INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.70275

BRIEF COMMUNICATION

Prognostic value of a plasma protein-based biomarker test for chronic kidney disease complicating diabetes in Aboriginal Australians

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Key words
diabetes, Aboriginal, diabetic kidney disease, prognostic test.

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Received 4 August 2025; accepted 5 November 2025.

Abstract

The predictive value of PromarkerD tests for incident diabetic kidney disease or rapid decline in estimated glomerular filtration rate was evaluated in 1010 non-Aboriginal and 71 Aboriginal adults with diabetes. Areas under the receiver operating characteristic curves were not significantly different ($P \geq 0.081$) for first- (non-Aboriginals 0.890 (95% confidence interval 0.864 to 0.915) and Aboriginals 0.769 (0.624 to 0.915)) and second-generation (0.890 (0.862 to 0.917) and 0.711 (0.543 to 0.878)) tests. PromarkerD has potential renal prognostic value in Aboriginals with diabetes.

It has long been recognised that Aboriginal and Torres Strait Islander people with type 2 diabetes (T2D) have among the highest rates of end-stage kidney disease (ESKD) in the world.[1] In addition to associated increased cardiovascular disease morbidity and premature mortality,[2,3] this patient group faces significant sociodemographic, geographical and economic challenges associated with optimal prevention and management of ESKD.[4,5] Early identification of Aboriginal and Torres Strait Islander people with T2D who are at risk of a rapid decline in estimated glomerular filtration rate (eGFR) could, therefore, facilitate targeted lifestyle and pharmacological strategies that substantially delay progression to ESKD,[6] with clear benefits for individuals and their communities.

PromarkerD is a biomarker-based blood test that has clinically useful predictive value for future renal function decline in T2D,[7,8] and it is also at least as prognostically accurate in type 1 diabetes (T1D).[9] The test is based on measurement of the plasma concentrations of three proteins, apolipoprotein A-IV (ApoA4), CD5 antigen-like (CD5L) protein (or apoptosis inhibitor of macrophage) and insulin-like growth factor binding protein 3 (IBP3) and utilises a small number of other variables that are readily available in routine care. The original development of PromarkerD was conducted in the Fremantle Diabetes Study Phase II (FDS2) cohort, which was drawn from a representative multi-ethnic urban Australian

Funding: FDS2 was supported by the National Health and Medical Research Council project grants 513781 and 1042231. The present sub-study was supported by the Australian Centre for Accelerating Diabetes Innovations. Sample analysis was performed in the Western Australian (WA) Proteomics Facility, a node of Proteomics Australia and is supported by infrastructure funding from the Western Australian State Government in partnership with Bioplatforms Australia under the Commonwealth Government National Collaborative Research Infrastructure Strategy. TMED was supported by a Medical Research Future Fund Practitioner Fellowship (1154192). These funding bodies had no involvement in the study design, data collection, analysis and interpretation of results or writing this manuscript.
Conflict of interest: Proteomics International and the University of Western Australia are beneficiaries of patent PCT/AU2011/001212 which relates to the biomarkers described in this manuscript. TMED, KEP, RJL and WAD are named as inventors of this patent. There are no other potential conflicts of interest relevant to this article.

population.[10] To date, there has been no analysis of the performance of PromarkerD by ethnic/racial group. The aim of the present study was, therefore, to assess the prognostic accuracy of PromarkerD in Aboriginal versus non-Aboriginal participants recruited to FDS2 from the primary catchment area of Fremantle Hospital (FH; $n \approx 150\,000$), with extension of the Aboriginal sample to include individuals with diabetes who were resident in the approximately equivalent population base comprising the adjacent FH secondary catchment area.[11]

The FDS2 is a community-based, longitudinal observational study with recruitment from 2008 to 2011 and biennial in-person assessments from entry to up to 6 years subsequently.[10] The Aboriginal Diabetes Substudy (ADSS) recruited participants in the secondary catchment area between 2013 and 2014. The FDS2 protocol was approved by the Fremantle Hospital Human Rights Committee (reference 07/397) and the ADSS by the Western Australian Aboriginal Health Ethics Committee (reference 485). All participants provided witnessed informed consent. At baseline and biennial reviews, all FDS2 participants underwent comprehensive assessments including questionnaires, clinical examinations and fasting biochemical tests performed in a single nationally accredited laboratory.[10] The ADSS utilised the same methodology.

