Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1691 – PromarkerD testing in patients with type 2 diabetes to determine the risk of developing diabetic kidney disease

Applicant: Proteomics International Pty Ltd

Date of MSAC consideration: 24-25 November 2022

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting MBS listing of PromarkerD, a predictive test for developing diabetic kidney disease [DKD] over 4 years, proposed for people with type 2 diabetes mellitus (T2DM) and comprising three routinely available clinical characteristics (age, high-density lipoprotein [HDL] cholesterol and estimated glomerular filtration rate [eGFR]) with three biomarkers (ApoA4, CD5L, IBP3) was received from Proteomics International Pty Ltd by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of PromarkerD testing in patients with type 2 diabetes to determine the risk of developing DKD. MSAC considered that the clinical utility of the test was uncertain because the evidence that the test would change clinical management was based on a survey of intent, not actual evidence of change, was at high risk of bias, and the test had a low positive predictive value (PPV). MSAC also had concerns about the evidence for the prognostic value of the test, given its high risk of bias; and the safety of the test, given its low PPV and the lack of detail provided on the proprietary "black box" algorithm. MSAC considered the cost-effectiveness was uncertain as the model used for the economic evaluation did not include the test outcomes to allow comparisons with the current clinical approach. In addition, MSAC considered the economic modelling and financial estimates were uncertain and contained errors and omissions. MSAC also considered the proposed MBS fee was high and unjustified, and the uncertainty regarding test uptake also impacted the financial estimates.

Consumer summary
This is an application from Proteomics International requesting Medicare Benefits Schedule (MBS) listing of PromarkerD, a test that predicts the risk of developing diabetic kidney disease in patients with type 2 diabetes.
The kidneys remove waste and extra water from the blood. They also produce hormones that help to control blood pressure. People with diabetes often have high amounts of glucose in their blood (called high blood sugar), which can cause damage to the blood vessels in the

Consumer summary

kidneys. When the kidneys are damaged, they can't function properly. This can cause waste to build up in the body, leading to a variety of health problems.

PromarkerD is a blood test that measures the concentration of ApoA4, CD5L and IBP3, which are three elements in a patient's blood. These are combined with other clinical factors (age, cholesterol and kidney function) and entered into the PromarkerD software. The software then works out if a patient has a low, moderate or high risk of developing diabetic kidney disease.

MSAC considered that the PromarkerD test did not address an unmet clinical need. This is because people with type 2 diabetes are often monitored very closely for diabetic kidney disease already, and the results from the PromarkerD test would be unlikely to change how these patients are managed. MSAC also questioned the accuracy of the test, and was concerned about the risk of false positive (a patient receives a positive result when they actually are not at risk of developing disease) and false negative (a patient receives a negative result when they actually are at risk of developing disease) results. MSAC was also not convinced that the test was good value for money.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support listing the PromarkerD test on the MBS. MSAC considered that there was not enough high-quality evidence to show that the test is safe and effective. MSAC was also not convinced that the test was addressing an unmet need or was good value for money.

3.   Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Proteomics International is requesting MBS listing of PromarkerD, a predictive test for assessing the risk of patients with type 2 diabetes developing DKD over the next four years. This test is proposed for people with type 2 diabetes, a urine albumin:creatinine ratio (uACR) of 30 mg/mmol or less, and an estimated glomerular filtration rate (eGFR) of at least 60 ml/min/1.72 m^2. PromarkerD measures the patients' levels of three protein biomarkers in human plasma (ApoA4, CD5L and IBP3), which are then entered into a proprietary software along with their age, high-density lipoprotein (HDL) cholesterol level and eGFR. The software then characterises a patient as having a low, moderate or high risk of developing DKD within the next four years based on these inputs.

