

Proteomics International

LABORATORIES LTD

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PromarkerD significantly outperforms current standard of care tests in predicting future kidney function decline

- **Study shows PromarkerD is significantly better than current standard of care tests eGFR and ACR for predicting future decline in kidney function in patients with type 2 diabetes**
- **PromarkerD correctly identified 84% of patients with normal kidney function that went on to experience kidney function decline that would be missed by standard of care tests**
- **For patients whose kidney function did not decline PromarkerD demonstrated a higher “rule-out” rate and considerably less false positives than standard of care testing**
- **PromarkerD predictive testing for diabetic kidney disease could reduce the risk of dialysis or kidney transplant leading to significant cost savings for healthcare systems**
- **Results presented today at the American Society of Nephrology Kidney Week 2021 meeting**

Proteomics International Laboratories Ltd (Proteomics International; ASX: PIQ) is pleased to announce the results of a study demonstrating that the PromarkerD test for diabetic kidney disease outperforms current standard of care tests in predicting kidney function decline in type 2 diabetes.

The research, presented today at Kidney Week 2021, the annual meeting of the American Society of Nephrology (ASN), compared the PromarkerD test to current standard of care tests, the estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR). The study updates and extends previous analysis [ASX: 10 and 17 September 2019] and constitutes a core body of evidence underpinning the performance of PromarkerD for submissions to global regulators.

The results showed PromarkerD outperformed the current tests in predicting the onset of diabetic kidney disease during the four-year follow-up period. The study involved retrospective analysis of more than 850 community-based patients with type 2 diabetes from the Fremantle Diabetes Study Phase II.

In the study, PromarkerD correctly identified 84% of patients with normal kidney function who went on to experience kidney function decline in the next four years. Critically, all of these patients would have been missed by the eGFR and ACR tests which constitute the current gold standard of care under the global KDIGO (Kidney Disease Improving Clinical Outcomes) guidelines for risk classification¹. PromarkerD also identified 89% of patients with abnormal kidney function who declined further over the course of the study.

The PromarkerD test measures the level of three plasma biomarkers in the blood. These are combined with clinical data in a validated algorithm to provide a PromarkerD score categorised as low, moderate or high risk.

The study found patients classified by PromarkerD as high risk were 21 times more likely to develop diabetic kidney disease (DKD) within four years than those classified as low risk. Patients classified as moderate risk by PromarkerD were 8 times more likely than low-risk patients to develop the disease.

¹ Kidney Disease Improving Clinical Outcomes (KDIGO) Guideline Development Working Group, *Kidney Int. Suppl.* 2013;3:1-150

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PromarkerD also had significantly higher (P <0.001) predictive performance (AUC = 0.88) compared to eGFR (0.82), ACR (0.63), and eGFR and ACR combined (0.82).

Across all KDIGO categories of diabetes and kidney disease PromarkerD exhibited an excellent “rule-out” rate (Negative Predictive Value [NPV] >96%), for categorising patients at low risk of developing DKD, and demonstrated considerably less false positives compared to standard of care testing.

Proteomics International managing director Dr Richard Lipscombe said PromarkerD testing can help improve the management of diabetes for both patients and the healthcare system. “PromarkerD gives doctors the data they need to support early introduction of preventive medications to slow the progression of DKD in high-risk patients, closer monitoring of risk factors in moderate-risk patients, and rationalised treatment options in low-risk patients,” he said.

ASN Kidney Week² is the largest nephrology conference in the United States, attracting over 10,000 attendees. This year, the virtual event will be held from 4-7 November 2021. The results are being presented as a scientific e-poster (see attached copy) titled:

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

The conference forms part of the Company's ongoing strategy to engage with Key Opinion Leaders (KOL's), physicians and industry representatives at global health forums to show the benefits of implementing PromarkerD testing. In October, Proteomics International's announced results of a clinical utility study demonstrating that PromarkerD tests were more important to physicians than the current standard of care tests with more than three-quarters of physicians reporting they were very or extremely likely to use PromarkerD in the future [ASX: 18 October]. In May and June, the Company presented an economic health benefit study demonstrating the potential cost savings to the US healthcare system if PromarkerD was adopted, compared to the current standard of care [ASX: 2 July].

