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PromarkerD

WE'RE CHANGING LIVES

A new blood test for predicting diabetic kidney disease

A Comparison of PromarkerD to Standard of Care Tests for Predicting Renal Decline in Type 2 Diabetes

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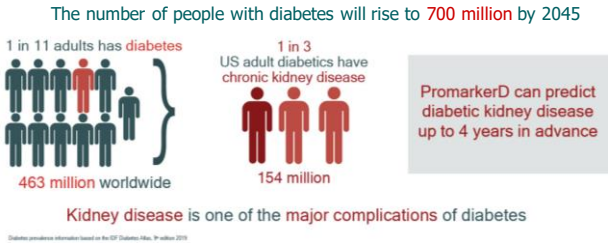
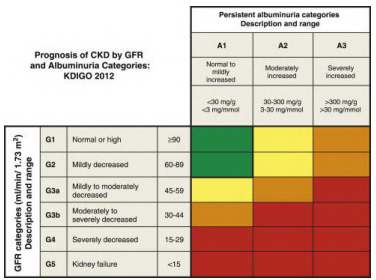
Background & Aim

- Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease and is associated with increased morbidity and mortality.[1]
- Current standard of care (SoC) for the definition, classification and prognosis of chronic kidney disease (CKD) is defined by the KDIGO guidelines[2], and includes measurement of both estimated glomerular filtration rate (eGFR) and urinary albumin: creatinine ratio (ACR), but both tests have limitations in predicting future renal decline.[3]
- The KDIGO GFR and albuminuria grid depicts the risk of CKD progression, morbidity and mortality by color: low (green), moderate (yellow), high (orange), and very high (red) risk.
- PromarkerD is a simple biomarker-based blood test that can predict future renal function decline classified as low (green), moderate (orange) or high (red) risk in individuals with type 2 diabetes (T2D).[4,5]





Risk Score	Intervention	Testing Regimen[6]
Low Risk	• Standard diabetes management	Test Annually
Moderate Risk	• More frequent monitoring • Optimisation of lifestyle • Review of glycemic targets and management • Review non-glycemic risk factors • Avoidance of potentially nephrotoxic drugs • Utilisation of therapeutic drugs	Test every 3-6 months
High Risk	• Very close monitoring • Intensive management strategies based on those for 'Moderate risk' above with optimisation of treatments for diabetes and other risk factors	Test every 3 months

Interpretation of Risk Scores (based on recommendations from the ADA DKD Consensus report)[6]

- The aim of this study was to compare the biomarker-based PromarkerD test with SoC for predicting future renal decline in the next 4 years in community-based patients with T2D.

[1] https://www.cdc.gov/kidneydisease/pdf/Chronic-Kidney-Disease-in-the-US-2021-h.pdf, [2] Kidney Disease Improving Clinical Outcomes (KDIGO) Guideline Development Working Group, Kidney Int. Suppl. 2013;3:1-150, [3] Dunkler et al., CJASN. 2015;10:1371-1379, [4] Peters et al., Diab Care. 2017;40:1548-1555, [5] Peters et al., J Diab Comp. 2019;33:107406, [6] Tuttle et al., Diabetes Care. 2014;37(10):2864-2883.