MSAC noted that the current best practice guidelines from Diabetes Australia recommend that people with type 2 diabetes should be screened annually for DKD using uACR and eGFR. MSAC noted that a persistent uACR above 2.5–3.0 mg/mmol is indicative of microalbuminuria. Patients who initially demonstrate microalbuminuria should have their uACR tests repeated several times over at least three months to confirm that the elevated uACR is not transient, prior to assessing their risk of DKD. MSAC noted that an uACR of 25–30 mg/mmol is indicative of macroalbuminuria. MSAC noted that under current best practice guidelines, patients with type 2 diabetes and DKD with either hypertension and/or albuminuria should already be receiving either an ACE inhibitor or an angiotensin receptor blocker (ARB) to delay progression of DKD and treat hypertension if present. The current clinical guidelines recommend that treatment should be started early to prevent progression.

MSAC noted that consultation feedback was broadly not supportive, indicating that more data were required to demonstrate the benefit of the test. There were also concerns raised about whether the best biomarkers were included in the test, and that the application did not provide an analysis comparing the performance of PromarkerD against other proteomic-derived biomarkers that are currently being studied and developed.

MSAC noted that there is a risk of leakage if the item descriptor does not specify PromarkerD and the eligible population.

MSAC noted that, in the pre-MSAC response, the applicant agreed with ESC that the eligible population should be restricted to patients who are currently in the low-risk category (i.e. those with eGFR ≥60 mL/min/1.73 m² and/or uACR <2.5 mg/mmol if male or <3.5 mg/mmol if female). MSAC noted the Department's proposal that the thresholds for the uACR levels that confer eligibility should be detailed in an explanatory note. MSAC considered that, because of these changes to the proposed population, the economic model would need to be revisited. MSAC noted that the applicant also agreed to removing the retesting suggestions for people with moderate- or high-risk scores. Retesting would now be restricted to patients assessed as low-risk of developing DKD by the test and their retesting interval would be restricted to a minimum of four years.

MSAC noted that the proposed fee for the test is $250, which exceeds the schedule fees of other MBS items in Group P2 – Chemical (all less than $100). MSAC noted that the applicant stated in the pre-ESC response that the fee covers all components of the test blood draw, enzyme-linked immunosorbent assay test for PromarkerD biomarker detection, HDL cholesterol and kidney function tests (uACR and eGFR), and PromarkerD algorithm use through the proprietary PromarkerD Hub. The fee therefore accounts for components of the test that are not provided under the proposed service (i.e. HDL cholesterol and kidney function tests) as well as the cost of developing the technology, and the ongoing supply of the PromarkerD test kits. MSAC questioned the appropriateness of this as there would be cases where patients have already undertaken some or all of the tests not provided under the proposed services and cases where they have not undertaken any of these tests.

MSAC noted that the comparator is usual care. MSAC considered PromarkerD to be an additional test to usual care, not a replacement, as patients with diabetes should always be screened with uACR at least once a year, in accordance with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. MSAC clarified that PromarkerD is a predictive test, meaning it is a "risk assessment" and not a true "test" of disease presence. MSAC also considered that usual care may also involve:

- screening for the presence of microalbuminuria
- considering treating the patient for hypertension, dyslipidaemia and other cardiovascular disease (CVD) risks (given that many patients with diabetes have high CVD risk).

MSAC considered that there are many aspects of a patient's risk profile that inform shared decision making and treatment of the patient. For example, if a patient has normal uACR and is deemed to be at low risk of DKD using PromarkerD but is hypertensive or has high cholesterol levels, (and therefore is at high CVD risk), the patient will likely be treated with anti-hypertensive and/or hyperlipaemia medication(s). Therefore, MSAC considered the clinical utility of the test to be uncertain and questioned how it would change management. MSAC noted that, in addition to DKD, management of patients with diabetes is also focused on optimising treatment of all risk factors associated with diabetes related complications. MSAC considered that the test may possibly only be useful for its negative predictive value (NPV) in patients who will not accept any treatment or who are reluctant to be screened. However, MSAC considered that if the main clinical utility of the test is its NPV, one downside of this is that this may then lead to the clinician and patient being falsely reassured and inadvertent underscreening for other risk factors.

