Australian Government

Department of Health

MSAC Application 1691:

PromarkerD testing in patients with type 2 diabetes (T2DM) to determine the risk of developing diabetic kidney disease

Ratified

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC).

Table 1 PICO for predictive test for diabetic kidney disease in people with type 2 diabetes mellitus

Component	Description
Population	Patients would be eligible to use PromarkerD if they met the following criteria: a. Type 2 diabetes mellitus (T2DM) diagnosis; and b. Estimated glomerular filtration rate (eGFR) of greater than or equal to 60ml/min/1.73m^2; and c. Albumin: Creatinine Ratio (uACR) test results of less than or equal to 30mg/mmol.
Prior tests	Tests required to confirm diagnosis of T2DM. Prior measurement of eGFR and uACR is required. Prior measurement of HDL cholesterol is required. The application did not provide any requirements for the timeframe within which the eGFR, uACR and HDL cholesterol tests must be conducted. The applicant provided additional information that the eGFR and HDL cholesterol results should be no older than six months. There was no timeframe specified for uACR.
Intervention	PromarkerD is an *in vitro* quantitative blood test designed to predict incident diabetic kidney disease (DKD) or progression of DKD in patients with T2DM. The test measures three novel plasma protein biomarkers (Apolipoprotein A4 (ApoA4), CD5 antigen-like (CD5L) and Insulin growth factor binding protein 3 (IBP3)). The concentrations of these biomarkers, along with the clinical factors (age, high-density lipoprotein (HDL) cholesterol, eGFR), are entered into the PromarkerD Hub, a static proprietary software algorithm which characterises patients as low-risk, moderate-risk, or high-risk of developing DKD (defined as eGFR below 60 mL/min/1.73m^2) within 4 years, or a decline in eGFR of ≥30% over 4 years.
Comparator/s	The comparator nominated in the application was 'no comparator', as PromarkerD would be added to the current testing regimen. The applicant stated that there is no direct comparator as current standard of care diagnoses DKD after clinical symptoms appear rather than predicting risk of DKD.
Reference standard	While no reference standard was formally defined in the application, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for evaluation and management of chronic kidney disease, as used by Kidney Health Australia (Figure 1), provide a table of kidney function stages based on eGFR and uACR. These kidney function stages are used to guide treatment for patients with T2DM. Clinical observation study details investigating whether patients were correctly predicted to progress to DKD using the KDIGO guidelines compared to using PromarkerD are provided in the Assessment framework section below.

Component	Description
Outcomes	The following key outcomes were listed in the application. Clinical effectiveness outcomes: • Life Years Saved • End Stage Renal Disease (ESRD) • Quality Adjusted Life Years (QALYs) Test outcomes: • Sensitivity • Specificity • Positive predictive value (PPV) • Negative predictive value (NPV) Additional information provided by the applicant stated that among the individuals at risk of DKD identified by PromarkerD, the subsequent change in management prevents/delays the occurrence of DKD and thus improves patient quality of life, reduces need of dialysis and reduces the risk of end-stage kidney failure. Treatment goals (based on Kidney Health Australia – CKD Management in Primary Care) include: • Glycaemic control <7% • 50% reduction in uACR • Maintain blood pressure below 130/80 mmHg • BMI <25
Assessment questions	What is the effectiveness and cost-effectiveness of the use of PromarkerD versus current standard of care in people with T2DM?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of the use of PromarkerD for people with type 2 diabetes mellitus (T2DM) was received from Proteomics International Pty Ltd by the Department of Health.

The clinical claim made in the application was that PromarkerD can quantify the risk of incident diabetic kidney disease in an individual with T2DM up to 4 years before clinical symptoms develop. Additionally, PromarkerD can predict rapid renal decline (decrease in estimated glomerular filtration rate [eGFR] by 30% or more over 4 years).

No clinical claim was provided in the application to state whether PromarkerD results in superior, noninferior or inferior health outcomes compared to standard practice in patients with T2DM. The applicant subsequently clarified the clinical claims to be:

- **Superior clinical effectiveness:** PromarkerD is more sensitive and specific in the early identification of at-risk patients compared to standard of care to allow early intervention and prevention of diabetic kidney disease (DKD). The early intervention can prevent or delay onset of DKD, which is a leading cause for dialysis, end-stage kidney failure and reduce lifespan in people with diabetes – causing a significant cost burden to patient and healthcare system.
- **Non-inferior safety:** PromarkerD test is a simple blood test and results are intended for earlier personalised treatment, no additional risk identified compared to eGFR/Albumin: Creatinine Ratio (uACR).
- **Superior cost effectiveness:** Reducing or delaying the onset of DKD, which is a leading cause for dialysis, end-stage kidney failure and reduce lifespan in people with diabetes would result in significant improvements in health outcomes for patients and reduced healthcare treatment costs, making PromarkerD a cost-effective diagnostic test.

The clinical claims made by the applicant are not consistent with the advice under TG1.2, pp21-23 of the MSAC Guidelines (Version 1.0, May 2021). The applicant, in response to the Pre-PASC PICO indicated that the clinical claim are in accordance with the following claim provided on page 23 of the MSAC Guidelines:

> "an improvement in the information provided, such that patients with a specific medical condition are more accurately categorised (which may or may not lead to improved health outcomes, depending on how each patient is managed)."

PICO criteria

Population

Almost one million Australian adults (5.3% of those aged 18 and over) had T2DM in 2017-18 (Australian Bureau of Statistics (ABS) 2017–18 National Health Survey). Diabetes is the leading cause of chronic kidney disease (CKD) in developed countries. The AusDiab study found 27.6% of people with diabetes had CKD and that the prevalence of CKD was three times higher in those with diabetes compared to those without.

The natural history of CKD in people with T2DM has been characterised by changes in albumin excretion rate (AER) which may progress through three phases, namely normoalbuminuria (AER <20 μg/min), microalbuminuria (AER 20-200 μg/min) and proteinuria (macroalbuminuria) (AER >200 μg/min). The proportion of people with T2DM who develop microalbuminuria is in the order of 25% after 10 years. The

eGFR in people with T2DM typically begins to decline in the late microalbuminuric stage and, without intervention declines at an average rate of 8-12 ml/min/1.73 m^2/year. The stage of proteinuria, also called overt nephropathy, is typically characterised by decline in eGFR and a subsequent rise in serum creatinine. Increased serum creatinine above the normal range occurs relatively late and indicates a loss of at least 50% of total kidney function. Kidney disease generally remains asymptomatic until about 75% of kidney function has been lost (Chadban 2009).

End stage renal disease (ESRD) generally follows five to 10 years after eGFR decline, dependent on the level of intervention. In observational studies, overt nephropathy has been shown to develop in approximately 20% to 50% of microalbuminuric people with T2DM over ten years. The risk of a major cardiovascular event in subjects with overt kidney disease and T2DM is 30% over ten years (RACGP 2020).

In Australia, CKD contributed to 11% of all deaths in 2018 according to the Australian Institute of Health and Welfare (AIHW 2020) National Mortality Database, with CKD the underlying cause of death in around 3,600 deaths and an associated cause of death in a further 13,200 deaths. Overall, kidney and urinary diseases accounted for 1.4% of Australia's total burden of disease in 2015. CKD represented the majority of burden from this disease group comprising 1.2% of total burden in 2015 (increasing from 0.8% in 2003 and 0.9% in 2011). Of the total CKD burden, 77% was due to fatal burden and 23% to non-fatal burden.

DKD refers to specific pathological, structural and functional changes seen in the kidneys of people with diabetes that result from consistently high blood sugar levels which damages the blood-filtering capillaries in the kidneys. Clinically, DKD is characterised by progressive kidney damage reflected by increasing albuminuria, impairment in renal function (decline in glomerular filtration rate [GFR]), elevated blood pressure, and excess morbidity and mortality due to cardiovascular complications, and if left unchecked, DKD can progress to ESRD. Individuals with ESRD require haemodialysis and eventually kidney transplantation. Diabetes is the leading cause of ESRD among patients commencing kidney replacement therapy, with 38% of cases attributable to diabetes (AIHW 2020).

PromarkerD would be used to test patients with T2DM before kidney damage or clinical symptoms occur (kidney function stage 1 or 2). Patients would be eligible for the proposed medical service if they met the following criteria:

a. Patients diagnosed with T2DM; and
b. eGFR ≥60ml/min/1.73m^2; and
c. uACR ≤30mg/mmol.

According to the Fremantle Diabetes Study, it was reported that 84.6% of patients with T2DM have an eGFR of ≥60ml/min/1.73m^2 and uACR ≤30mg/mmol. It is not clear why the application does not include those with type 1 diabetes mellitus (T1DM) as any form of diabetes confers the same risk of diabetic kidney disease. *PASC questioned the exclusion of those with T1DM.* The applicant stated that data for use of PromarkerD were available for T2DM only.

Figure 1 provides an overview of the Kidney Health Australia risk categories that use eGFR and uACR to determine kidney function stage. These categories are identical to those published by the globally recognised Kidney Disease Improving Global Outcomes (KDIGO) guidelines for evaluation and management of chronic kidney disease (Levin 2013). Patients would be eligible for PromarkerD if they have kidney function stage 1 or 2 combined with normal albuminuria or microalbuminuria (i.e. green boxes or yellow boxes with kidney function stage 1 or 2). Patients who fall into higher risk categories would not be eligible for PromarkerD.

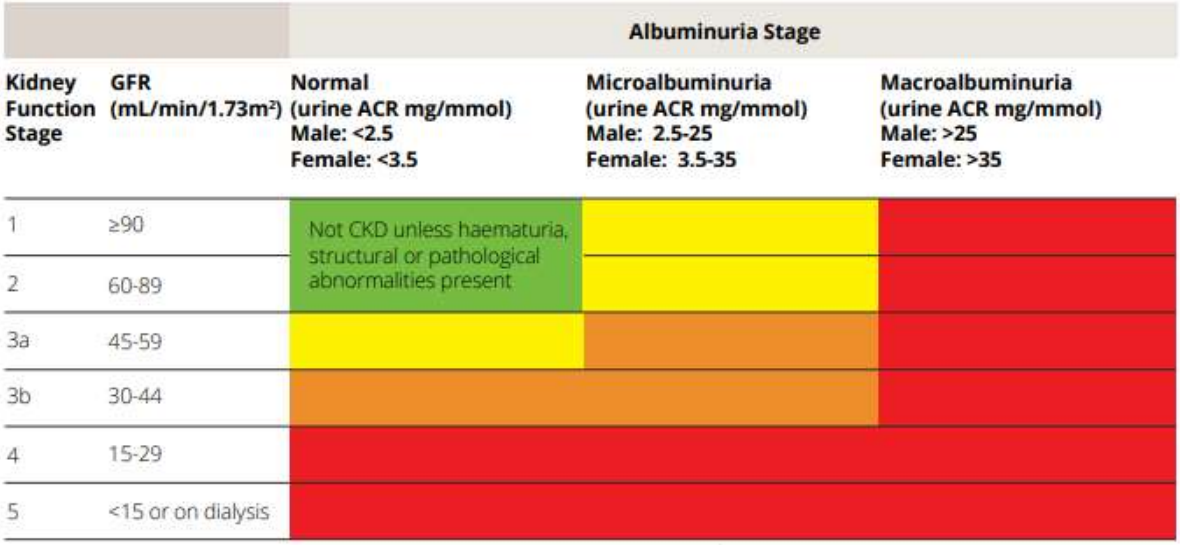

Figure 1 Kidney Health Australia (2020), risk categories of kidney function stage

ACR = albumin creatinine ratio; GFR = glomerular filtration rate

PASC questioned the inclusion of patients with micoralbuminuria which was indicative of existing kidney damage. The applicant explained that microalbuminuria is a weak predictor of kidney damage and can be caused by other factors (e.g. high blood pressure). With appropriate treatment this condition can be normalised. *PASC noted that this was a 'yellow' category in the KDIGO guidelines as used by Kidney Health Australia and interventions to reduce the progression of kidney disease should be undertaken for this group of patients. PASC requested the assessment report include a justification for the inclusion of this patient group.*

Current Australian guidelines use a patient's glycosylated haemoglobin (HbA1c) as a basis for determining appropriate treatment (Australian Diabetes Society 2021). Treatment should be reviewed if target HbA1c is not reached, with a target HbA1c of ≤7.0% commonly recommended.