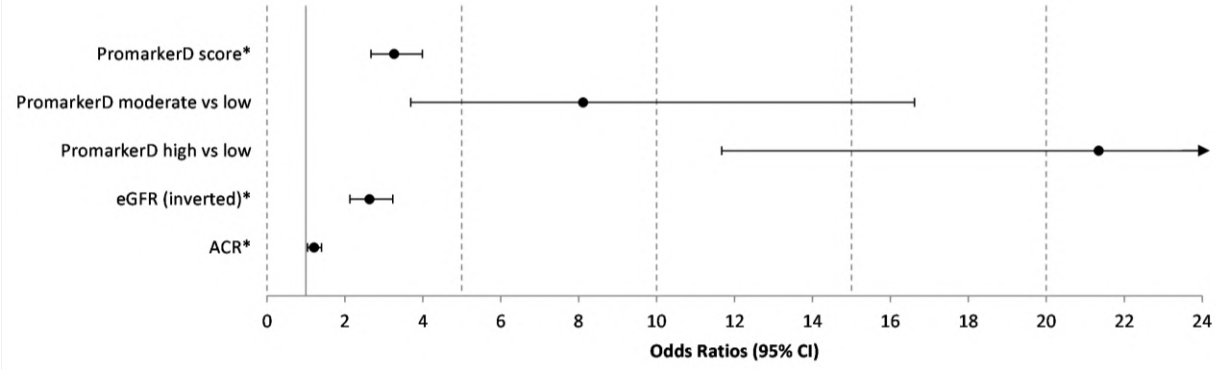
Methods

- Baseline PromarkerD scores were measured in 857 individuals with T2D from the Fremantle Diabetes Study Phase II (FDS2) (mean age 65 years, 54% males, median diabetes duration 7 years, mean eGFR 82 mL/min/1.73m^2 and geometric mean ACR 26 mg/g).[1,2]
- PromarkerD scores combine 3 protein biomarker concentrations (CD5L, ApoA4, IGFBP3) measured by mass spectrometry with clinical data (age, serum HDL-cholesterol, eGFR) using a validated algorithm, and are categorized as low, moderate or high risk for renal decline in the next 4 years.
- The primary endpoint was decline in renal function defined as incident DKD (reduction in eGFR to <60 mL/min/1.73m^2 during follow-up) or eGFR decline ≥30% in those with baseline eGFR <60 mL/min/1.73m^2.
- Logistic regression modeling was used to compare the association of i) PromarkerD, ii) eGFR, iii) ACR, and iv) eGFR + ACR, with renal decline during 4 years of follow-up.
- Model performance was assessed by the ROC area under the curve (AUC) and Sn, Sp, PPV and NPV determined at the maximum Youden Index.
- The proportion of patients in each PromarkerD or KDIGO risk category[3] by outcome status was compared and the Sn, Sp, PPV and NPV of positive vs negative test results determined:
  - For PromarkerD, moderate or high risk scores were treated as positive results, whereby patients would be flagged for early intervention and/or closer monitoring of disease. A low PromarkerD risk score was set as a negative result.
  - For KDIGO, a positive result was defined as moderate, high or very high risk, with low risk set as negative.

[1] Peters et al., Diab Care. 2017;40:1548-1555, [2] Peters et al., J Diab Comp. 2019;33:107406, [3] KDIGO Guideline Development Working Group, Kidney Int. Suppl. 2013;3:1-150. Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

Association with future renal decline

- At baseline, participants were classified by PromarkerD as low (63%), moderate (13%) or high risk (24%), and by KDIGO[1] as low (58%), moderate (31%), high (7%), or very high risk (4%) for renal decline in the next 4 years.
- During 4.2±0.3 years of follow-up, 107 (12.5%) patients experienced a decline in renal function.
- Higher PromarkerD scores had a stronger association with renal decline (OR=3.26, 95% CI 2.67-3.99 per 1 SD increase) compared to lower eGFR and higher ACR (OR=2.63 (2.13-3.23)^ and 1.21 (1.04-1.40) per 1 SD increase, respectively).
- PromarkerD moderate and high risk scores were increasingly prognostic for renal decline (OR 8.11 (3.69-16.62) and 21.34 (11.67-39.02) versus low risk, respectively; both *P* <0.001).



Logistic regression was used to compare the association of PromarkerD score, eGFR and ACR with decline in renal function. The odds ratio (OR) and 95% confidence intervals (CI) are shown. *OR are per 1-SD increase in the respective variable. PromarkerD moderate and high risk scores were compared to low risk scores as reference. ^The OR for eGFR was inverted for ease of comparison. PromarkerD score remained significantly associated with outcome after adjusting for eGFR and ACR (OR=2.78 (2.19-3.53) per 1 SD increase).

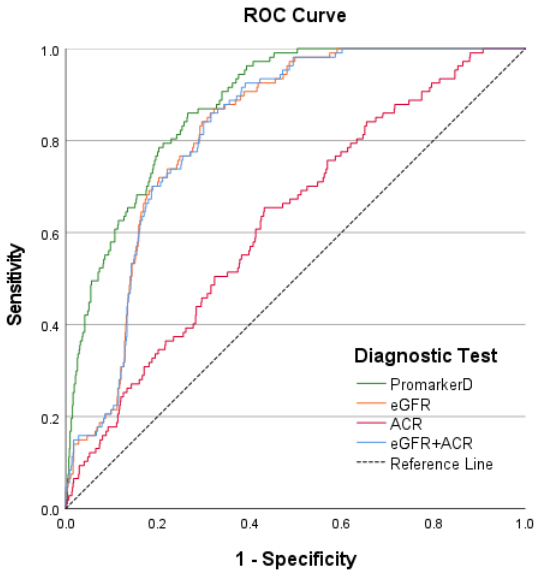
[1] KDIGO Guideline Development Working Group, Kidney Int. Suppl. 2013;3:1-150. Renal decline defined as incident DKD (reduction in eGFR to <60 mL/min/1.73m^2 during follow-up) or eGFR decline ≥30% in those with baseline eGFR <60 mL/min/1.73m^2 in the next 4 years.