The PromarkerD constituent protein biomarkers ApoA4, CD5L and IBP3 were measured in unthawed baseline plasma samples stored at −80°C by CaptSure enzyme-linked immunosorbent assay (TGR BioSciences, an Abcam company, Adelaide, South Australia) as previously described.[12] The original PromarkerD test uses the three biomarker concentrations and age, serum high-density lipoprotein cholesterol and eGFR.[7,8] The second-generation PromarkerD test, which has equivalent prognostic accuracy in T2D, utilises only two biomarker concentrations (ApoA4 and CD5L) as well as age and eGFR.[13] Both tests produce a risk score which is the predicted probability (0%–100%) output from a logistic regression model of adverse kidney outcomes.[7,8]

Renal function was assessed in all participants at baseline and in those returning for reviews between 3 and 5 years later or with a serum creatinine available from the medical record during the same period (both considered Year 4 in the present analyses). The eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine.[14] The primary outcome was kidney function decline evaluated by one of two definitions. The first was incident diabetic kidney disease (DKD), defined as an eGFR <60 mL/min/1.73 m^2 at Year 4 in individuals whose baseline eGFR was ≥60 mL/min/1.73 m^2. The second was a decline in eGFR of either ≥30% or ≥40% between baseline and Year 4 in participants with a baseline eGFR <60 mL/min/1.73 m^2.

All statistical analyses were performed using the computer package IBM SPSS Statistics 29 (IBM Corporation, Armonk, NY, USA). Demographic and clinical data are presented as mean ± standard deviation (SD) or proportions (%), where applicable. The original PromarkerD test predicts the 4-year risk of incident DKD or ≥30% eGFR decline, while the second-generation test predicts incident DKD or ≥40% eGFR decline. Test performance was assessed by the area under the receiver operating characteristic curve (ROC-AUC). PromarkerD test scores were stratified into low-, moderate- and high-risk categories using pre-specified thresholds: 10% for moderate-risk, and either 20% (original test) or 36% (second-generation test) for high-risk, selected to maximise sensitivity and specificity. The sensitivity, specificity, positive and negative predictive values (PPV and NPV) were determined at the prespecified test cut-offs and the maximum Youden Index (sensitivity+specificity-1). ROC-AUCs were compared for each version of the test between non-Aboriginals and Aboriginals.[15]

The present sample included 1010 (62.4%) out of the 1619 non-Aboriginal participants recruited to FDS2 who had valid Year 4 renal function data (see Table 1). Similarly, there were 71 Aboriginal participants in the present analyses (see Table 1) comprising 52 from FDS2

Table 1 Baseline characteristics by study (FDS2 or ADSS) and Aboriginal status

Variable	All	FDS2 Non-Aboriginal	FDS2 Aboriginal	ADSS Aboriginal	FDS2 + ADSS Aboriginal
Number	1081	1010	52	19	71
Age (years)	63.0 ± 12.6	63.5 ± 12.5	55.4 ± 11.9	56.2 ± 12.5	55.6 ± 11.9
Sex (% male)	54.1	55.1	34.6	52.6	39.4
Type 2 diabetes (%)	87.3	86.8	92.3	100.00	94.3
Diabetes duration (years)	8.6 (2.4–15.6)	8.5 (2.3–15.6)	11.0 (3.0–18.0)	8.0 (3.0–11.0)	10.0 (3.0–16.8)
HbA_{1c} (%)	6.9 (6.3–7.8)	6.8 (6.2–7.7)	9.6 (7.2–11.1)	7.7 (6.3–8.7)	8.7 (6.8–10.8)
Serum HDL-cholesterol (mmol/L)	1.26 ± 0.36	1.27 ± 0.36	1.16 ± 0.34	1.02 ± 0.26	1.12 ± 0.33
eGFR (mL/min/1.73m^2)	83.3 ± 19.6	83.1 ± 19.4	84.5 ± 24.2	86.9 ± 20.6	85.2 ± 23.2

HbA1c, glycated haemoglobin; HDL-cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

(46.0% of the 113 Aboriginal participants recruited to FDS2; 37 with a face-to-face assessment at Year 4 and 15 with an eGFR from hospital records 3–5 years after the baseline assessment) and 19 from the ADSS (six with a face-to-face Year 4 assessment and 13 with eGFR from hospital records 3–5 years after baseline).