HbA1c is used also to determine eligibility of PBS listed drugs. There are three sodium-glucose co-transporter 2 (SGLT2) inhibitors currently listed on the PBS – dapagliflozin, empagliflozin and ertugliflozin. Eligibility criteria for patients with T2DM includes that they must have a HbA1c measurement of greater than 7.0%.

The application provided estimates of the likely eligible population and utilisation of the PromarkerD test, see Table 2.

Table 2 Estimated eligible population and utilisation of the PromarkerD test

	2022	2023	2024	2025
Australian Adult Population (aged 18+)	20,757,917	21,082,471	21,411,852	21,744,502
Prevalence of Type 2 Diabetes	5.3%	5.3%	5.3%	5.3%
Total Prevalent Patients with Type 2 Diabetes	1,100,170	1,117,371	1,134,828	1,152,459
Prevalent Patients with ≥60ml/min/1.73m² eGFR AND <3mg/mmol uACR (KDIGO green zone)	**58.0%**	**58.0%**	**58.0%**	**58.0%**
Prevalent Patients with ≥60ml/min/1.73m² eGFR AND 3-30mg/mmol uACR (KDIGO yellow zone)	**26.6%**	**26.6%**	**26.6%**	**26.6%**
Proportion of patients eligible for PromarkerD	**84.6%**	**84.6%**	**84.6%**	**84.6%**
Number of patients eligible for PromarkerD	**930,715**	**945,267**	**960,035**	**974,950**

	2022	2023	2024	2025
Annual Eligible Population	232,679	236,317	240,009	243,738
PromarkerD Uptake Rate	2.5%	5.0%	7.5%	10.0%
Estimated PromarkerD Population	5,817	11,816	18,001	24,374
Rate of Moderate-High Risk Patients	15%	15%	15%	15%
Number of Moderate-High Risk Patients	850	1,728	2,632	3,564
Total PromarkerD Services	6,667	13,543	20,632	27,937

Source: Table 3, p21 of the application

The application estimated there would be 1.1 million adults with type 2 diabetes (applying a prevalence rate of 5.3% to the Australian adult population in 2022). From this prevalent population, the application stated 84.6% of patients are expected to have both an eGFR of greater than or equal to 60ml/min/1.73m^2 and uACR test result of less than or equal to 30mg/mmol (the eligible population). Patients are required to have both an eGFR ≥60ml/min/1.73m^2 AND uACR ≤30mg/mmol.

The application proceeds to divide the eligible population by four on the basis that the test will be conducted every four years to estimate the annual population. This is not a correct approach to estimating the annual tested population. All patients meeting the criteria would be eligible in Year 1 (2022), and levels of testing would be dependent on the uptake rate. Based on the application's assumption of a 2.5% uptake rate in the first year of listing, up to 23,268 (930,715 x 2.5%) patients would be tested in Year 1 (2022). Retesting of those with low-risk PromarkerD scores (the majority of these patients) would not occur again until 2026 (in four years) – these retested patients would need to be added to the 'new' population tested in 2026, based on the assumed uptake rate for that year. The application further expects that 30% (although stating 30% on p21 of the application, a rate of 15% is applied in the table above) of eligible patients will have a moderate- to high-risk score and will therefore be eligible for one test every two years as opposed to four years. This value was divided by two (one test per two years) and added to the annual PromarkerD population to calculate the total number of PromarkerD services. Again, this is not a correct approach to estimating utilisation; retesting of 15% (or 30%) of the Year 1 population (3,490 [23,268*15%]), should have been added to the number of tests expected among 'new' patients in 2024, based on the assumed uptake rate for that year. *PASC questioned whether the population for retesting should include those with 'moderate' or 'high' risk PromarkerD scores as this would already initiate intensified treatment that would be maintained over time. PASC stated that justification of continued retesting of those with 'moderate' and 'high' risk PromarkerD scores would need to be addressed in the assessment report.*

The estimates of the financial implications will need to be corrected and clarified in the assessment report.

Prior tests

In order to determine which patients are eligible for PromarkerD, and because the use of PromarkerD requires the input of several clinical factors, the tests required prior to the use of PromarkerD are:

- Tests required to confirm diagnosis of T2DM;
- Measurement of eGFR; and
- Measurement of uACR.

PASC confirmed the prior tests to be tests to diagnose T2DM, i.e., eGFR and uACR.

It is generally recommended that people with T2DM undergo annual measurement eGFR and uACR (RACGP, Management of type 2 diabetes handbook for general practice). *No timeframe for the eGFR and uACR tests were provided in the application other than that they are required prior to use of PromarkerD.* The applicant provided additional information that the eGFR and HDL results should be no older than six months. The applicant suggested that as uACR is not a required input of the PromarkerD test itself, the uACR results may be from the same period as the eGFR result, i.e. no older than 6 months.

The "age" of test results will be important to the financial estimates as patients with test results deemed "too old" may receive these test more than annually, as recommended.

Intervention

PromarkerD is an *in vitro* quantitative blood test designed to predict incident DKD or progression of DKD in patients with T2DM before kidney damage occurs.

PromarkerD detects three protein biomarkers (analytes) in human plasma:

- Biomarker-1 Apolipoprotein A4 (ApoA4);
- Biomarker-2 CD5 antigen-like (CD5L); and
- Biomarker-3 Insulin growth factor binding protein 3 (IBP3).

The concentration of the biomarkers, along with clinical factors (age, HDL-cholesterol, eGFR), are entered into the PromarkerD Hub, a static proprietary software algorithm which characterises each patient as having low-risk, moderate-risk or high-risk of developing DKD (defined as eGFR below 60 mL/min/1.73m^2) within the next four years or a decline in eGFR of ≥30% over four years.

PASC noted that the PromarkerD risk score was based on the analysis of three biomarkers (ApoA4, CD5L and IBP3) AND the patient's age, HDL-cholesterol and eGFR. Although the applicant indicated that HDL-cholesterol and eGFR should not be more than 6 months old, PASC questioned whether the pathologist would routinely have this information easily accessible to input to the PromarkerD hub. The applicant asked whether these details could be provided by the general practitioner (GP). *PASC considered that provision of this information by the GP would be unlikely and that it was more likely the tests for HDL-cholesterol and eGFR would need to done (or repeated) at the time of PromarkerD testing. PASC stated that this (re)testing of HDL and eGFR needs to be considered in the costings.*

PromarkerD clinical process

The steps involved in the use of PromarkerD are:

1) A patient with T2DM would be seen by their managing clinician (most commonly a GP) regularly for general monitoring and annual standard of care tests, including eGFR and uACR to assess their kidney function.
2) The managing clinician would request PromarkerD for patients with a recent history of eGFR and uACR results who meet the eligibility criteria.
3) Patients would be referred to pathology for a blood draw.
4) Blood samples would be sent to accredited pathology laboratories where the PromarkerD kit would be used to measure each protein biomarker in the sample via ELISA (enzyme-linked immunosorbent assay).
5) Test results would be interpreted and uploaded into the PromarkerD hub by pathologists to produce a risk score.

6) The PromarkerD risk score would be provided to managing clinicians who would then relay that information to patients.
7) The test risk score would inform further patient care such as monitoring frequency, lifestyle modification, initiation of more aggressive treatment measures, patient education on risk factors.

The PromarkerD ELISA is provided to laboratories in three parts with each part containing reagents to measure one of the biomarkers. The three parts are intended to be used together. The test is intended to be used by laboratory trained personnel.

The PromarkerD ELISA is based on the principle of a traditional sandwich format. It uses a platform whereby the analyte and two chemically tagged antibodies are added to the PromarkerD assay microplate at the same time. (This is in contrast to standard ELISA formats, as no assay-specific antibodies are present on the microplate itself). The microplate is instead coated with a proprietary Capt*Sure*™ reagent, which immobilises the antibody/biomarker complex via a Capt*Sure*™ tag on each primary antibody. Any surface that is Capt*Sure*™ reagent coated can bind any Capt*Sure*™-tagged antibody. After a short incubation period, unbound assay reagents and analytes are washed away and immuno-complexes containing both antibodies are detected.

The three absolute biomarker concentrations, along with the three clinical factors are processed by the PromarkerD Hub algorithm. The PromarkerD Hub algorithm generates a report with prognostic and diagnostic risk scores calculated for DKD. The prognostic risk score estimates patient risk of developing DKD within the next four years, defined as incident diabetic kidney disease (eGFR <60mL/min/1.73m^2), as shown in Figure 2. The cut-offs that are proposed for use in clinical practice to determine risk are as described by Peters (2020) - cut offs of <10% for low-risk, 10% to <20% as moderate-risk and ≥20% as high-risk.

Figure 2 Prognostic risk score estimates provided by PromarkerD

Source: PromarkerD instructions for use

The PromarkerD instructions for use state that patients found to be at low-risk should be retested annually, those at moderate-risk should be retested every three to six months and those at high-risk should be retested every three months. This is in contrast to retesting durations proposed in the application, where it was proposed that patients with a low-risk PromarkerD score be limited to one test every four years and patients who receive a moderate- or high-risk PromarkerD result are retesting every two years. This is discussed further in the proposal for public funding section below.

PASC noted the discrepancies in the retesting frequency requested and those recommended in the PromarkerD kit. PASC considered that the frequency of retesting and the rationale for retesting needs to be clarified in the assessment report.

Selection of biomarkers

The application did not include details of why ApoA4, CD5L and IBP3 were selected for inclusion in the PromarkerD test. The applicant provided the following additional information to support the selection of these biomarkers.

