1D90Z
	ICD-9-CM, Vol 1 or 2 (diagnosis codes)	996.81, V42.0
	ICD-10-CM	T86.10, T86.11, T86.12, T86.13, T86.19, Z94.0, Z48.22
	ICD-9-CM, Vol 3 (procedure codes)	00.91, 00.92, 00.93, 55.53, 55.61, 55.69
	ICD-10-PCS	0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2
	DRG	652, 008
	CPT4	50360, 50365, 50370, 50380

Abbreviations: CPT, Current Procedural Terminology; DRG, Diagnosis-related Group; HCPCS, Healthcare Common Procedure Coding System; ICD-9/10-CM, International Classification of Diseases, 9th/10th Revision, Clinical Modification; ICD-10-PCS, International Classification of Diseases, 10th Revision, Procedure Coding System.

Supplementary Table S2. Diagnosis codes for comorbidities

Comorbidity	ICD-9-CM	ICD-9-CM
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428	I09.81, I11.0, I13.0, I13.2, I50.1-I50.9
Hypertension	362.11, 401-405, 437.2	H35.031-H35.039, I10-I13.2, I15.0-I15.9, I16, I67.4, N26.2
Myocardial infarction	410, 412	I21.01-I22.9, I25.2
Stroke	430, 431, 432, 433.x1, 434.x1	G45.0-G45.2, G45.4-G46.8, I60-I64, I65, I66, I67.1, I67.2, I67.4- I67.82, I67.841-I69.998
Type 1 diabetes mellitus	250.x1, 250.x3	E10
Type 2 diabetes mellitus	250.x0, 250.x2	E11

Abbreviation: ICD-9/10-CM, International Classification of Diseases, 9th/10th Revision, Clinical Modification.

Supplementary Table S3. Baseline characteristics of patients with CKD and type 2 diabetes stratified by risk of CKD progression

	Low risk N = 110,399 (A)	Medium risk N = 253,188 (B)	High risk N = 49,590 (C)	SMD (A) vs. (B)	SMD (B) vs. (C)
Demographics					
Age at index date, years	58.0 ± 13.0	64.8 ± 12.1	66.5 ± 12.2	0.540	0.144
Sex				0.041	0.019
Female	59,850 (54.2)	132,019 (52.1)	25,396 (51.2)		
Male	50,549 (45.8)	121,169 (47.9)	24,194 (48.8)		
Race				0.080	0.092
White	87,728 (79.5)	205,533 (81.2)	38,586 (77.8)		
African American	13,311 (12.1)	31,328 (12.4)	7,379 (14.9)		
Asian	2,777 (2.5)	4,242 (1.7)	733 (1.5)		
Other/unknown	6,583 (6.0)	12,085 (4.8)	2,892 (5.8)		
Region				0.053	0.065
Midwest	64,086 (58.0)	152,047 (60.1)	28,299 (57.1)		
Northeast	14,606 (13.2)	34,213 (13.5)	7,465 (15.1)		
South	21,484 (19.5)	44,667 (17.6)	9,434 (19.0)		
West	6,763 (6.1)	14,994 (5.9)	2,908 (5.9)		
Other/unknown	3,460 (3.1)	7,267 (2.9)	1,484 (3.0)		
Health insurance provider					
Commercial	83,883 (76.0)	171,947 (67.9)	31,265 (63.0)	0.180	0.102
Medicare	40,194 (36.4)	137,150 (54.2)	31,152 (62.8)	0.363	0.176
Medicaid	17,924 (16.2)	38,470 (15.2)	10,495 (21.2)	0.029	0.155
Uninsured	15,764 (14.3)	33,389 (13.2)	7,528 (15.2)	0.032	0.057
Other payer type	5,416 (4.9)	13,040 (5.2)	3,355 (6.8)	0.011	0.068
Unknown	3,894 (3.5)	10,327 (4.1)	2,391 (4.8)	0.029	0.036
Comorbidities*					
Type 2 diabetes	110,399 (100.0)	253,188 (100.0)	49,590 (100.0)	0.000	0.000
Hypertension	82,960 (75.1)	205,546 (81.2)	42,482 (85.7)	0.147	0.121
Type 1 diabetes	4,938 (4.5)	11,823 (4.7)	3,837 (7.7)	0.009	0.127
Stroke	4,252 (3.9)	15,321 (6.1)	4,904 (9.9)	0.102	0.142
Myocardial infarction	3,827 (3.5)	13,684 (5.4)	5,346 (10.8)	0.094	0.198
Heart failure	4,006 (3.6)	20,407 (8.1)	10,456 (21.1)	0.190	0.376
Medication use					
ACEi	42,597 (38.6)	102,236 (40.4)	19,476 (39.3)	0.037	0.023
ARB	21,826 (19.8)	51,892 (20.5)	9,535 (19.2)	0.018	0.032
SGLT2i	5,925 (5.4)	10,230 (4.0)	964 (1.9)	0.063	0.123
Steroidal MRA	2,666 (2.4)	9,038 (3.6)	3,548 (7.2)	0.068	0.160
GLP-1 RA	8,303 (7.5)	14,886 (5.9)	1,891 (3.8)	0.066	0.096
Laboratory test results†					
eGFR‡, ml/min/1.73m²	90.1 ± 20.6	78.8 ± 20.8	61.3 ± 24.6	0.544	0.767
eGFR stages				0.516	0.775
G1 (≥90 ml/min/1.73m²)	62,661 (56.8)	85,760 (33.9)	7,103 (14.3)		
G2 (60-89 ml/min/1.73m²)	31,125 (28.2)	106,935 (42.2)	17,587 (35.5)		
G3a (45-59 ml/min/1.73m²)	15,933 (14.4)	48,306 (19.1)	11,112 (22.4)		
G3b (30-44 ml/min/1.73m²)	678 (0.6)	11,542 (4.6)	8,224 (16.6)		
G4 (15-29 ml/min/1.73m²)	2 (0.0)	645 (0.3)	4,877 (9.8)		