MSAC noted that the evidence base comprised three categories: prognostic evidence for longitudinal accuracy which relied on two studies of prognostic models (Peters et al. 2019[1] and 2020[2]), change in patient management (one survey of clinician intent) and health outcomes (seven trials comparing different interventions). MSAC noted that the commentary determined that the evidence base for prognostic accuracy and change in patient management was at a high risk of bias. MSAC noted that the commentary did not assess the risk of bias for the health outcomes evidence, given the lack of evidence for longitudinal accuracy and change in patient management that could be linked to the use of PromarkerD. MSAC also noted that there are concerns about a lack of independent validation of the studies cited as they appear to have been undertaken by inter-related authors, and there could be potential conflicts of interest where authors are employed by organisations that are commercial beneficiaries of the test.

Regarding comparative safety, MSAC noted that there are safety issues associated with false positive and false negative results from the test. MSAC noted that some patients may have their treatment increased based on a false positive risk score, with subsequent potential harms from the treatment. Alternatively, false negative results may lead to complacency, and cause delays in routine screening for renal disease as well as other non-renal related risks. MSAC noted that these issues were initially dismissed by the applicant-developed assessment report (ADAR) though the pre-MSAC response acknowledged these concerns and in particular the low positive predictive value of the test (which implies a high false positive rate).

MSAC noted in reviewing the evidence on prognostic test accuracy that although the methodology used to determine test accuracy seems appropriate, issues remain around the external validity study of Peters et al. 2020, and there is a high risk of bias for both the two key studies. MSAC noted that the commentary calculated the following additional measures:

- C-statistic (area under the curve, concordance index) for test discrimination – this was found to be adequate
- calibration as a measure of accuracy of predicted risk probabilities – this showed moderate (in Peters et al. 2019) to poor (in Peters et al. 2020) calibration
- PPV and NPV – PPV appears to be low (30.4% from Peters et al. 2019 and 58.8% from Peters et al. 2020, compared with NPV of 98.1% and 86.4%). As noted previously, in the pre-MSAC response, the applicant states that the strength of PromarkerD is its ability to rule out patients at low risk (i.e. a high NPV) rather than the PPV.
- ability to predict decline in eGFR (greater than 30%) over four years – this was found to be poor.

For change in management, MSAC noted that the evidence only consisted of a survey of intent, and not actual evidence of change. MSAC noted the pre-MSAC response that stated that real-world evidence of change in management could not be undertaken as it would be unethical. MSAC noted that the results of the American survey by Fusfeld et al. (2022)[3], reported in the ADAR, showed that PromarkerD was not considered to be the most important factor in making a decision for prescribing or replacing therapy.

As noted previously, due to the lack of evidence for change in management, the linked evidence for health outcomes was not assessed.

[1] Peters KE, Davis WA, Ito J, et al. (2019). Validation of a protein biomarker test for predicting renal decline in type 2 diabetes: The Fremantle Diabetes Study Phase II. *Journal of Diabetes and its Complications*, 33, 107406.

[2] Peters KE, Xu J, Bringans SD, et al. (2020). PromarkerD Predicts Renal Function Decline in Type 2 Diabetes in the Canagliflozin Cardiovascular Assessment Study (CANVAS). *Journal of clinical medicine*, 9, 3212.

[3] Fusfeld L, Murphy JT, Yoon Y, et al. (2022). Evaluation of the clinical utility of the PromarkerD in-vitro test in predicting diabetic kidney disease and rapid renal decline through a conjoint analysis. PLoS One. Aug 1;17(8):e0271740.

MSAC identified several other issues. MSAC considered that there is insufficient information provided about the main features of PromarkerD to understand what effect the individual input variables have on the output of the prediction models (the pre-MSAC response stated that input variables will not be provided as the applicant is taking a "black box" algorithm approach to PromarkerD as per the MSAC Guidelines). It is also not possible to determine the incremental benefit of the PromarkerD biomarkers in addition to the clinical factors alone (uACR, eGFR) because the evidence for the clinical factors as prognostic markers has not been reported.