The clinical evidence to support the selection of plasma biomarkers in the PromarkerD test comes from a range of cross-sectional and longitudinal studies. An iterative process was used for the development and validation of PromarkerD that involved the following stages: discovery, verification, analytical validation, diagnostic disease correlation (cross-sectional), prognostic utility development (longitudinal), internal validation (longitudinal) and external validation. A number of potential biomarkers were identified in the discovery phase that were correlated with kidney disease in individuals with T2DM. The diagnostic and prognostic utility of these biomarkers was then assessed in a larger representative community-based cohort of individuals with T2DM from the Fremantle Diabetes Study Phase II (FDS2) to determine if there was an association with kidney measures (ACR and eGFR, cross-sectionally), renal decline (longitudinally), and whether the biomarkers added additional benefit to known clinical variables for predicting renal decline. Following this, a diagnostic and prognostic algorithm was developed using a subset of 345 individuals from FDS2, internally validated using an independent cohort of 447 patients from FDS2 (separate to the 345 used during development), and externally validated in a cohort of 3,500 patients with T2DM at high-risk of cardiovascular disease from the large-scale CANagliflozin CardioVascular Assessment Study (CANVAS).

Early Discovery, Verification, Analytical Validation and Disease Correlation (Cross-sectional)

In the earlier cross-sectional discovery work, 11 biomarkers were found to be analytically validated from the mass spectrometry workflow (presented at the International Diabetes Federation World Diabetes Congress [IDF WDC] in 2015). These biomarkers were then analysed, with ApoA4, CD5L and IBP3 (among others) found to be significantly correlated with eGFR and ACR in the FDS2 or Busselton Diabetes Study (Table 3). The data from the FDS2 cohort were subsequently published (Bringans 2017).

Table 3 Candidate biomarkers correlated with kidney disease measures ACR and eGFR (IDF WDC 2015)

Protein Name	vs ACR*	vs eGFR*
ADIPO	0.55	0.43
APOA4	**<0.001**	**<0.001**
APOB100^	0.11	0.99
APOC3	0.50	**0.020**
CD5L^	**<0.001**	**0.041**
C1QB	0.21	0.30
C8B^	0.24	0.65
CFHR2	**0.002**	**<0.001**
HBB	**0.001**	0.41
IBP3	**<0.001**	**0.001**
AMBP	0.070	**0.001**

uACR = Albumin: Creatinine Ratio; eGFR = estimated glomerular filtration rate
* p-value based on Spearman's correlation
^ Analysed in Busselton Diabetes Study

All 11 candidate biomarkers were then measured in the FDS2 cohort and a series of multivariate models derived for assessing diagnostic outcomes (Table 4). All biomarkers in the models were found to be significant and independent associates of the respective renal complication (unpublished data).

Table 4 Multivariate biomarker models for renal complications in the Fremantle Diabetes Study Phase II

Renal complication	No. with/without renal complication	Model^	AUC	Sensitivity	Specificity	PPV	NPV
ACR ≥3.0 mg/mmol	264/326	**ApoA4**, ApoB100, **CD5L**, CFHR2, HBB	0.67	67%	62%	59%	70%
ACR ≥30.0 mg/mmol	71/519	**ApoA4**, **CD5L**, **IBP3**, ApoB100, C1QB	0.75	72%	70%	25%	95%
eGFR <60 ml/min/1.73m^2	94/496	**ApoA4**, CFHR2, **IBP3**, AMBP	0.75	68%	78%	37%	93%
CKD risk ≥2	121/469	**ApoA4**, **CD5L**, C1QB, **IBP3**	0.79	74%	76%	45%	92%

uACR = Albumin: Creatinine Ratio; eGFR = estimated glomerular filtration rate; PPV = positive predictive value; NPV = negative predictive value
^ Only biomarkers were considered for diagnostic models. Untransformed biomarkers were used in each model. CKD risk as described by the KDIGO guidelines. Performance metrics were determined at the maximum Youden Index for each model.

Longitudinal Development

For the prognostic utility, the number of biomarkers was minimised to those that provided the most benefit in addition to clinical variables, to predict renal outcomes in the next four years. Given the low number of ESRD endpoints experienced in the FDS2 cohort, surrogate endpoints for DKD progression were explored. Four different definitions of renal decline were assessed with a different predictive model defined for each (Peters 2017). Peters (2017) reported that the biomarkers added significant independent value to known clinical variables in predicting renal decline. Of note was that the biomarkers that were significantly associated with outcomes differed by outcome definition and whether univariate or multivariate modelling was used.

Longitudinal Validation

Validation of the models was described by Peters (2019) in two stages: (1) validation of separate models for each definition of renal decline, and (2) development and validation of a simple consensus model that

could be used across the different definitions of renal decline. Given the range of clinical variables required for the different models in Peters (2017), a simplified consensus model was derived for the PromarkerD model/algorithm. The three clinical variables (age, serum HDL-cholesterol and eGFR) which were chosen for incorporation into PromarkerD were based on accessibility in routine diabetes care and statistical significance across the different definitions of renal decline, and were combined with the three plasma proteins ApoA4, CD5L and IBP3. Alternative biomarkers (C1QB, CFHR2 and ApoC3) were considered for entry in the PromarkerD consensus model, but did not provide sufficient added prognostic benefit. The consensus model provided similar discriminative ability to the previous models, but improved on performance in terms of calibration across the three definitions of renal decline (Peters 2019).

Table 5 Updated clinical evidence to support PromarkerD

Study	Biomarkers investigated	ApoA4	CD5L	IBP3	Other
IDF/WDC 2015 conference presentation. Biomarkers of DKD	**ApoA4** **CD5L** **IBP3** plus others	<0.001 ACR and eGFR	<0.001 ACR and 0.041 eGFR	<0.001 ACR and 0.001 eGFR	
Bringans 2017 – discovery of biomarkers correlated with DKD (cross-sectional)	**ApoA4** ApoC3 **IBP3** **CFHR2** **HBB** **AMBP** C1QB ADIPO	ACR and eGFR p≤0.002 for pep 1 and 2	Not tested	pep1 ACR <0.001, eGFR p = 0.060 pep2 ACR and eGFR p<0.02	CFHR2 (pep2) ACR 0.10, eGFR <0.001 AMBP (pep 1) ACR 0.017, eGFR 0.049 C1QB was investigated but no association found.
Peters 2017 – development of clinical + biomarker models for predicting future DKD. Both bivariate and multivariate analysis	**ApoA4** **ApoC3** CD5L **C1QB** IBP3 **CFHR2**	P <0.001	P = 0.59	P = 0.22	ApoC3 (0.031), C1QB (0.012), CFHR2 (<0.001) Many other factors also statistically significant (e.g. diuretic use, triglycerides, uric acids, serum creatinine) IBP3 was not significant in multivariate model (p=0.573), but its inclusion provided an improvement in model fit, discrimination and reclassification. (p1552, Peters 2017). C1QB was significant but not part of algorithm.
Peters 2019 (Fremantle)	ApoA4 CD5L IBP3	ApoA4, CD5L, IBP3 (plus age, serum HDL-cholesterol and eGFR) were used by PromarkerD to predict diabetic kidney disease. Individual biomarker data not provided – performance data only			C1QB was not analysed as it previously predicted a group-based rapidly declining eGFR trajectory but this outcome definition was not included in this study. (page 2, Peters 2019)

DKD = diabetic kidney disease; IDF/WDC = International Diabetes Federation World Diabetes Congress
Biomarkers found to have an association with decline in kidney function are in **bold** text

The additional information provided by the applicant stated that there is a growing body of evidence to support the utility of biomarkers in the diagnosis of T2DM and in detecting early stage kidney disease. The biological plausibility of the three PromarkerD biomarkers (biochemical functions outlined in Table 6) is as follows:

i. Raised ApoA4 levels are an early marker of mild to moderate CKD, predict CKD progression in patients recruited from renal outpatient clinics and are strongly associated with CKD independent of known risk

factors in the general population. There is also evidence for increased renal ApoA4 excretion in diabetic nephropathy.

ii. In human acute kidney injury, serum levels of free CD5L increase in correlation with increasing serum creatinine and consequently kidney impairment.

iii. A number of renal and systemic perturbations of the growth hormone/insulin-like growth factor system, of which IBP3 is a member, are known to occur in diabetic nephropathy. Patients with type 1 diabetes and microalbuminuria have decreased circulating IBP3 levels and higher urinary levels of IBP3 compared to normoalbuminuric patients. The urinary levels of IBP3 have been shown to directly correlate with urine albumin excretion ($p < 0.001$) (Miyazaki 2011).

Table 6 Biochemical functions of PromarkerD biomarkers

ApoA4	CD5L	IBP3
ApoA4 is one of the most abundant and versatile apolipoproteins facilitating lipid transport and metabolism. ApoA4 is synthesised in the small intestine, packaged onto chylomicrons, secreted into intestinal lymph and transported via circulation to several tissues, including adipose. In addition to facilitating fatty acid uptake and lipid metabolism, ApoA4 is involved in various aspects of glucose homeostasis, including inhibition of gluconeogenesis in hepatocytes promotion of glucose uptake in adipocytes and enhancement of insulin secretion in pancreatic islets. ApoA4 is proposed as an early diagnostic biomarker for prediabetes, liver fibrosis, and impaired renal function.	CD5L has been implicated in the modulation of leukocyte apoptosis, autophagy and inflammation, adipose lipolysis, B cell proliferation, antimicrobial responses, atherosclerosis, among others. CD5L may also have an additional role related to vascular damage—this time, localised in the small arteries and arterioles in the kidney, causing nephrosclerosis. This is one of the main pathologies underlying chronic kidney disease, and it may lead to ischemic changes in the glomeruli and interstitium, consequently compromising renal function. Plasma levels of CD5L are altered in several conditions that arise in an inflammatory context, making it a potentially useful biomarker.	IBP3, also known as IGFBP3, is in the insulin-like growth factor binding protein (IGFBP) family and encodes a protein with an IGFBP domain and a thyroglobulin type-I domain. The protein forms a ternary complex with insulin-like growth factor acid-labile subunit (IGFALS) and either insulin-like growth factor (IGF) I or II. In this form, it circulates in the plasma, prolonging the half-life of IGFs and altering their interaction with cell surface receptors. It is involved in glucose metabolism and apoptosis.

Privacy and data management

In additional information provided after the application was submitted, the applicant stated that physical, technical and organisational measures are adopted to ensure the security of personal data collected for use with PromarkerD. This includes the prevention of loss or damage, unauthorised alteration, access or processing and other risks to which it may be exposed by virtue of human action or the physical or natural environment. Personal data related security measures are applied whenever appropriate to protect data held on the PromarkerD system and include:

- PromarkerD Hub is password restricted to authorised parties only.
- Periodic review of current user logins to ensure currency and validity of the PromarkerD Hub access.
- Firewalls and virus protection are employed at all times to prevent the possibility of hackers accessing the PromarkerD Hub system. All data are encrypted.
- Cloud based computing infrastructure is hosted by providers with associated logical and physical security implementations.
- Safe disposal of e-waste to ensure no data are retrievable upon end-of-life of physical products used to previously store data.