Glossary

Sensitivity (Sn) (true positive rate)	The ability of a test to correctly identify those with the disease.
Specificity (Sp) (true negative rate)	The ability of the test to correctly identify those without the disease.
Negative Predictive Value (NPV)	The probability that people who get a negative test result truly do not have the disease. In other words, it is the probability that a negative test result is accurate.
Positive Predictive Value (PPV)	The probability that a patient with a positive (abnormal) test result actually has the disease. When the occurrence of a disease is low, the positive predictive value will also be low, even using a test with high sensitivity and specificity.
AUC	"Area Under the ROC Curve". A receiver operating characteristic curve, or ROC curve, is a graphical plot that illustrates the performance of a classifier system.
Interpreting AUC values	Conventionally the clinical significance of AUC is: > 0.7 acceptable discrimination > 0.8 excellent discrimination > 0.9 outstanding discrimination
PromarkerD algorithm	The power of the PromarkerD test system is that it can be calibrated to provide optimal results: <ul style="list-style-type: none"> • Maximise sensitivity or PPV to capture those at high risk of progressing towards dialysis or kidney transplant • Maximise specificity or NPV to rule-out those who are at low risk of progressing towards dialysis or kidney transplant

² www.asn-online.org/education/kidneyweek/

Authorised by the Board of Proteomics International Laboratories Ltd (ASX.PIQ).

ENDS

About PromarkerD (www.PromarkerD.com)

Diabetic kidney disease (DKD) is a serious complication arising from diabetes which if unchecked can lead to dialysis or kidney transplant. PromarkerD is a prognostic test that can predict future kidney function decline in patients with type 2 diabetes and no existing DKD. The patented PromarkerD test system uses a simple blood test to detect a unique 'fingerprint' of the early onset of the disease by measuring three serum protein biomarkers, combined with three routinely available conventional clinical variables (age, HDL-cholesterol and estimated glomerular filtration rate (eGFR)). A cloud-based algorithm integrates the results into a patient risk report. In clinical studies published in leading journals PromarkerD correctly predicted up to 86% of otherwise healthy diabetics who went on to develop diabetic kidney disease within four years. The PromarkerD test is CE Mark registered in the European Union.

Further information is available through the PromarkerD web portal.

To visit the PromarkerD virtual booth please see: www.PromarkerD.com/product

About Proteomics International Laboratories (PILL) (www.proteomicsinternational.com)

Proteomics International (Perth, Western Australia) is a wholly owned subsidiary and trading name of PILL (ASX: PIQ), a medical technology company at the forefront of predictive diagnostics and bio-analytical services. The Company specialises in the area of proteomics – the industrial scale study of the structure and function of proteins. Proteomics International's mission is to improve the quality of lives by the creation and application of innovative tools that enable the improved treatment of disease.

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Promarker^D

WE'RE CHANGING LIVES

A new blood test for predicting diabetic kidney disease



Poster P00737
November 2-7, 2021

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

Kirsten E. Peters^{1,2}, Scott D. Bringans¹, Wendy A. Davis², Richard J. Lipscombe¹, Timothy M.E. Davis²

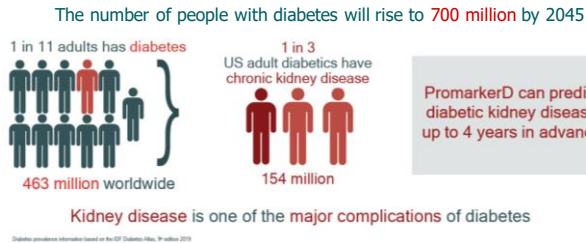
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Disclosures: This study was funded by Proteomics International. PromarkerD biomarker concentrations and risk scores were measured using archived samples from the Fremantle Diabetes Study Phase II by Proteomics International using a patented test owned by the company. The Fremantle Diabetes Study Phase II was funded by the National Health and Medical Research Council of Australia project grants 513781 and 1042231.

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 guidelines², 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}



Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012		Persistent albuminuria categories Description and range		
		A1	A2	A3
GFR categories (ml/min/1.73 m ²) Description and range	G1 Normal or high	>90		
	G2 Mildly decreased	60-89		
G3a Mildly to moderately decreased	45-59			
	G3b Moderately to severely decreased	30-44		
G4 Severely decreased	15-29			
G5 Kidney failure	<15			
		Normal to mildly increased <30 mg/g <30 mg/mol	Moderately increased 30-300 mg/g 3-300 mg/mol	Severely increased >300 mg/g >300 mg/mol

PromarkerD



Risk Score	Intervention	Testing Regimen ⁶
Low Risk	<ul style="list-style-type: none"> Standard diabetes management 	Test Annually
Moderate Risk	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