For the first-generation PromarkerD assay, there were 117 renal events among the non-Aboriginal participants (11.6%) and 17 events in the 71 Aboriginal participants (23.9%) over an average of 4 years. Two non-Aboriginal participants had follow-up time <3.0 years with baseline eGFR >90 mL/min/1.73m^2 and minimal eGFR decline and were therefore assumed not to have achieved the primary renal outcome. There were three Aboriginal participants with a follow-up <3.0 years who had a baseline eGFR <90 mL/min/1.73m^2 (two ≥60 mL/min/1.73 m^2 with eGFR at follow-up <60 mL/min/1.73m^2 and one <60 mL/min/1.73 m^2 but with rapidly declining eGFR ≥40% during follow-up), and all three were considered to have achieved the primary renal outcome. Fifty non-Aboriginal and 14 Aboriginal participants had a follow-up time ≥ 5.0 years, but the kidney outcome did not change if the follow-up eGFR was linearly interpolated backwards to <5 years. For the second-generation test, there were 107 renal events among the non-Aboriginal participants (10.6%) and 14 events in the 71 Aboriginal participants (19.7%) over an average of 4 years.

The results of ROC-AUC analyses are shown in Figure 1. For the first-generation PromarkerD test, the non-Aboriginals had a ROC-AUC of 0.890 (95% CI: 0.864 to 0.915) and the Aboriginals one of 0.769 (0.624 to 0.915). The difference between these two values was not statistically significant ($P = 0.107$). For the second-generation test, the non-Aboriginals had a ROC-AUC of 0.890 (0.862 to 0.917) and the Aboriginals one of 0.711 (0.543 to 0.878). The difference between these two values was also not statistically significant ($P = 0.081$). The sensitivity, specificity, PPV and NPV are summarised in Table 2. There were high NPVs (≥0.85) for both generation tests and at both moderate- and high-risk cut-offs except for Aboriginal participants for the high-risk thresholds.

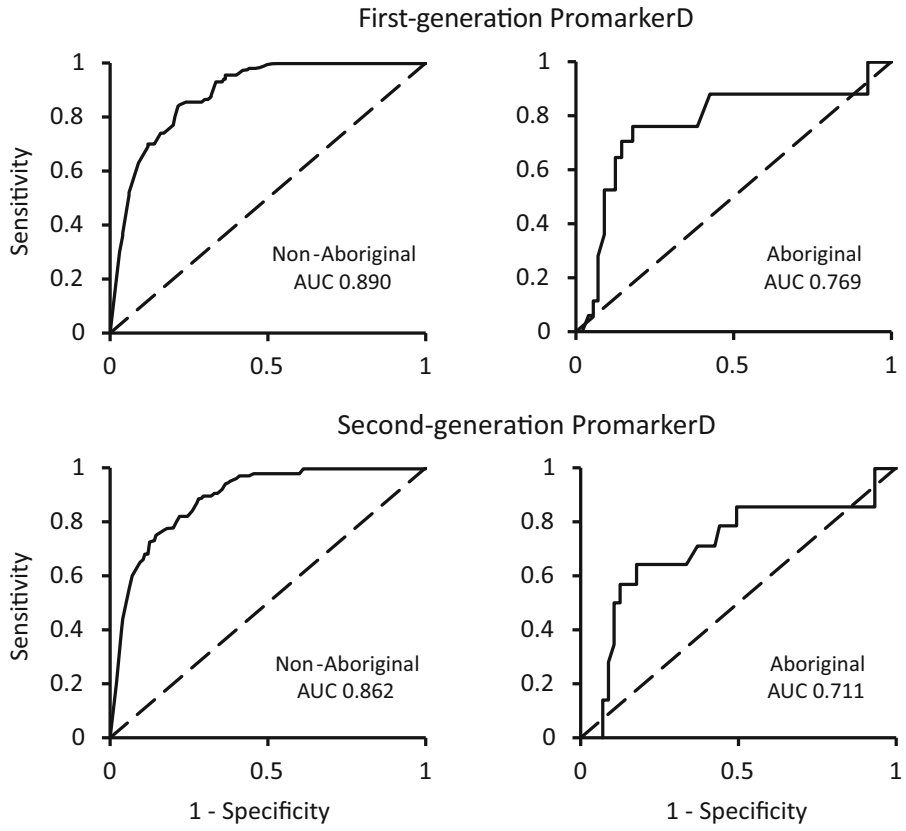

Figure 1 Receiver operating characteristic curves (ROC) for first- and second-generation PromarkerD tests in non-Aboriginal and Aboriginal participants. The areas under the ROCs (AUC) are shown.