The PromarkerD Hub consists of the Web App interface and the Secure App hosted on the Microsoft Azure secure cloud based computing infrastructure. With the PromarkerD Hub Security Architecture:

- Users enter a domain name (https://hub.promarkerd.com/#!) into the local internet browser which then looks up an IP address of the Azure Load Balancer.
- All data transferred to and from the browser to the entry point of the load balancer is encrypted using SSL (Secure Sockets Layers) for data in transit, and is authenticated with a private certificate installed on the server.
- All data traffic coming in and out of the Azure cloud are protected by a firewall and defined by a Network Security Group (NSG) access protocol. Data packets are also monitored by the default Microsoft Security Services Centre in the Azure cloud.
- The Load Balancer then makes requests to the Azure Virtual Machine (VM) within Docker containers, depending on load and other variables (such as geography or time). Users then interact with the PromarkerD WebApp securely, accessing data in the PostgreSQL database installed on an Azure Encrypted Storage disk using AES-256 encryption for data at rest.
- The SecureApp is installed on a VM located in a Delegated Subnet of the VNET that can communicate with the VMs running the WebApp, but is not exposed to the external-facing network. The SecureApp application then processes the incoming CSV files and returns PDF result reports to the WebApp.
- All files are saved onto Azure Storage disks which are encrypted by default.

As part of the pre-PASC response, the applicant advised that the actual patient result data are stored in the Secure SQL Database located on an encrypted hard disk drive at the Azure data centre in Sydney (physically).

Reference standard (for investigative technologies only)

No reference standard was defined in the application. Given PromarkerD is a predictive test, the reference standard should be the health outcome (development of DKD).

PASC accepted that the reference standard was the health outcome (development of DKD). PASC however, also noted the KDIGO guidelines and observational data presented regarding KDIGO and progression.

Comparator(s)

The application stated that there is no comparator test to PromarkerD as it is proposed as an add-on to usual care. The test would be added to the current testing regimen. Patients with T2DM currently should have laboratory risk factors (e.g. eGFR, uACR, lipids, HbA1c, etc) measured annually as part of usual monitoring. Should abnormalities in renal function be found and tracked properly by primary care and pathologists – e.g., decreasing eGFR over time, increasing uACR over time – primary care clinicians can elevate interventions. If renal function is declining rapidly or has passed a threshold of 30 ml/min eGFR, the patient is referred to a specialist for maximal intervention.

PASC accepted that the comparator was standard care as PromarkerD would be added to the current testing regimen.

The KDIGO guidelines for evaluation and management of chronic kidney disease, as used by Kidney Health Australia (Figure 1), was used to assess the sensitivity/specificity of PromarkerD. Clinical observation study details investigating whether patients were correctly predicted to progress to DKD using the KDIGO guidelines compared to using PromarkerD are provided in the Assessment framework section below.

Outcomes

The application stated that the following are the key health outcomes that will need to be measured in assessing the clinical claim for PromarkerD.

Clinical Effectiveness Outcomes:

- Life Years Saved
- ESRD
- Quality Adjusted Life Years (QALYs)

Given PromarkerD is a predictive test, any changes in the nominated (and relevant) clinical outcomes are predicated on 'change in management'. The application did not suggest any change in management outcomes (other than 'patients initiated on treatment' under 'Other test related outcomes'). Similarly, the application did not nominate any specific 'intermediate outcomes' (such as lipids, blood pressure and glycaemic control) that result as a consequence of change in management and lead to the health outcomes of interest (i.e. a decrease in incident DKD (eGFR <60mL/min/1.73m^2) and eGFR decline ≥30%).

PASC noted that as PromarkerD is presented as a predictive test, this would estimate the differences in the proportion of people who will develop DKD over time according to different test results if clinical management changes in response to one or more of these different test results. Therefore any changes in nominated and relevant clinical outcomes are predicated on 'change in management'. The decision question was thus what changes of management will be associated with PromarkerD? Would (or should) those changes in management occur in the absence of PromarkerD if optimal patient management is considered? PASC considered that it was unclear whether PromarkerD would change clinical decisions and result in changes in management that would lead to changes in clinical outcomes and costs. PASC noted that many of the possible changes in clinical management were relevant to all people with T2DM, such as managing HbA1c, blood pressure, lipids, and management of body weight. PASC noted that the application stated that SGLT2 inhibitors reduced PromarkerD scores and may prevent progression to DKD. PASC noted that the PBS restrictions for SGLT2 inhibitors may not allow this use. PASC considered that evidence for how PromarkerD leads to change in clinical practice (clinical utility) and the impact of this on clinical outcomes has not been demonstrated and needs to be addressed.

Test outcomes:

- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)

Clinical utility of test:

- Predictive effect of testing of patients to detect DKD

Other test-related considerations:

- Patients initiated on treatment
- Estimated number of patients being tested
- Number needed to test
- Cost of testing per patient

The application did not make any claims regarding the value of knowing. *PASC noted that the application relates to "an improvement in the information provided…" as in the MSAC Guidelines (p23). PASC advised that MSAC generally places a greater value on changes in clinical management that lead to improvements in clinical outcomes.*

Additional information provided by the applicant stated that PromarkerD prevents/delays the occurrence of DKD and thus improves patient quality of life, reduces need of dialysis and reduces the risk of end-stage kidney failure. Treatment goals (based on Kidney Health Australia – CKD Management in Primary Care) include:

- Glycaemic control; HbA1c <7%.
- 50% reduction in uACR.
- Maintain blood pressure below 130/80 mmHg.
- BMI <25.

Assessment framework (for investigative technologies)

The application identified one study (Peters 2020) that investigated the use of PromarkerD for predicting future renal function decline in individuals with T2DM who were enrolled in the CANVAS trial (patients were randomised to receive either placebo (n=1195) or canagliflozin (n=2373)). PromarkerD scores were measured at baseline and used to predict incident CKD (eGFR <60mL/min/1.73m^2) and eGFR decline ≥30% over four years. The participants had a median PromarkerD score of 2.9%, with 70.5% categorised as low-risk, 13.6% as moderate-risk and 15.9% as high-risk for developing incident CKD. After adjusting for treatment, baseline PromarkerD moderate-risk and high-risk scores were found to be increasingly prognostic for incident CKD (odds ratio 5.29 and 13.52 versus low-risk, respectively; both p <0.001).

The application reported that a cohort of patients from the FDS2 database (n=857) were analysed in and assigned to their respective KDIGO risk categories as per their eGFR (≥60 mL/min/1.73m^2) and uACR (≤30 mg/mmol) measurements. A total of 725 patients were assigned to the categories. These patients were then categorised under their PromarkerD risk score at baseline – low, moderate or high. Whether patients progressed to DKD, (defined as eGFR <60 mL/min/1.73m^2) was assessed after four years. A total of 69/81 patients were found to be correctly classified as moderate- or high-risk (sensitivity = 85.2%) and a total of 501/644 were correctly classified as low-risk (specificity = 77.8%), see Table 7. The application noted that this compares favourably to the sensitivity and specificity of simply using KDIGO (and Kidney Health Australia) risk categories prognostically, at 44.4% and 70.2% respectively.

Table 7 Assignment of patients from the Fremantle Diabetes Study 2 according to KDIGO and PromarkerD risk categories

		Patients at 4 years - Incident DKD (eGFR <60)				
		No outcome		Outcome		Total
	N	N	%	N	%	N
Yr0 KDIGO Low-risk (Green) Category	**497**	452	90.9%	45	9.1%	497
Yr0 KDIGO Moderate-risk (Yellow) Category	**228**	192	84.2%	36	15.8%	228
Low-risk + moderate-risk TOTAL	**725**	**644**	**88.8%**	**81**	**11.2%**	**725**
Yr0 PromarkerD Risk Category						
Low-risk	**513**	501	97.7%	12	2.3%	513
Moderate-risk	**75**	60	80.0%	15	20.0%	75
High-risk	**137**	83	60.6%	54	39.4%	137
Moderate/High-risk	**212**	**143**	**22.2%**	**69**	**85.2%**	**725**

DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate, KDIGO = Kidney Disease Improving Global Outcomes

The applicant provided additional information regarding FDS2 data when both 857 participants and 725 participants were analysed (data unpublished), see Table 8.

Table 8 Assignment of patients from the Fremantle Diabetes Study 2 according to PromarkerD risk categories

PromarkerD Score	Moderate-risk cut-off (%)	High-risk cut-off (%)
Full cohort (n=857)		
Sensitivity	86.9	68.2
Specificity	70.4	82.8
PPV	29.5	36.1
NPV	97.4	94.8
Target cohort (n=725)		
Sensitivity	85.2	66.7
Specificity	77.8	87.1
PPV	32.5	39.4
NPV	97.7	95.4

PPV = positive predictive value; NPV = negative predictive value

No studies were identified that linked the use of PromarkerD to a change in clinical decisions or final health outcomes. Consequently, a linked evidence approach will be necessary, as presented in Figure 3.

PASC noted the linked evidence approach and indicated there was a lack of clarity as to whether the PromarkerD test result led to changes in clinical management that would lead to a reduction in DKD.

PASC noted that the intervention is a test (including the associated algorithm) AND the subsequent changes in clinical management that may lead to a reduction in DKD. PASC questioned whether changes in clinical outcome were a result of the test and algorithm, or whether the changes simply result from changes in clinical management.

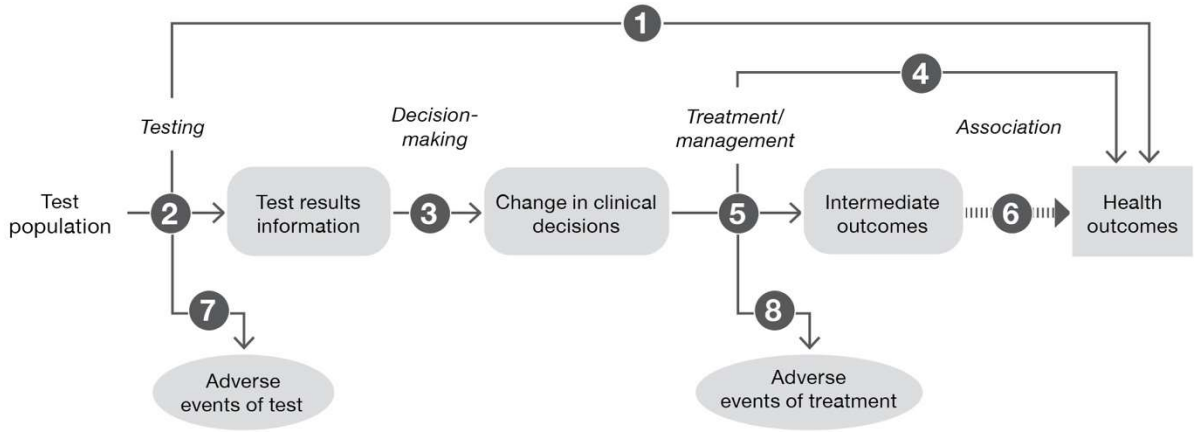

Figure 3 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

If changes in clinical outcomes are to be demonstrated as a result of the use of PromarkerD, evidence of the renoprotective effects of SGLT-2 inhibitors in patients with T2DM is likely to be required. The evidence for renoprotection of SGLT-2 inhibitors in the proposed population (baseline eGFR≥60 ml/min/1.73m^2) may be uncertain:

- Noting that canagliflozin is not currently marketed in Australia, based on the post hoc analysis of patients treated with placebo or canagliflozin as part of the CANVAS trial reported in Peters (2020), during the four year trial period, 274 of 982 (27.9%) patients in the placebo arm and 652 of 1994 (32.6%) patients in the canagliflozin arm developed incident CKD. If SGLT2 inhibitors were protective against incidence of CKD, it should be expected that the incidence of CKD would be lower in the canagliflozin arm, rather than as reported. The proportion experiencing a decline of ≥30% in eGFR was also similar (187/1179 (15.9%) in placebo arm and 377/2346 (16.1%) in canagliflozin arm). The main CANVAS trial, which included patients with baseline eGFR<60 ml/min/1.73m^2 reported renal outcomes only as a composite outcome (40% reduction in eGFR, renal replacement therapy or renal death) which favoured canagliflozin (HR = 0.60, 95% CI 0.47, 0.77).
- Results from the CREDENCE trial (Perkovic 2019), a double blind RCT of canagliflozin and placebo in 4397 patients with T2DM and baseline eGFR of 30 to <90 ml/min/1.73m^2, showed that while patients treated with canagliflozin had a lower risk for the renal specific composite outcome of ESRD, doubling of serum creatinine, or renal death (ITT HR = 0.66, 95% CI 0.53, 0.81) with a median follow up of 2.62 years, there was no statistically significant difference in the subgroup of patients with baseline eGFR of 60 to <90 ml/min/1.73m^2 (HR = 0.81, 95% CI 0.52, 1.26), with 35/905 (3.9%) and 43/904 (4.8%) patients reporting any event in the composite outcome in the canagliflozin and placebo group, respectively. It should however be noted that the test for interaction was not statistically significantly different based on baseline eGFR (p=0.18), therefore caution is required when interpreting this result.
- Subgroup results from the EMPA-REG OUTCOME trial (Wanner 2016) of empagliflozin vs placebo appeared to provide some evidence of efficacy in T2DM patients with eGFR≥60 ml/min/1.73m^2 with a median observation time of 3.1 years, reported a statistically significantly lower risk for 'incident or worsening nephropathy' (defined as progression to macroalbuminuria, a doubling of the serum creatinine level, accompanied by an eGFR of ≤45 ml per minute per 1.73 m^2, the initiation of renal-replacement therapy or death from renal disease) in patients treated with empagliflozin compared to placebo (HR values not reported – see Figure 4). Statistical significance was not reached in the post hoc subgroup analyses of doubling of serum creatinine, initiation of renal replacement therapy or death due

to renal disease in patients with baseline eGFR 60 to <90 ml/min/1.73m^2 (values not reported – see Figure 5). Patients treated with empagliflozin appeared to have maintained kidney function based on adjusted mean eGFR over time compared to patients treated with placebo (see Figure 6). However it is noted that in the approved product information (PI) it is noted that empagliflozin increases serum creatinine and decreases eGFR and renal function abnormalities can occur after initiating empagliflozin.

- While one trial of dapagliflozin in patients with CKD (DAPA-CKD) (Heerspink 2020) was identified, patients enrolled in DAPA-CKD had baseline eGFR of 25 to 75 ml/min/1.73m^2 and no subgroup results for those with ≥60 ml/min/1.73m^2 was reported. In the approved PI, it was noted that use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR. "In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m^2 in the dapagliflozin group and -0.8 mL/min/1.73 m^2 in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m2 in the dapagliflozin group and -8.6 mL/min/1.73 m2 in the placebo group." It was also noted that dapagliflozin has a TGA indication (but not PBS listing) for reducing the risk of progressive decline in kidney function in adults with proteinuric chronic kidney disease (CKD Stage 2, 3 or 4 and urine ACR ≥30mg/g), which is a more severe population than the proposed population for PromarkerD testing.

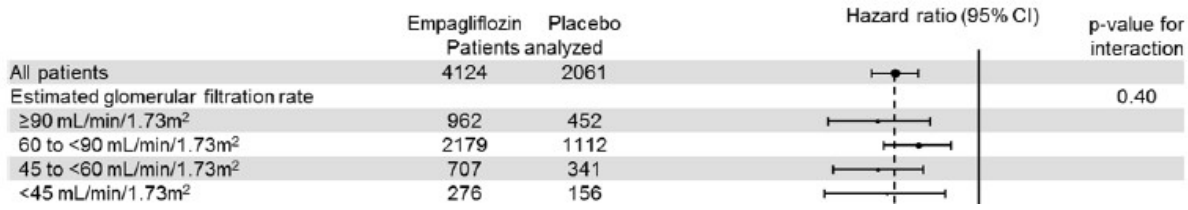

Figure 4 Incident or worsening nephropathy in EMPA-REG OUTCOME by baseline eGFR

Source: Figure S1, supplementary appendix to Wanner 2016 (EMPA-REG OUTCOME)

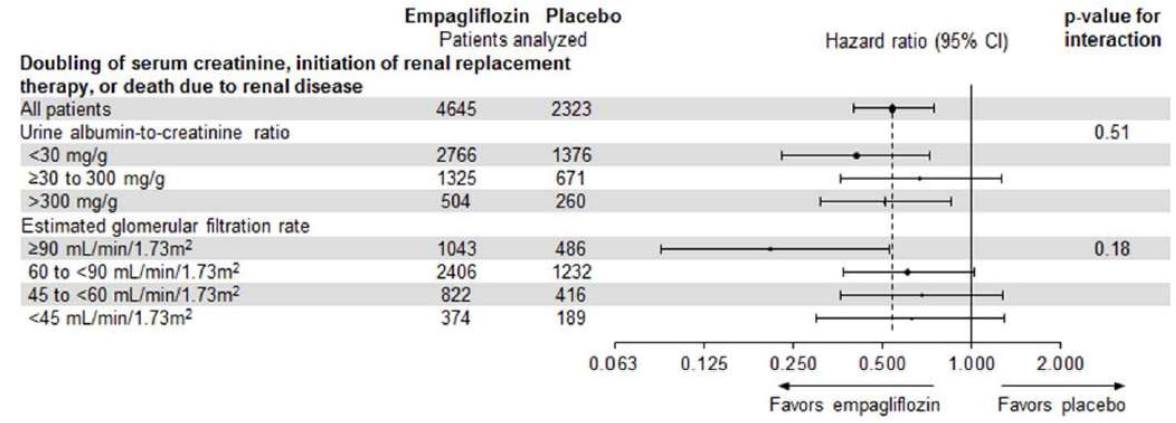

Figure 5 Post hoc subgroup analysis of doubling of serum creatinine, initiation of renal replacement therapy or death due to renal disease in EMPA-REG OUTCOME

Source: Figure S6, supplementary appendix to Wanner 2016 (EMPA-REG OUTCOME)

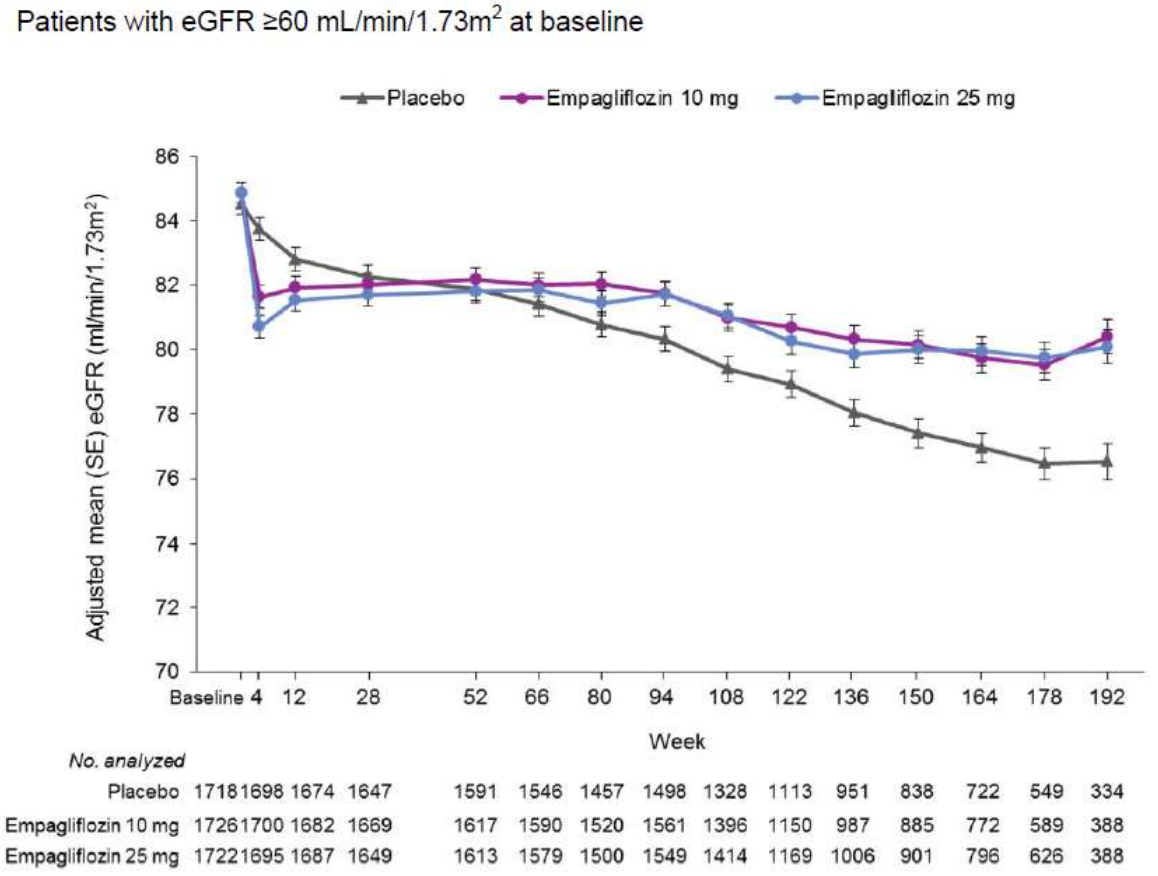

Figure 6 eGFR according to CKD-EPI formula over 192 weeks in patients with baseline eGFR ≥60 ml/min/1.73m2 in EMPA-REG OUTCOME

Source: Figure S7, supplementary appendix to Wanner 2016 (EMPA-REG OUTCOME)

The prognostic accuracy of PromarkerD was uncertain and was dependent on the renal outcome and also population studied. In Peters (2019; a previous study using FDS2 data), PromarkerD had a relatively low sensitivity (54.2% using optimal cutoff) at detecting decline of ≥30% in eGFR compared to detecting incident DKD (88.9% using optimal cutoff). The sensitivity in Peters (2020) using CANVAS data however showed lower sensitivity for both ≥30% decline in eGFR (45.9%) and incident kidney disease (73.2%). As such, it may be concluded that PromarkerD was not particularly sensitive in detecting patients who may experience a ≥30% decline in eGFR over four years, despite the clinical claim.