MSAC also noted that there is no information about the algorithm used to generate the results, nor is it clear whether or how comorbidities have been accounted for in the PromarkerD algorithm. MSAC noted that the pre-MSAC response stated that the value of additional clinical markers such as comorbidities does not change the model predictions. However, MSAC considered that treatment decisions for diabetes management are multifactorial and not based on test outcomes alone. The ADAR did not discuss how PromarkerD will interact with, for example, patients with a family history of diabetes or renal disease, or a previous or high risk of CVD.

MSAC noted that the economic evaluation was a cost-effectiveness analysis and a cost-utility analysis, using a time horizon of 30 years. It used a complex individual Monte Carlo simulation state transition model (10,000 patients in the cohort), with a cycle length of one year. MSAC noted that the economic model did not include test outcomes, accuracy of the test or test frequency, and non-DKD clinical events only figure into the risk of DKD, not the costs or outcomes. MSAC also noted concerns around the stability of the results, the suitability of the Nelson equation and its applicability to the Australian population, that only one-way sensitivity analyses were presented, and that the model overestimates prescribing and compliance with treatment (which would result in a bias towards a lower incremental cost-effectiveness ratio (ICER).

MSAC also noted that the ICER is highly sensitive to the mean PromarkerD risk category. MSAC noted that the trial data population's mean for PromarkerD risk category scores (0 = low, 1 = moderate, 2 = high) was used as an input in the simulation. The sensitivity analysis for PromarkerD risk simply adjusted this mean of the categorical variable up and down by 20%. MSAC noted that, according to the sensitivity analysis, a change of 20% (upwards and downwards) changes the ICER substantially – a 20% decrease in the mean score resulted in an ICER of ▮▮▮▮▮, while a 20% increase in the mean score resulted in an ICER of ▮▮▮▮▮. MSAC noted that the pre-MSAC response claimed that it is more appropriate to use the overall mean risk category score in the sensitivity analysis, but MSAC considered that it may be more appropriate to estimate the impact of certain proportions of the patient population changing risk categories.

Regarding financial impacts, PBS costs were not included in the financial analysis based on the ADAR's rationale that the test was "not expected to impact other health budgets during the first six years of listing". However, the pre-ESC response stated that "the listing of PromarkerD will generate a minor cost (<$10M) to the Pharmaceutical Benefits Scheme (PBS) in each of the first six years of listing, as a result of introducing new treatment to type 2 diabetes mellitus patients". MSAC considered that this may be an underestimate. For instance, MSAC queried whether the financial analysis accounted for PBS costs of additional treatments for those in the low-risk category who are then reclassified to a higher risk category. MSAC noted that after restricting the eligible population to only those in the low-risk (green) category (i.e. those with eGFR $\geq$60 mL/min/1.73 m^2 and/or uACR <2.5 mg/mmol if male or <3.5 mg/mmol if female) the net costs of listing PromarkerD taking into account both the MBS and PBS over six years ranged from $5.7 million in 2022 to $28 million in 2027.

MSAC also noted that there was uncertainty around the uptake of the test. The applicant estimated uptake as 15%; however, the commentary estimated this would more likely be 30%. This increases the estimated net cost to the MBS to $45 million in Year 6 (though this estimate is based on the original proposed population).

MSAC also noted that the ADAR did not adequately address implementation concerns around the capability of pathologists to process the results of PromarkerD test kits if PromarkerD were listed, and the need for extra medical consultations and blood collection for repeat testing (and the costs associated with these).

Overall, MSAC considered that there was insufficient evidence to support the clinical claim that PromarkerD would change clinical management or outcomes, as this test does not negate the need for other tests such as screening uACR. A study is needed where the change in management from using PromarkerD is properly evaluated by comparing a patient population with access to the test against a control population, so that outcomes can be followed up over time. There are also safety concerns in relation to low PPV. Additionally, evidence is required for prognostic test accuracy that is not highly biased and addresses the relevant sections in the MSAC guidelines, including TG15.2 "Testing to determine prognosis" and TC15.5 "Multifactorial algorithms". Evidence is also required that links improved health outcomes to the test. Also, the economic model needs to be amended to reflect the new proposed population and retesting frequency. Test outcomes should be included in a decision tree component as it would allow comparisons with the current clinical approach based on KDIGO guidelines. Finally, a breakdown of component costs is required to justify the proposed fee.