	Low risk N = 110,399 (A)	Medium risk N = 253,188 (B)	High risk N = 49,590 (C)	SMD (A) vs. (B)	SMD (B) vs. (C)
G5 (<15 ml/min/1.73m ²)	0 (0.0)	0 (0.0)	687 (1.4)		
UACR§, mg/g	53.4 ± 54.3	109.3 ± 175.2	710.9 ± 1,290.9	0.430	0.653
UACR stages				0.386	1.006
A1 (<30 mg/g)	15,358 (13.9)	39,638 (15.7)	5,953 (12.0)		
A2 (30-300 mg/g)	93,390 (84.6)	187,943 (74.2)	18,319 (36.9)		
A3 (>300 mg/g)	1,651 (1.5)	25,607 (10.1)	25,318 (51.1)		
Serum potassium, mmol/l	4.2 ± 0.4	4.3 ± 0.5	4.4 ± 0.6	0.132	0.201
Blood urea nitrogen, mmol/l	5.3 ± 1.6	6.4 ± 2.4	10.1 ± 5.5	0.580	0.859
Serum albumin, g/l	41.9 ± 3.6	40.5 ± 4.3	36.3 ± 6.2	0.344	0.797
Serum calcium, mmol/l	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.2	0.056	0.392
Hemoglobin, g/l	142.0 ± 12.3	134.4 ± 16.6	114.9 ± 19.8	0.522	1.067
Blood glucose, mmol/l	8.4 ± 3.4	9.0 ± 4.3	9.7 ± 5.3	0.156	0.128
Serum bicarbonate, mmol/l	26.1 ± 2.7	26.1 ± 3.3	25.2 ± 4.8	0.005	0.216
Missing	104,593 (94.7)	238,068 (94.0)	45,107 (91.0)		
AST, IU/l	25.5 ± 14.2	25.9 ± 21.0	29.7 ± 41.3	0.024	0.114
ALT, IU/l	31.7 ± 21.4	29.4 ± 29.6	30.5 ± 67.7	0.089	0.020
ALKP, IU/l	79.7 ± 25.1	84.1 ± 37.3	103.0 ± 80.6	0.140	0.301
Serum phosphate, mmol/l	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3	0.074	0.397
Missing	105,549 (95.6)	236,391 (93.4)	39,315 (79.3)		
Serum chloride, mmol/l	101.9 ± 3.0	101.8 ± 3.8	102.4 ± 5.3	0.050	0.128

Data are presented as mean ± standard deviation for continuous variables or n (%) for categorical variables.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; SMD, standardized mean difference; SGLT2i, sodium glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

Notes:

* Comorbidities were identified using diagnosis codes listed in Supplementary Table S2.