Clinical management algorithms

Limited information regarding the proposed change in clinical management for patients using PromarkerD was provided in the application. The applicant subsequently provided the following information.

Based on the KDIGO definitions of kidney function (Figure 1), patients with T2DM whose renal marker measurements fall in the green boxes (normal uACR and eGFR ≥60 mL/min/1.73m^2) and the kidney function stage 1/2 yellow boxes (microalbuminuria and eGFR ≥60 mL/min/1.73m^2) would be eligible for a PromarkerD test. Table 9 details the current Kidney Health Australia action plan. If a patient falls in the green boxes (Figure 1), they currently would not undergo any particular treatment plan for their kidney health.

Table 9 Kidney Health Australia current action plan for monitoring kidney disease in patients with T2DM

Action plan	Frequency of review	Clinical assessment	Laboratory assessment	Other assessments
Yellow clinical action plan	Every 12 months	Blood pressure Weight Smoking	Urine ACR eGFR Biochemical profile including urea, creatinine and electrolytes HbA1c Fasting lipids	Assess absolute cardiovascular risk Blood pressure reduction Lifestyle modification Lipid lowering treatment Glycaemic control Avoid nephrotoxic medication or volume depletion Whole of practice approach to CKD
Orange clinical action plan	Every 3-6 months	Same as yellow	Same as yellow *plus* Full blood count Calcium and phosphate Parathyroid hormone (6-12 monthly if eGFR <45 mL/min/1.73m2)	Same as yellow *plus* Assess risk of atherosclerotic events and consider treating with an anti-platelet agent in keeping with existing cardiovascular guidelines Avoid nephrotoxic medication or volume depletion and adjust doses to levels appropriate for kidney function Assess for common issues (acidosis, albuminuria, anaemia, cognitive decline, depression, dietary protein, Haematuria, Hyperkalaemia, lipids, malnutrition, mineral and bone disorder, muscle cramps, oedema, pruritus, restless legs, sleep apnoea, uraemia) Appropriate referral to nephrologist when indicated
Red clinical action plan	Every 1-3 months	Same as yellow/orange *plus* Oedema	Same as yellow/orange	Same as yellow/orange *plus* Discuss treatment options, including dialysis, transplant and non-dialysis supportive care if eGFR <30 and progressing to kidney replacement therapy Discuss advance care plans if appropriate

Source: Adapted from Chronic Kidney Disease (CKD) Management in Primary Care in Section 4: Managing CKD in Primary Care

The applicant provided updated current (Figure 8) and proposed (Figure 9 in the attachment) algorithms. These are presented in the attachment to this PICO, while Figure 7 was developed during the PICO confirmation based on the information provided in Figure 8 and Figure 9 in order to provide some clarity and focus on the patient population for whom the PromarkerD test is intended.

In the current algorithm, patients with T2DM are tested annually for DKD risk factors, among these risk factors are eGFR and uACR. For those with eGFR ≥60 mL/min/1.73m^2 and normoalbuminuria, standard diabetes management is maintained. For those with eGFR ≥60 mL/min/1.73m^2 and microalbuminuria, various reviews of lifestyle factors and clinical targets for blood pressure, lipids are considered. Although not specified in the applicant's algorithm, the applicant confirmed that both of these patient groups continue annual screening of DKD risk factors.

In the proposed algorithm, patients with eGFR ≥60 mL/min/1.73m^2 and normoalbuminuria or microalbuminuria will be eligible for the PromarkerD test. PromarkerD recategorises patients as either low-, moderate- or high-risk of developing DKD in the next four years. For those who are:

- Low-risk: standard diabetes management is maintained and annual screening of DKD risk factors is assumed to continue. A PromarkerD test is repeated in four years.

- Moderate risk: various reviews of lifestyle factors and clinical targets for blood pressure, lipids are considered. Although the applicant provided greater detail for the types of interventions that could be used, it is consistent with the current management of those with microalbuminuria (although they may have normal albumin). Screening for DKD risk factors is increased to every six months. A PromarkerD test is repeated in two years.
- High-risk: all measures considered for those who are moderate-risk apply. Screening for DKD risk factors is increases to every one to three months. A PromarkerD test is repeated in two years. Referral to a nephrologist or diabetologist may also be considered.

While patients with T2DM may not initiate specific treatments if they are considered to be at low-risk, they should still receive appropriate treatment or lifestyle advice for risk factors such as weight, cholesterol, blood pressure and glycaemic control. As shown in the treatment algorithms, annual screening is carried out and appropriate treatment should be initiated as required. It is therefore unclear why this would change with the use of PromarkerD.

PASC discussed the proposed clinical management algorithm. PASC noted that it is the subsequent changes in clinical management that may lead to a reduction in DKD and queried whether more intensive guideline-directed treatment for all patients with T2DM would reduce DKD. PASC questioned the value of retesting those with 'moderate' or 'high' risk scores given their treatment will have been intensified and would be maintained over time.

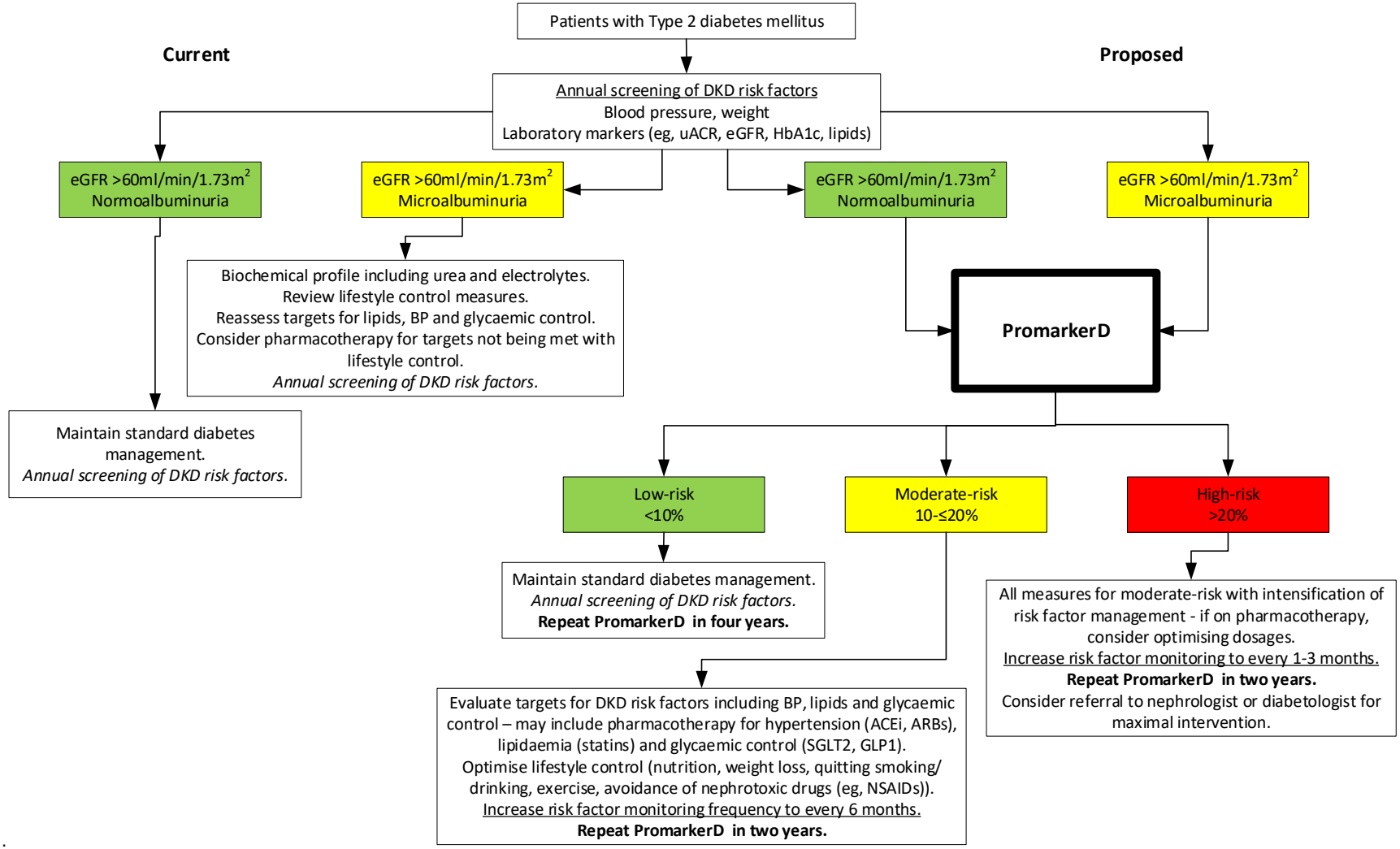

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Figure 7 Current and proposed algorithms for patients with T2DM and normoalbuminuria or microalbuminuria and eGFR ≥60 mL/min/1.73m²

ACEi = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BP = blood pressure; DKD = diabetic kidney disease; eGFR = Estimated glomerular filtration rate; GLP1 = glucagon-like peptide-1; HbA1c = glycosylated haemoglobin; microalbuminuria (uACR mg/mmol) = male: 2.5-25, female: 3.5-35; normoalbuminuria (uACR mg/mmol) = male: <2.5, female: <3.5; NSAIDs = non-steroidal anti-inflammatory drugs; SGLT2 = sodium-glucose co-transporter 2; uACR = albumin: creatinine ratio

The applicant provided further data from the Fremantle study showing the proportion of patients with various DKD risk factors who subsequently developed DKD. This is shown in Table 10. *No references were provided and the data could not be verified independently.*

Table 10 DKD risk factors and incidence of DKD in Fremantle study

	N patients that developed outcomes		
DKD risk factor (Definition of 'uncontrolled')	**Controlled**	**Uncontrolled**	***P*-value**
HbA1c (≥7.0%)	43 (10.3)	38 (12.4)	0.38
Serum total cholesterol (≥4.0 mmol/L)	41 (13.5)	40 (9.5)	0.088
Serum HDL cholesterol (<1.0 mmol/L)	58 (10.1)	23 (15.0)	0.088
Serum triglycerides ≥2.0 mmol/L	58 (10.5)	23 (13.1)	0.34
Hypertension >140/90 mmHg	62 (10.1)	19 (17.4)	0.025

DKD = diabetic kidney disease; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein

The applicant noted that both controlled and uncontrolled patients developed outcomes equally except for hypertensive patients who more often developed outcomes compared to normotensive patients (p=0.025), and suggested that even if patients developed control of risk factors like lipids, there is value in repeat testing. The applicant is requested to provide further detail with respect to these results, for example, (i) the total number of patients in the sample and (ii) what does 'controlled' and 'uncontrolled' refer to (eg, is it in reference to each risk factor separately)?