Model performance – ROC AUC

- PromarkerD had significantly higher predictive performance (AUC 0.88, 95% CI 0.85-0.91) compared to SoC tests for predicting decline in renal function in the next 4 years (all P <0.001).
- PromarkerD had higher Sp and PPV compared to SoC tests, and similar Sn and NPV.

Diagnostic Test	Incident DKD or eGFR Decline ≥30% in 4yrs				
N with outcome/total (%)	107/857 (12.5%)				
	AUC (95% CI), Sig. P-value*	Sn (%)	Sp (%)	PPV (%)	NPV (%)
PromarkerD	**0.88 (0.85-0.91)**	**86**	**74**	**32**	**97**
Moderate risk#		**87**	70	30	97
High risk#		68	**83**	36	95
eGFR	0.82 (0.79-0.85)*	87	68	28	97
ACR	0.63 (0.58-0.68)*	65	57	18	92
eGFR+ACR	0.82 (0.79-0.85)*	86	68	28	97

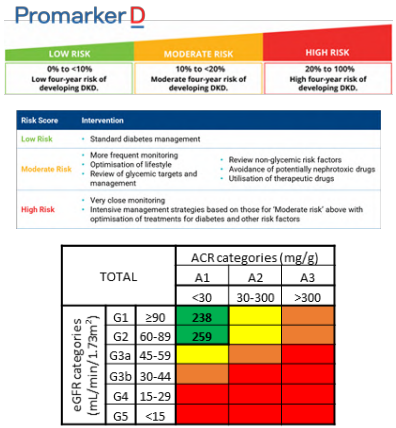
The PromarkerD test compared to eGFR, ACR and the combination of eGFR+ACR for predicting decline in renal function. ROC, receiver operating characteristic; AUC, area under the curve; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value. Performance metrics (Sn, Sp, PPV, NPV) are provided at the maximum Youden Index (Sn+Sp-1). This provides the maximum achievable Sn and Sp for each test. # The test performance of PromarkerD is also provided at the moderate risk (≥10%) and high risk (≥20%) test cut-offs which are intended for use in clinical practice. *Testing the null hypothesis that the difference in AUC between each model and the PromarkerD model is zero (all P <0.001).



Decline in renal function defined as incident DKD (reduction in eGFR to <60 mL/min/1.73m^2 during follow-up) or eGFR decline ≥30% in those with baseline eGFR <60 mL/min/1.73m^2 in the next 4 years.

PromarkerD benefits KDIGO low risk patients

- Of the 497 patients in the green KDIGO low risk category with normal kidney function, 45 (9%) developed incident DKD in the next 4 years and would be missed by usual SoC tests eGFR and ACR.
- PromarkerD results:
  - 84% of patients that developed outcome had positive PromarkerD scores and were flagged for early intervention and/or closer monitoring of disease → 30 of the 45 patients classified as high risk and 8 as moderate risk.
  - 78% (354/452) of the patients that did not develop outcome were classified as low risk.
  - High negative predictive value or "rule-out" capability, with 98% (354/361) of patients with low risk results not developing outcome.



The proportion of FDS2 participants in each PromarkerD or KDIGO risk category by outcome status

PromarkerD Risk Category	Incident DKD (eGFR <60)		
	No outcome	Outcome	Total
Low risk	**354**	7	361 (72.6%)
Moderate risk	40	**8**	48 (9.7%)
High risk	58	**30**	88 (17.7%)
Total	452	45 (9%)	497

FN: 7
TP: 38 FP: 98 136

Sn	**84%**	38/45
Sp	**78%**	354/452
PPV	28%	38/136
NPV	**98%**	354/361

KDIGO CKD Risk Category	Incident DKD (eGFR <60)		
	No outcome	Outcome	Total
Low risk (green)	452	**45**	497