4.   Background

MSAC has not previously considered PromarkerD as a predictive test for developing DKD.

5.   Prerequisites to implementation of any funding advice

The PromarkerD test has been included on the Australian Register of Therapeutic Goods (ARTG) since March 2020, together with software that runs the algorithm, which has been on the register since July 2019. Table 1 provides details of the Therapeutic Goods Administration (TGA) status from the ARTG for PromarkerD and its consumables under number 330723.

In the ADAR, the applicant notes that PromarkerD was submitted to the TGA on 26 May 2022 (application ID: DV-2022-IVA-11507-1) and the manufacturer's evidence was approved. This aligns with Step 6.6 of the TGA guidance for in-vitro diagnostic devices (IVD).[4] The next step will be the TGA's final evaluation and eventual listing on the ARTG, which is expected to be complete ███████.

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[4] TGA Guidance for IVD sponsors – a roadmap to market: https://www.tga.gov.au/guidance-ivd-sponsors-roadmap-market

Table 1   PromarkerD and consumables listed on the ARTG

Product name & sponsor	ARTG summary	Intended purpose
Proteomics International Pty Ltd – Clinical Chemistry IVDs	**ARTG ID**: 330723 **Start date**: 04/03/2020 **Category**: Medical Device Class 1 **GMDN**: CT287 Clinical Chemistry IVDs	PromarkerD Capt*Sure*™ ELISA is an in-vitro quantitative test intended for the detection of 3 protein biomarkers (analytes) in human plasma. This quantitative test result together with 3 clinical variables is intended to enter into an algorithm (PromarkerD Hub) to generate the prognostic and diagnostic risk scores of diabetic kidney disease (DKD) in patients with type 2 diabetes. The test is designed to be used by clinical laboratory trained personnel.
Proteomics International Pty Ltd – Software IVDs	**ARTG ID**: 320671 **Start date**: 24/07/2019 **Category**: Medical Device Class 1 **GMDN**: CT944 Software IVDs	PromarkerD is an in-vitro quantitative test intended for the detection of 3 biomarkers (analytes) in human plasma. This quantitative test result together with 3 clinical variables is intended to be entered into an algorithm to generate the prognostic and diagnostic risk scores of diabetic kidney disease in patients with type 2 diabetes. The test is designed to be used by clinical laboratory trained personnel.

ARTG = Australian Register of Therapeutic Goods, ELISA = enzyme-linked immunosorbent assay, IVDs = in vitro diagnostic medical devices,
Source: Therapeutic Goods Administration, ARTG Public Summary, accessed by assessment group 21 July 2022

6.   Proposal for public funding

The proposed population requested for PromarkerD is patients with T2DM who may be at risk of developing DKD. Patients would be eligible for the proposed medical service if they met the following criteria:

- patients diagnosed with T2DM; and
- eGFR ≥60 ml/min/1.73m^2; and
- uACR ≤30 mg/mmol.

PromarkerD is an in-vitro quantitative blood test designed to predict incident DKD or progression of DKD in patients with T2DM within 4 years of receiving the test. The test measures 3 novel plasma protein biomarkers (ApoA4, CD5L and IBP3) combined with clinical factors (age, serum HDL cholesterol, eGFR) to generate prognostic risk scores for DKD in patients with T2DM. The concentrations of the biomarkers, along with the clinical factors, are entered into the PromarkerD Hub, a static proprietary software algorithm that 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.

The applicant proposed one new MBS item (see Table 2).

Table 2   Presentation of an existing, amended or newly proposed MBS item

Category 6 – Pathology Services
MBS item 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 60 ml/min/1.73m^2; and c. Urine Albumin: Creatinine Ratio (uACR) test results of less than or equal to 30 mg/mmol.   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, perform the next test in 2 years.
Fee: **$250 Benefit: 75% = $187.50 85% = $212.50**

The applicant states that the fee has been determined on the basis of the costs of developing the technology in addition to ongoing supply of the PromarkerD test kits, with an industry standard profit margin. There are no tests similar to PromarkerD currently listed on the MBS.