Based on this information alone, it was unclear if hypertension led to DKD, or if the worsening renal function had led to high blood pressure (or worse response to treatment). It was also noted that blood pressure measurements were not part of the PromarkerD algorithm, whereas HDL-cholesterol, in which there was no statistically significantly difference in incidence of DKD between patients with controlled or uncontrolled HDL, was included.

The results from the Fremantle study were inconsistent with the treatment targets proposed by the applicant which included lipid and glycaemic control, as there appear to be a lack of correlation between control of blood glucose and lipids with DKD outcome. While blood pressure appears to be correlated to the development of DKD, it was unclear if a more aggressive target (i.e. lower blood pressure) was required or if the relationship between hypertension and DKD was causal. As such, it was unclear what surrogate outcomes would represent meaningful treatment targets for patients who were identified to have moderate- to high-risk of DKD with the PromarkerD test.

Proposed economic evaluation

As the clinical claim included the use of PromarkerD in addition to standard of care, a cost effectiveness or cost-utility analysis would be appropriate (Table 11). The application did not provide sufficient detail to allow assessment of whether there is evidence available to conduct such an analysis.

PASC noted that the clinical claim led to a cost-effectiveness or cost-utility analysis being the appropriate economic evaluation, however PASC considered there may be insufficient information in the application to support the clinical claim.

Table 11 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

The applicant further clarified that the economic analysis will model the improvement in health outcomes as a result of the use of PromarkerD in patients with T2DM, with the clinical outcome evidence used to establish the population tested with PromarkerD, the definitions of DKD and end stage outcomes. The economic modelling of long-term impacts of kidney disease on health outcomes have been established by a systematic review of economic modelling of chronic kidney disease. The economic analysis should estimate the improvement in life years (LYs) and quality adjusted life years (QALYs) by the prevention or delayed onset of DKD and by extension, ESRD, dialysis and mortality. It should also estimate the reduction in health costs to treat DKD, ESRD and dialysis.

With regards to the economic evaluation, there is significant complexity with regards to the treatment options and the associated surrogate or intermediate outcomes. The applicant has nominated a large range of treatments including pharmacotherapy for hypertension, lipidemia and glycaemic control as well as other management such as 'optimise lifestyle control' including nutrition, weight loss, smoking/alcohol cessation, exercise and avoidance of nephrotoxic drugs. These treatments all have different targets such as aiming to control blood pressure, lipids and glycaemic control as well as nutritional targets, weight loss and other lifestyle goals. The relationship between each surrogate outcome with DKD will need to be established separately, and presumably not all of them would be equal, and any economic evaluation would need to consider all the complexities of having multiple possible treatments and multiple treatment targets.

For example, in patients categorised by the PromarkerD algorithm as moderate- to high-risk, a patient with uncontrolled hypertension would likely have a different change in management and treatment goals (e.g. change in blood pressure medication with a therapeutic surrogate goal to achieve normotensive status with the ultimate goal of preventing/delaying DKD) compared to a patient with uncontrolled HbA1c (e.g. change in glycaemic control medication with a therapeutic surrogate goal to achieve target HbA1C with the ultimate goal of preventing/delaying DKD). As such, they may represent separate cohorts which likely will have to be modelled separately in the economic evaluation due to the different intervention used, with different cost and efficacy of treatments and different surrogate treatment outcomes, and the ICER (with respect to DKD) in the uncontrolled hypertension cohort would likely be different to the ICER in the uncontrolled glycaemic control cohort. Further, there may be patients who have more than one

uncontrolled risk factor and therefore require more than one change in management and treatment goals, compounding the complexity of the economic evaluation. Alternatively, a single economic model which includes all of the surrogate outcomes and then a dynamic translation to the incidence of DKD would have to be constructed. That is, the model would need to consider the interactive relationship between hypertension, glycaemic control, lipid control, weight, smoking/drinking status (and possibly others) and with the risk of DKD, such that the risk of DKD would be different based on variation on one or more of these identified risk factors which could be influenced by treatment in order to quantify the cost and benefit of the treatment changes associated with a categorisation by the PromarkerD algorithm as moderate to high-risk.

PASC noted that the applicant proposed a complex economic evaluation, probably a Monte Carlo patient simulation model.

Proposal for public funding

The application requested MBS funding for PromarkerD with a new MBS item number, see table below. Suggested changes to the item descriptor to remove ambiguity are included in italics. Public funding other than via the MBS is not being sought.

Category 6 – Pathology Services
MBS item XXXX Proposed item descriptor: A test to quantify the risk of diabetic kidney disease incidence in proceeding 4 years in: a. Patients diagnosed with type 2 diabetes; and b. Estimated glomerular filtration rate (eGFR) of greater than or equal to 60ml/min/1.73m^2; and c. Albumin: Creatinine Ratio (uACR) test results of less than or equal to 30mg/mmol. For any patient with a low-risk score, performed once every 4 years. *For any patient without a previous moderate- to high-risk score, perform the next test in 4 years.* For patients with a previous moderate- to high-risk score, performed once every 2 years. *For patients with a previous moderate- to high-risk score, perform the next test in 2 years.* **Fee:** $250 **Benefit:** 75% = $187.50 85% = $212.50

While the proposed item descriptor requires that eGFR and uACR test results, and eGFR and HDL-cholesterol are required as inputs for PromarkerD, the application did not state within what timeframe these tests need to be conducted. The applicant further clarified that HDL-cholesterol, eGFR and uACR results should be no older than six months.

The application requested that patients be limited to one PromarkerD test every 4 years for patients with a low-risk score and to once every two years for patients with a moderate to high-risk score. In subsequent information provided by the applicant it stated that the proposed frequency of testing is based on advice from key opinion leaders and that the duration for repeat use of PromarkerD will be explored in a survey to be conducted with primary care physicians. These timeframes will require additional justification. It is not clear why patients who are found to have a moderate- to high-risk, should have a PromarkerD test performed every two years when the PromarkerD results provide a four-year risk of developing DKD. Additionally, there appears to be little consistency established for the duration of retesting. The PromarkerD instructions for use (Figure 2) suggest retesting should be conducted every three months (high-risk), three to six months (moderate-risk) or annually (low-risk). Burcheral (2021) assumed that

testing would be conducted every six months (high-risk), eight months (moderate-risk) or one year (low-risk).

Subsequent to the application, the applicant provided additional information that the proposed MBS fee ($250) was determined based on the costs of developing the technology and ongoing supply with an industry standard profit margin.

PASC considered there was a lack of clarity regarding the requested fee, specifically what component related to ELISA and what component related to the algorithm. The applicant clarified that the proposed fee includes all components of the test including ELISA and algorithm. However, it is not clear whether "all components" also includes the HDL-cholesterol and eGFR tests that are required by the algorithm to predict the risk score. If HDL-cholesterol and eGFR are to be excluded as a component of the proposed service, and if the results are not available to pathologists or are more than 6 months old at time of PromarkerD testing, HDL-cholesterol and eGFR tests will need to be repeated and subsequently contribute to the cost effectiveness analysis. PASC considered that the HDL-cholesterol and eGFR tests would likely need to be repeated at time of PromarkerD testing. *PASC requested the assessment report provide a breakdown of the components of the $250 fee.*

There are no tests similar to PromarkerD currently listed on the MBS with which to compare MBS fees.

If PromarkerD is to be used to identify patients at increased risk of developing DKD and the applicant proposes that patients be allowed to initiate SGLT2 inhibitors as a result of the risk factor determined by PromarkerD, a codependent application for PromarkerD and canagliflozin (or another SGLT2 inhibitor if a class effect can be proven) may be required. Currently, dapagliflozin, empagliflozin and ertugliflozin are listed on the PBS with patients requiring an HbA1c measurement of greater than 7.0% to be eligible.

Summary of public consultation input

Two organisations provided responses to the targeted consultation, the Endocrine Society of Australia (ESA) and the Royal College of Pathologists of Australasia (RCPA).

Both organisations were not supportive of the application.

RCPA considered that more supportive data may be required to support this application, including:

- the clinical utility of the three biomarkers, along with others (HDL, etc.), chosen to calculate the risk of developing kidney disease in diabetic patients
- the evidence behind the proposed frequency of testing, and
- the validity of the PromarkerD Hub, the software tool that contains a proprietary algorithm used to calculate the risk of developing, or further progression of DKD.

ESA considered that it would be beneficial if a biomarker was available to better predict development of renal disease in patients with diabetes. However, ESA was concerned that the application did include an analysis of the utility of the proposed three biomarkers compared to other currently researched and/or developed proteomic-derived biomarkers for prediction of the development of CKD in patients with Type 2 diabetes mellitus.

ESA questioned whether patients with microalbuminuria should be included in the eligible test population, as microalbuminuria is a well-established marker of progression to CKD, and the test would add limited additional value to clinicians.

ESA was concerned about a lack of independent validation as the studies cited appear to have been all undertaken by inter-related authors and there could be potential conflicts of interest where authors are employed by organisations, which are beneficiaries of the patent.

PASC noted that the consultation feedback was broadly not supportive, indicating more data were required to demonstrate the benefit of the test and others raising concerns regarding whether the best biomarkers were included. The feedback also questioned the value of the test among those with existing microalbuminuria.

PASC also noted there was no feedback from the number of consumer organisations that were targeted. PASC questioned whether this test would be acceptable to patients.

Next steps

The applicant indicated this application would proceed as an ADAR (applicant-developed assessment report).

Applicant Comments on the PICO Confirmation

Population

A large proportion of patients with kidney damage or reduced kidney function are asymptomatic meaning early detection and treatment of diabetic kidney disease is essential to prevent further kidney injury. PromarkerD offers additional benefit to patients with microalbuminuria (or other risk factors) as it provides a timeframe for development of DKD to target therapies, and has increased sensitivity compared to standard of care to identify those at highest risk to improve disease management. Despite guidelines for annual monitoring of eGFR and uACR in people with T2DM, only 49% of Australian patients are appropriately screened or monitored for kidney disease in primary care [1]. The prognosis of the remaining half is unknown. Diabetes and DKD are multifactorial diseases, whereby the use of one predictor such as microalbuminuria is problematic as it is not necessarily an indication of all factors.

Additionally, PromarkerD retesting of those with 'moderate' or 'high' risk scores will allow longitudinal monitoring over time, assessing both changes in DKD risk and response to treatment or management changes.

[1] Manski-Nankervis, J.E.; Thuraisingam, S.; Lau, P.; Blackberry, I.; Sluggett, J.K.; Ilomaki, J.; Bell, J.S.; Furler, J. Screening and diagnosis of chronic kidney disease in people with type 2 diabetes attending Australian general practice. *AJPH* **2018**, 24:280-86).