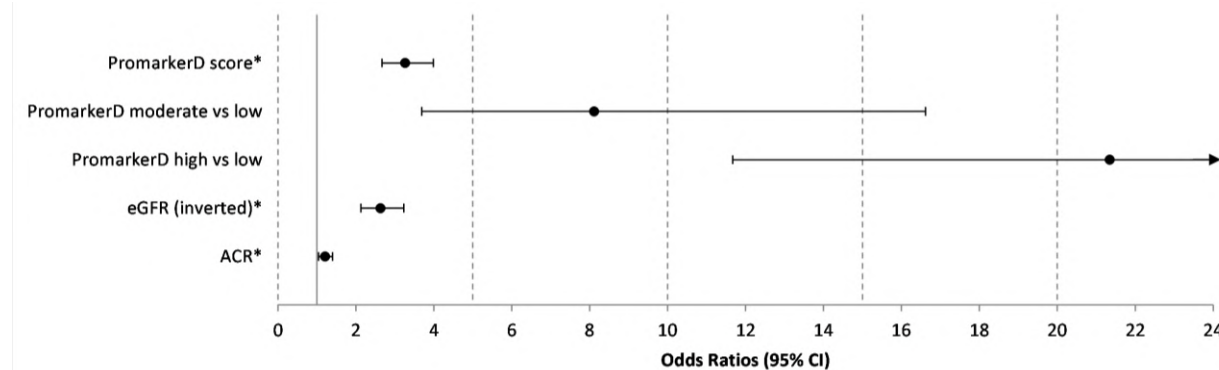
- The aim of this study was to compare the biomarker-based PromarkerD test with SoC for predicting future renal decline in the next 4 years in community-based patients with T2D.

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/1.73m² 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/1.73m² during follow-up) or eGFR decline ≥30% in those with baseline eGFR <60 mL/min/1.73m².
- 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 category³ 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.

Association with future renal decline

- At baseline, participants were classified by PromarkerD as low (63%), moderate (13%) or high risk (24%), and by KDIGO¹ 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 $P < 0.001$).



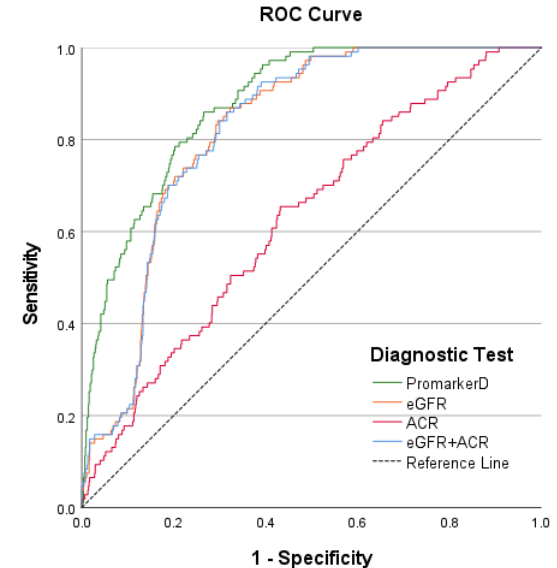
Logistic regression was used to compare the association of PromarkerD score, eGFR and ACR with decline in renal function. The odds ratio (OR) and 95% confidence intervals (CI) are shown. *OR are per 1-SD increase in the respective variable. PromarkerD moderate and high risk scores were compared to low 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).

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 $\geq 30\%$ 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 ($\geq 10\%$) and high risk ($\geq 20\%$) 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 $P < 0.001$).



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.

PromarkerD

LOW RISK	MODERATE RISK	HIGH RISK
0% to <10% Low four-year risk of developing DKD	10% to <20% Moderate four-year risk of developing DKD	20% to 100% High four-year risk of developing DKD

Risk Score	Intervention
Low Risk	Standard diabetes management
Moderate Risk	More frequent monitoring Optimisation of lifestyle Review of glycaemic targets and management Review non-glycaemic risk factors Avoidance of potentially nephrotoxic drugs Utilisation of therapeutic drugs
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

TOTAL		ACR categories (mg/g)		
		A1	A2	A3
		<30	30-300	>300
eGFR categories (mL/min/1.73m ²)	G1	≥90	238	
	G2	60-89	259	
	G3a	45-59		
	G3b	30-44		
	G4	15-29		
G5	<15			

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
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Sn/PPV	0%
Sp	100%
NPV	91%

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 $\geq 30\%$ 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 \rightarrow 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.

PromarkerD

LOW RISK	MODERATE RISK	HIGH RISK
0% to <10% Low four year risk of developing DKD.	10% to <20% Moderate four-year risk of developing DKD.	20% to 100% High four-year risk of developing DKD.
Risk Score	Intervention	
Low Risk	<ul style="list-style-type: none"> Standard diabetes management More frequent monitoring Optimization of Lifestyle 	<ul style="list-style-type: none"> Review non-glycemic risk factors Avoidance of potentially nephrotoxic drugs
Moderate Risk	<ul style="list-style-type: none"> Review of glycemic targets and management 	<ul style="list-style-type: none"> Utilization of therapeutic drugs
High Risk	<ul style="list-style-type: none"> Very close monitoring Intensive management strategies based on those for "Moderate risk" above with optimization of treatments for diabetes and other risk factors. 	

TOTAL		ACR categories (mg/g)			
		A1 <30	A2 30-300	A3 >300	
eGFR categories (mL/min/1.73m ²)	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	124
FP		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	298
FP		

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

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 $\geq 30\%$ 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.