The applicant states that the fee contains all components of the test:

- blood draw
- ELISA test for PromarkerD biomarker detection
- HDL cholesterol and kidney function tests (uACR and eGFR)
- PromarkerD algorithm use through the proprietary PromarkerD Hub.

There is no discussion in this ADAR of the implications of PromarkerD for pathology services.

7.   Population

One population, intervention, comparator and outcomes (PICO) set was defined for the proposed technology, PromarkerD. It is a new predictive test and does not replace current practice.

Table 3   PICO criteria for assessing PromarkerD predicative 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 60 ml/min/1.73m^2; and c. albumin: creatinine ratio (uACR) test results of less than or equal to 30 mg/mmol.
Prior tests	Tests required to confirm diagnosis of T2DM. Prior measurement of eGFR and uACR is required. Prior measurement of serum HDL cholesterol is required. eGFR and HDL cholesterol results should be no older than 6 months.

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 60 ml/min/1.73m^2; and c. albumin: creatinine ratio (uACR) test results of less than or equal to 30 mg/mmol.
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 3 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	The comparator nominated is 'no comparator', as PromarkerD would be added to the current testing regimen. There is no direct comparator as current standard of care diagnoses DKD after clinical symptoms appear rather than predicting risk of DKD.
Outcomes	**Safety** N/A **Effectiveness** Life years saved End-stage renal disease (ESRD) Quality-adjusted life years (QALYs) **Health care system outcomes** N/A **Test outcomes** Sensitivity Specificity Positive predictive value (PPV) Negative predictive value (NPV) 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 • maintenance of blood pressure below 130/80 mmHg • BMI <25.

Systematic review questions

What is the safety, effectiveness and cost effectiveness of PromarkerD compared to current standard of care in people with T2DM?

Abbreviations

T2DM = type 2 diabetes mellitus, eGFR = estimated globular filtration rate, uACR = urine albumin creatinine ratio, HDL = high-density lipoprotein, CKD = chronic kidney disease, DKD = diabetic kidney disease, ESRD = end-stage renal disease, QALY = quality-adjusted life years, PPV = positive predictive value, NPV= negative predictive value.

The proposed population for PromarkerD includes patients with T2DM who may be at risk of developing DKD. PromarkerD would be used to test patients with T2DM before kidney damage or clinical symptoms occur (kidney function Stage 1 or 2). While the risk of DKD is also relevant for people with type 1 diabetes mellitus (T1DM), currently data for the use of PromarkerD is only available for people with T2DM.

Patients would be eligible for the proposed medical service if they met the following criteria:

- patients diagnosed with T2DM; and
- eGFR ≥60 ml/min/1.73m^2; and
- uACR ≤30 mg/mmol.

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 KDIGO guidelines for evaluation and management of chronic kidney disease (CKD)[5] (Levin et al 2013). According to the applicant, patients would be eligible for PromarkerD if they have kidney function Stage 1 or 2 combined with normoalbuminuria 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 a reimbursed PromarkerD test.

Kidney Function Stage	GFR (mL/min/1.73m²)	Albuminuria Stage		
		Normal (urine ACR mg/mmol) Male: <2.5 Female: <3.5	Microalbuminuria (urine ACR mg/mmol) Male: 2.5-25 Female: 3.5-35	Macroalbuminuria (urine ACR mg/mmol) Male: >25 Female: >35
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60-89			
3a	45-59			
3b	30-44			
4	15-29			
5	<15 or on dialysis			

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

<u>Abbreviations</u>
ACR = albumin creatinine ratio, GFR = glomerular filtration rate.

The applicant states that PromarkerD is not proposed for use in individuals with T2DM who fall into higher risk categories (eGFR <60 mL/min/1.73m^2 and/or macroalbuminuria). Patients in these categories already display clear indications of kidney damage and reduced kidney function and would hence be receiving more intensive treatment and monitoring. The proposed population for PromarkerD (those with eGFR ≥60 mL/min/1.73m^2 and normal urine ACR or microalbuminuria) represent the patients most likely to benefit from the test if it was funded on the MBS.