† Results from tests performed in the inpatient or emergency room setting were not used. Missing rates are reported for laboratory values that were missing in more than 30% of the patients.

‡ Baseline eGFR was calculated as the average of all eGFR results during the 6 months before and including the index date; for other laboratory values, the closest results during the 1 year before and including the index date were used.

§ When UACR test was not available, UACR was estimated based on urine protein-to-creatinine ratio (UPCR) test or if unavailable, urine dipstick test results using the following equations:

UPCR to UACR: $\exp(5.3920 + 0.3072 \times \log(\min(\text{PCR}/50, 1)) + 1.5793 \times \log(\max(\min(\text{PCR}/500, 1), 0.1)) + 1.1266 \times \log(\max(\text{PCR}/500, 1)))$

Dipstick to UACR: $\exp(2.4738 + 0.7539 \times (\text{if trace}) + 1.7243 \times (\text{if } +) + 3.3475 \times (\text{if } ++) + 4.6399 \times (\text{if } >+))$

Supplementary Table S4. Annual all-cause HRU in patients with CKD and type 2 diabetes stratified by risk of CKD progression*,†

	Low risk N = 110,399	Medium risk N = 253,188	High risk N = 49,590
HRU assessment duration, years	1.00 ± 0.05	0.98 ± 0.10	0.93 ± 0.21
Inpatient admissions			
Patients with at least 1 inpatient admission	14,514 (13.15)	49,594 (19.59)	19,689 (39.70)
Number of inpatient admissions	0.23 ± 0.91	0.45 ± 1.62	1.48 ± 3.80
Hospitalization duration, days	1.04 ± 5.72	2.23 ± 10.02	8.28 ± 23.59
ER visits			
Patients with at least 1 ER visit	23,552 (21.33)	58,498 (23.10)	16,065 (32.40)
Number of ER visits	0.49 ± 1.82	0.53 ± 1.78	0.92 ± 2.45
Outpatient visits			
Patients with at least 1 outpatient visit	110,154 (99.78)	252,526 (99.74)	49,195 (99.20)
Number of outpatient visits	25.07 ± 20.43	27.53 ± 22.89	34.88 ± 30.36

Data are presented as mean ± standard deviation for continuous variables or n (%) for categorical variables.