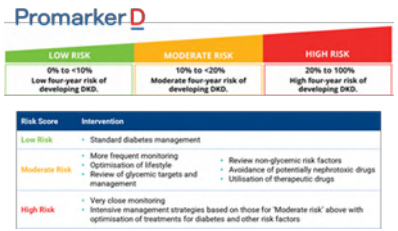
FN: 45

Sn/PPV	**0%**	
Sp	**100%**	452/452
NPV	91%	452/497

N.B. The outcome for this subgroup was incident DKD (reduction in eGFR to <60 mL/min/1.73m^2 during follow-up) as all patients had baseline eGFR ≥60 mL/min/1.73m^2. FN, false negative; TP, true positive; FP, false positive; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

PromarkerD benefits KDIGO at-risk patients

- Of the 360 patients in the KDIGO at-risk categories, 62 (17%) developed incident DKD or had eGFR decline ≥30% in the next 4 years and would be captured by usual SoC tests eGFR and ACR, while 298 (83%) would be false positives.
- PromarkerD results:
  - 89% of patients that developed outcome had positive PromarkerD scores and were flagged for early intervention and/or closer monitoring of disease → 43 of the 62 patients classified as high risk and 12 as moderate risk.
  - 58% (174/298) of the patients that did not develop outcome were classified as low risk.
  - High negative predictive value or "rule-out" capability, with 96% (174/181) of patients with low risk results not developing outcome.



TOTAL			ACR categories (mg/g)		
			A1	A2	A3
			<30	30-300	>300
eGFR categories (mL/min/1.73m²)	G1	≥90		86	16
	G2	60-89		142	9
	G3a	45-59	35	26	3
	G3b	30-44	11	20	3
	G4	15-29	0	5	2
	G5	<15	0	0	2

The proportion of FDS2 participants in each PromarkerD or KDIGO risk category by outcome status

PromarkerD Risk Category	Incident DKD (eGFR <60) or eGFR 30% decline		
	No outcome	Outcome	Total
Low risk	**174**	7	181 (50.3%)
Moderate risk	53	**12**	65 (18%)
High risk	71	**43**	114 (31.7%)
Total	298	62 (17%)	360

→ FN 7; TP 55; FP 124; 179 →

Sn	**89%**	55/62
Sp	**58%**	174/298
PPV	31%	55/179
NPV	**96%**	174/181

KDIGO CKD Risk Category	Incident DKD (eGFR <60) or eGFR 30% decline		
	No outcome	Outcome	Total
Low risk (green)	0	0	0
Moderate (yellow)	222	41	263 (73.1%)
High risk (orange)	55	7	62 (17.2%)
Very high risk (red)	21	14	35 (9.7%)
Total	298	62	360

→ TN 0; TP 62; FP 298 →

Sp/NPV	**0%**	
Sn	**100%**	62/62
PPV	17%	62/360

[1] KDIGO Guideline Development Working Group, Kidney Int. Suppl. 2013;3:1-150. Renal decline defined as incident DKD (reduction in eGFR to <60 mL/min/1.73m² during follow-up) or eGFR decline ≥30% in those with baseline eGFR <60 mL/min/1.73m² in the next 4 years. FN, false negative; TP, true positive; FP, false positive; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

Conclusions

- PromarkerD significantly outperformed the conventional standard of care tests eGFR and ACR for predicting future decline in renal function in 857 community-based patients with type 2 diabetes.
- PromarkerD scores were more strongly associated with renal decline defined as incident DKD or eGFR decline ≥30% in the next 4 years compared to standard of care, and remained significantly associated with outcome after adjusting for eGFR and ACR.
- PromarkerD moderate and high risk scores were increasingly prognostic for renal decline.
- PromarkerD correctly identified 84% of patients with normal kidney function that went on to experience renal decline in the next 4 years that would be missed by KDIGO risk classification, classified 78% of those that did not develop outcome as low risk, and had an excellent "rule-out" rate. In these patients, PromarkerD testing would support cost effective individualized treatment via:
  - Early introduction of preventative medications in high risk patients
  - Closer monitoring of risk factors in moderate risk patients
  - Rationalized treatment options in low risk patients
- PromarkerD also identified 89% of patients with abnormal kidney function that declined further during follow-up, with a higher "rule-out" rate and considerably less false positives compared to standard of care testing.