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[5] Levin A, Stevens PE, Bilous RW, et al. (2013). Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney international supplements*, 3, 1-150

The Commentary noted that the ADAR does not sufficiently address key elements in the ratified PICO Confirmation as directed by PASC including:

- justification for the inclusion of the patients in the yellow risk group who show 'moderately increased albuminuria' (formerly known as microalbuminuria).
- providing evidence of detecting patients with a decline in eGFR of ≥30% over 4 years
- justification for retesting patients who return a moderate- or high- risk score
- the capability of pathology services to process PromarkerD test kits
- a breakdown of the components of the proposed fee.

In its pre-ESC response, the applicant noted that while patients in the yellow risk group should already be receiving intensified treatment as per the Kidney Health Australia guidelines, only 49% of Australian patients are appropriately screened or monitored for kidney disease in primary care. The pre-ESC response also justified the re-testing frequency for patients returning a moderate to high risk score on PromarkerD on the basis that this would allow longitudinal monitoring over time, assessing both changes in DKD risk and response to treatment or management changes.

8.　Comparator

There is no equivalent test or tests that quantitatively predict incident DKD in patients with T2DM. The PICO Advisory Sub-committee (PASC) agreed that the comparator to PromarkerD is standard medical management and no testing.

The applicant stated that patients with T2DM currently should have laboratory risk factors (e.g. eGFR, uACR, lipids, HbA_{1c}) 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/1.73m^2 eGFR, the patient is referred to a specialist for maximal intervention.

9.　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 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 not 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 for this group of patients.

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.

10. Characteristics of the evidence base

Table 4   Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Prognostic evidence (longitudinal accuracy)	Two studies of prognostic models One development and temporal validation study (Peters 2019) One external validation study (Peters 2020)	☐ k=2 n=3338	High risk of bias (evidence assessment group)
Change in patient management	Applicants conducted their own study that showed clinicians' intention regarding patient management but did not report evidence of actual change in management.	☐ k=1 n=178	High risk of bias (evidence assessment group)
Health outcomes	Seven trials were reported comparing different interventions including SGLT2, statins and blood-pressure-lowering regimens; however, given the lack of evidence for longitudinal accuracy and change in patient management, a full assessment of health outcomes should not be completed until these can be linked to PromarkerD.	☐ k=7 n=105266	The evidence assessment group did not assess risk of bias for these studies given the lack of evidence for the accuracy of PromarkerD and the lack of evidence for change in patient management.

Notes
k = number of studies, n = number of patients.

11. Comparative safety

The applicant has indicated in the ADAR that safety is not applicable, therefore there are no results to report.

The Commentary considered there to be very real harms to patients from false positive results. Being misdiagnosed as being at high risk of a life-threatening condition is psychologically and physically harmful to patients and is a waste of resources. The Commentary noted that a clinician was consulted about the poor PPV outcomes reported for PromarkerD and the subsequent high

proportion of false positive results. The clinician confirmed that there are harms related to the impact of false positive results that should be taken into account including unnecessary blood tests and venepuncture discomfort, patient anxiety (which can be considerable) and the cost of unnecessary tests and appointments on a finite health budget. The Commentary noted that the clinician suggested that, in some cases, more intrusive scans are likely to be done; particularly if contrast or radiolabelled agents are given, this can also (rarely) cause harm.

There are also harms associated with false negative results causing delays in management. A negative test is likely to falsely reassure the clinician and the patient and potentially delay treatment.

The Commentary considered that there is little evidence available regarding safety of PromarkerD. It was unclear whether PromarkerD is safer, of similar safety or less safe than clinical management without it.