Outcomes

The impact of PromarkerD on clinical practice and outcomes will be supported by a survey of Australian clinicians. Previous evidence provided by the Applicant from a clinical decision impact/utility study in the United States, demonstrated the importance of PromarkerD and other patient attributes to clinical decision making. A clinical survey of 400 physicians showed that PromarkerD was the first- or second-most important attribute driving physician decision making, outweighing eGFR and albuminuria, for increasing monitoring frequency, prescribing SGLT2i, and increasing blood pressure medication dose

Assessment framework (for investigative technologies)

The PASC noted that outcomes may improve only as a result of changes in clinical management, but the targets and extent of this clinical management can be guided more accurately with a PromarkerD test. This is comparable to any other investigative technology.

PromarkerD provides a timeframe for development of DKD to target therapies, and has increased sensitivity compared to standard of care to identify those at highest risk of DKD.

PromarkerD can improve outcomes by allowing patients who may nominally fall into KDIGO low-risk categories to be treated to the extent which the PBS restrictions allow. All patients will be trying to achieve optimal targets for glucose, lipids and blood pressure, but in practice these targets are not met and assessing DKD risk is one way to empower them. Reducing or delaying the progression of DKD and consequently the incidence of dialysis and kidney transplant would result in significant improvements in QOL for the patient and cost savings for health care systems

Clinical management algorithms

If all patients received the guideline-directed maximal treatment, it would reduce DKD at a large financial cost to the patient and healthcare system. PromarkerD could help stratify those patients who would benefit from this intensified regime the most – the high-risk patients.

PromarkerD would not change standard management of people with low-risk scores, but would provide an accurate 'rule-out' capability for these individuals where more aggressive management could be rationalised, limiting adverse effects and costs, and improving adherence.

Next steps

The applicant thanks the PASC, and the RCPA and ESA, for their time in providing valuable feedback and the assessment report will address the comments in the ratified PICO as previously stated. The applicant would like to clarify three particular issues at this stage.

1. *<u>The clinical utility of the three biomarkers, along with others (HDL, etc.), chosen to calculate the risk of developing kidney disease in diabetic patients</u>*
   The utility of clinical markers used for PromarkerD (age, HDL, eGFR) in assessing risk of DKD are all common practice and well validated. The utility of the biomarkers is described in detail in the Intervention section under 'Selection of biomarkers'.
2. *<u>Comparison with other biomarkers</u>*
   The assessment report will contain a comparison to other biomarkers proposed for prognostic tests. In particular, a comparison with KidneyIntelX can be provided. KidneyIntelX is currently only available in the United States. A large number of promising urinary and plasma biomarkers have been assessed in the context of CKD [1-7], but large-scale longitudinal validation is required to validate their value over and above that of known clinical risk factors. Most of these studies have been limited by small sample sizes, exclusion of patients without albuminuria and/or CKD, and/or inclusion of patients who are not representative of type 2 diabetes in the community such as those participating in clinical trials or who have been selected from hospital outpatient clinics. All other biomarkers are still in the evaluation stage, and none have progressed to the viability of those in the PromarkerD test.
3. *<u>Lack of independent validation</u>*
   The publications which have been used and will be used in this process to support PromarkerD are peer-reviewed. In the cases where new analysis is conducted, all data will be provided in the assessment report, and we ask that the data be evaluated on its merit.

[1] Lin CH, Chang YC, Chuang LM. Early detection of diabetic kidney disease: Present limitations and future perspectives. World J Diabetes 2016;7:290-301
[2] Bjornstad P, Cherney DZ, Maahs DM, et al. Diabetic Kidney Disease in Adolescents With Type 2 Diabetes: New Insights and Potential Therapies. Curr Diab Rep 2016;16:11
[3] Looker HC, Colombo M, Hess S, et al. Biomarkers of rapid chronic kidney disease progression in type 2 diabetes. Kidney Int 2015;88:888-896
[4] Niewczas MA, Gohda T, Skupien J, et al. Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. J Am Soc Nephrol 2012;23:507-515
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[7] Saulnier PJ, Gand E, Velho G, et al. Association of Circulating Biomarkers (Adrenomedullin, TNFR1, and NT-proBNP) With Renal Function Decline in Patients With Type 2 Diabetes: A French Prospective Cohort. Diabetes Care 2017;40:367-374

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Attachment

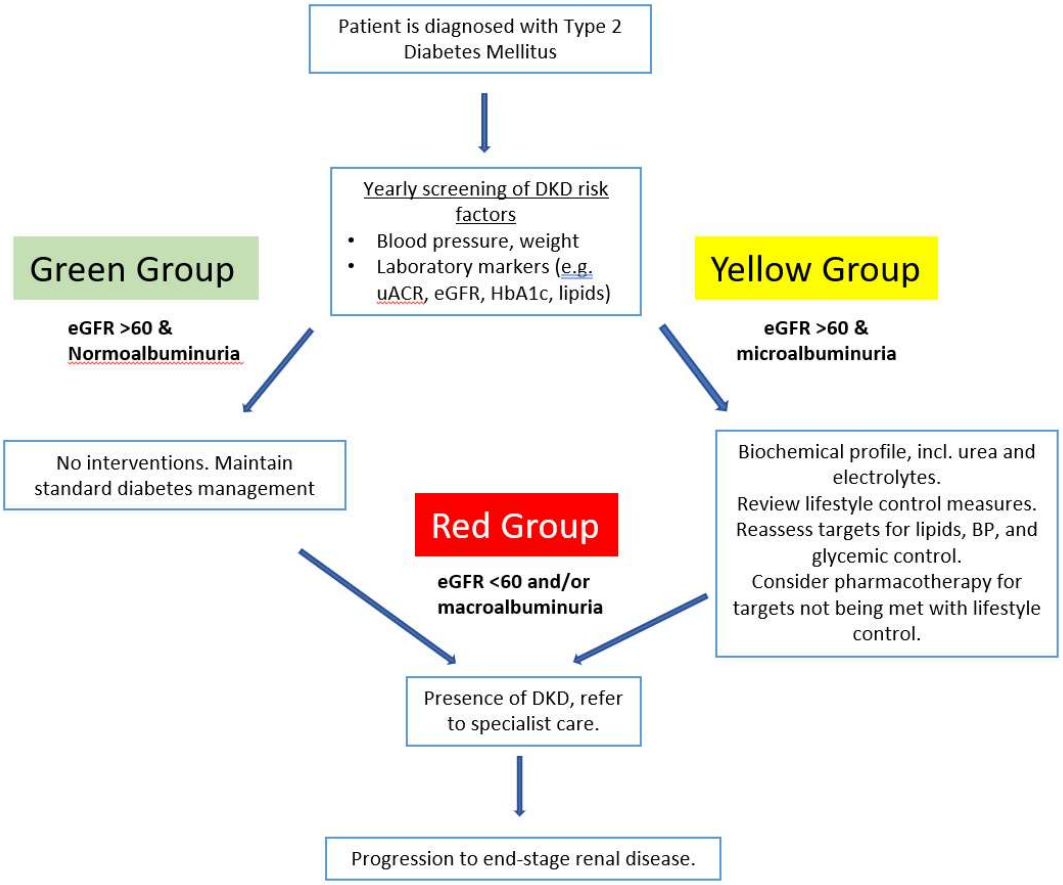

Figure 8 Treatment algorithm before listing of PromarkerD

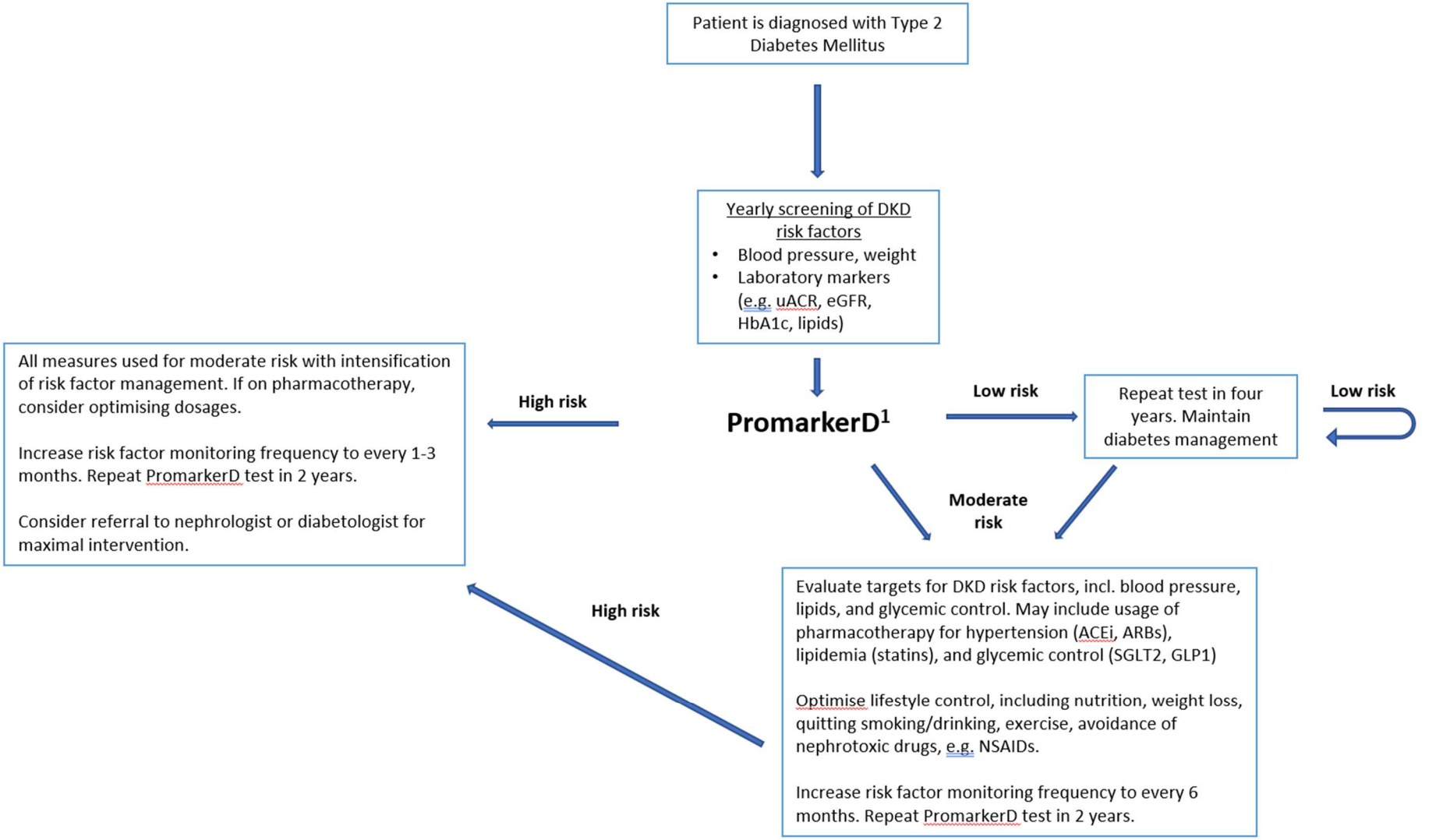

Figure 9 Treatment algorithm after listing of PromarkerD. PromarkerD test only for patients with normoalbuminuria or microalbuminuria and eGFR ≥60 mL/min/1.73m²