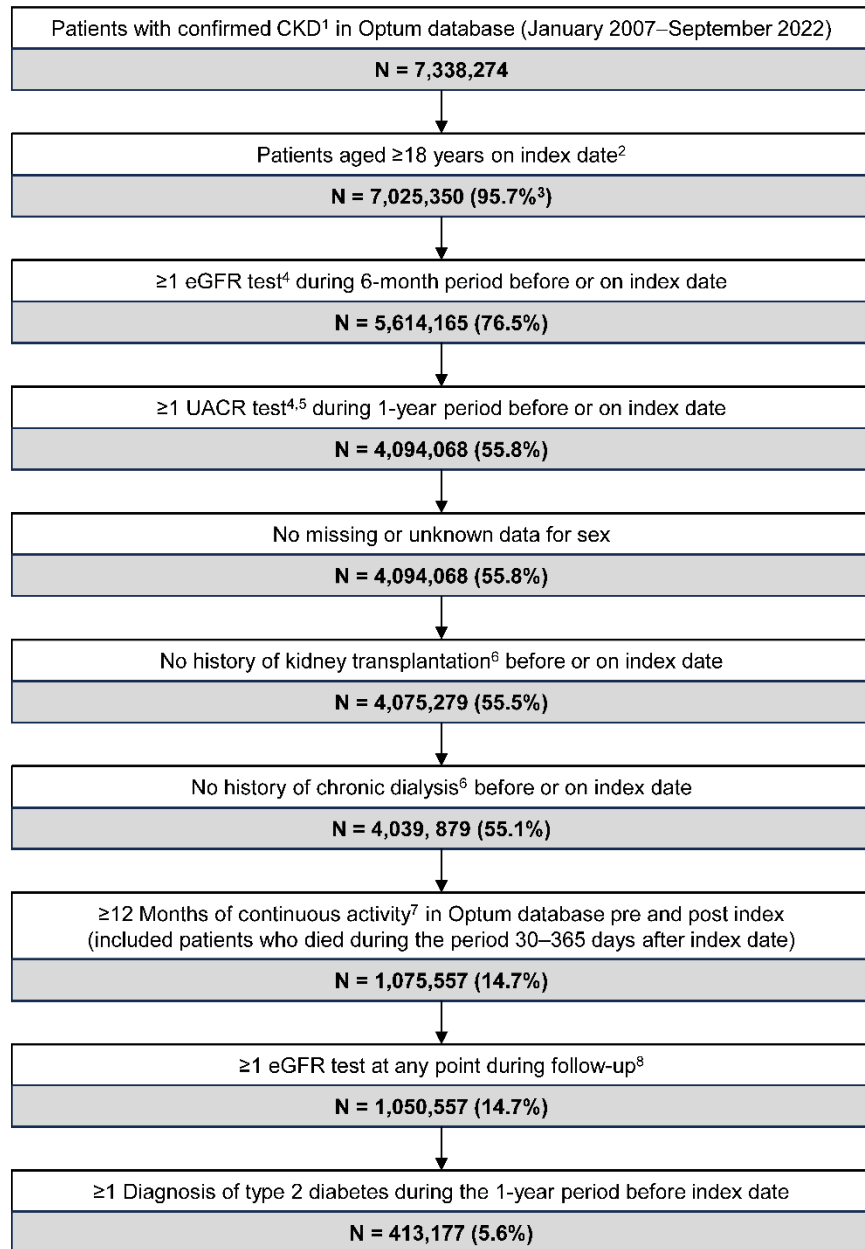
Abbreviations: CKD, chronic kidney disease; ER, emergency room; HRU, healthcare resource utilization.

Notes:

* HRU was assessed during the 1 year after the index date, or from the index date to the end of follow-up for patients who died within 1 year. The latter situation explains the HRU assessment duration of <1 year for the medium- and high-risk groups.

† Medical services that occurred in the emergency patient setting were classified as ER visits; those that occurred in settings including inpatient, skilled nursing facility inpatient, nursing home / assisted living, inpatient psychiatry, inpatient rehabilitation, swing bed, and long-term acute care were classified as inpatient visits; and all other medical services were classified as outpatient visits.

Supplementary Figure S1. Sample selection. ¹Case definition of CKD: 1) ≥ 2 reduced eGFR values (< 60 ml/min/1.73m²) measured 90–548 days apart; or 2) ≥ 1 abnormal UACR (≥ 30 mg/g). ²Index date was defined as the first date on which the patient met the case definition for CKD. ³Percentage of patients from the original sample (N=7,338,274). ⁴Results from laboratory tests performed in the inpatient or ER setting were not used. ⁵When UACR test results were not available, UACR was estimated based on urine protein-to-creatinine ratio (UPCR) test or if unavailable, urine dipstick test results using the following equations: for UPCR to UACR, $\exp(5.3920 + 0.3072 \times \log(\min(\text{PCR}/50, 1)) + 1.5793 \times \log(\max(\min(\text{PCR}/500, 1), 0.1)) + 1.1266 \times \log(\max(\text{PCR}/500, 1)))$; and for dipstick to UACR, $\exp(2.4738 + 0.7539 \times (\text{if trace}) + 1.7243 \times (\text{if } +) + 3.3475 \times (\text{if } ++) + 4.6399 \times (\text{if } > ++))$. ⁶Diagnosis and procedure codes used to identify chronic dialysis and kidney transplantation are listed in Supplementary Table S1. ⁷A patient was considered continuously active in the data until either a 6-month gap between consecutive medical records or the last recorded activity date, whichever came first. ⁸Follow-up was defined as the time from the index date to the end of continuous enrollment, death, or end of data cutoff, whichever was earliest. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.



Supplementary Figure S2. Performance of the Klinrisk model for prediction of 2-year risk of CKD progression in patients with CKD and type 2 diabetes. The area under the receiver operating characteristic curve (95% confidence interval) was 0.764 (0.764, 0.764).