Table 2 Measures of prognostic accuracy for first- and second-generation PromarkerD tests in non-Aboriginal and Aboriginal participants

Participant group and PromarkerD test	Sensitivity	Specificity	Positive predictive value	Negative predictive value
First-generation PromarkerD (positive/negative)				
Non-Aboriginal	0.85	0.78	0.34	0.98
Aboriginal	0.77	0.82	0.57	0.92
First-generation PromarkerD (moderate-risk ≥10%)				
Non-Aboriginal	0.86	0.71	0.28	0.97
Aboriginal	0.47	0.91	0.62	0.85
First-generation PromarkerD (high-risk ≥20%)				
Non-Aboriginal	0.74	0.83	0.36	0.96
Aboriginal	0.12	0.94	0.40	0.77
Second-generation PromarkerD (positive/negative)				
Non-Aboriginal	0.89	0.72	0.27	0.98
Aboriginal	0.64	0.83	0.47	0.90
Second-generation PromarkerD (moderate-risk ≥10%)				
Non-Aboriginal	0.86	0.73	0.27	0.98
Aboriginal	0.43	0.90	0.50	0.86
Second-generation PromarkerD (high-risk ≥36%)				
Non-Aboriginal	0.51	0.95	0.55	0.94
Aboriginal	0	0.95	0	0.79

Discussion

The present data show that, based on ROC-AUC analyses, both generations of the PromarkerD test have acceptable prognostic value (ROC-AUC >0.7) for DKD in Aboriginals with diabetes. The NPVs were generally high, including at moderate- and high-risk cut-offs. This indicates that a low PromarkerD risk score in Aboriginal people with diabetes could be used to inform rational management strategies that optimise adherence to treatment[16] and do not divert healthcare resources away from areas of greater need. A low score would also alleviate inappropriate concern in people with diabetes and their healthcare professionals regarding the future development of DKD. The modest to low PPVs need to be viewed in light of the small number of false positive results. In any case, intensive renal risk reduction management, if not needed for DKD, may have other benefits in these individuals, including for cardiovascular disease risk.

Although there were no statistically significant differences between the two groups, the fact that the tests in non-Aboriginals had excellent (ROC-AUC >0.8) rather than acceptable prognostic accuracy suggests that there may be some minor racial differences in either the constituent biomarkers or patterns of renal decline. Although there are no published data for racial differences in CD5L and IBP3 that would have implications for PromarkerD, Aboriginals may have a different apolipoprotein, including ApoA4, profile relative to other ethnic groups.[17] The effect of this on PromarkerD scores is uncertain. Although there are differences in body composition between Aboriginal and non-Aboriginal people in Australia, these have a minor impact on eGFR measurements,[18] and the present study was primarily concerned with temporal changes in eGFR rather than absolute values. Nevertheless, consistent with data showing a much greater potential for renal decline in Aboriginal groups,[19] renal events of interest in our Aboriginal participants occurred at around twice the rate of those in the non-Aboriginal participants.

Because of cultural, logistical and systemic barriers to regular care, which limited the number of Aboriginal participants in FDS2 and ADSS with valid longitudinal renal function data, the availability of diabetes-related point-of-care (POC) tests in Aboriginal communities can allow timely and culturally appropriate disease management.[20] There is the potential for the second-generation PromarkerD test to be POC, which would further assist the immediate management of Aboriginal people with diabetes.

The present data provide evidence that PromarkerD can identify the future risk of DKD in Aboriginals with diabetes. Given the diversity of clinical situations in which Aboriginal people are managed,[4,5] there is a need for further validation in other Australian Aboriginal groups with larger numbers of participants, including in usual-care contexts outside epidemiological studies.

Acknowledgements

We are grateful to FDS2 and ADSS participants and to FDS2 staff for help with collecting samples and recording clinical information. We are indebted to Kerry Hunt, Research Officer, Medical School, University of Western

Australia, Fremantle Hospital for her contribution to recruitment and screening of the Aboriginal participants. We thank the Biochemistry Department, Fremantle Hospital and Health Service for performing laboratory tests and Gareth Fernandez for calculating PromarkerD scores. FDS2 was supported by the National Health and Medical Research Council project grants 513781 and 1042231. The present sub-study was supported by the Australian Centre for Accelerating Diabetes Innovations. Sample analysis was performed in the Western Australian (WA) Proteomics Facility, a node of Proteomics Australia, and is supported by infrastructure funding from the Western Australian State Government in partnership with Bioplatforms Australia under the Commonwealth Government National Collaborative Research Infrastructure Strategy. TMED was supported by a Medical Research Future Fund Practitioner Fellowship (1154192). These funding bodies had no involvement in the study design, data collection, analysis and interpretation of results or writing of this manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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