12. Comparative effectiveness

Test accuracy
The applicant reported results for test accuracy. The Commentary noted that the ADAR did not address other parts of the MSAC Guidelines that are relevant to this review, specifically section 'TG 15.2 Testing to determine prognosis' and 'TG 15.5 Multifactorial algorithms'. The Commentary re-tabled the evidence related to the prognostic model and algorithm as follows:

Table 5: Summary of prognostic accuracy data

Measure	Specific measure used	Peters 2019 (Temporal validation cohort)	Peters 2020 (External validation cohort)
Number of participants	-	362	2976
Discrimination	c-statistic	NR	NR
	AUC	0.83 (0.77–0.88)	0.81 (0.80–0.83)
Calibration[6]	Calibration plots	Moderate calibration	Poor calibration
	Hosmer–Lemeshow	5.6, p=0.78	46.9 (p<0.001)
Diagnostic accuracy[7]	Sensitivity	86.1%	73.2%
	Specificity	78.2%	76.8%
	PPV	30.4%	58.8%
	NPV	98.1 %	86.4%
Reclassification	Net reclassification index (NRI)	NR	NR
	Integrated discrimination index (IDI)	NR	NR

Abbreviations
AUC = area under the curve, IDI = integrated discrimination index, NPV = negative predictive value, NR = not reported, NRI = net reclassification index, PPV = positive predictive value.

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[6] *The accuracy of risk estimates relating to the agreement between the estimated and observed number of events*

[7] *At the optimal cut-off defined by maximum Youden Index*

Additional information relating to TG 15.2 was provided in the pre-ESC response. However, on TG 15.2 the applicant stated that PASC had accepted that a "black box" algorithm was acceptable, which is supported in the MSAC guidelines (2019, pp. 34-35). The applicant stated that given that PromarkerD is a "black box" algorithm, it would not be necessary to provide the weight assigned to each of the variables in the algorithm.

Applicability

The external validation of a prediction model is essential to ensure the model can be used outside the context of its development; that is, the model is generalisable to the population it is intended to be used in.

The Commentary noted that the model was developed in a cohort from the Fremantle Diabetes Study and then a temporal validation study (Peters 2019) was conducted using a second cohort from the same study who were recruited at a later date. Best practice is to apply the predictive model to a population that is different from that which it was developed in. Temporal validation can overestimate results because the model was developed (calibrated) to apply to that population specifically. In the pre-ESC response, the applicants clarified that the temporal validation model did not include data from the same patients as the development model as these were separate patients from the same cohort and shown to be not clinically related.

The applicants did apply the model to an external validation model (Peters 2020); however, they used the CANagliflozin cardioVascular Assessment Study (CANVAS) study in which the patients had experienced previous cardiac events or were at high risk for future events. The Commentary considered that the external validation study would only be applicable to a subgroup of patients, not to the majority of low-risk patients in Australia. The diagnostic performance of PromarkerD was poorer in the external validation model.

The Commentary considered that the applicants should conduct an external validity study and apply their predictive model to a sufficiently large cohort of Australian patients who are representative of the population to determine whether the model is generalisable to patients outside of the Fremantle group.

However, in the pre-ESC response the applicants clarified that although the CANVAS cohort were defined as having prior cardiac events, or future risk of CVD, the cardiovascular risk profile of patients from the temporal validation study and CANVAS were similar.

Key limitations and missing data

The Commentary considered that there were several aspects of the evidence base regarding PromarkerD that were either insufficiently reported or missing, and identified the following:

- There is insufficient information provided about the main features of PromarkerD to understand what effect the individual input variables have on the output of the prediction models.
- It is not possible to determine the incremental benefit of the PromarkerD biomarkers in addition to the clinical factors alone (eGFR, uACR) because the evidence for the clinical factors as prognostic markers has not been reported.
- There is no discussion about the implications of a poor PPV and the consequences this will have for patients and providers if PromarkerD were to be implemented.
- It is unclear whether or how comorbidities have been taken into account in the PromarkerD algorithm. Treatment decisions for diabetes management are multifactorial and not based on test outcomes alone. The ADAR does not discuss how PromarkerD will interact with, for example, patients with a family history of diabetes or renal disease, previous or high risk of cardiovascular disease.
- There is no information about the practicalities or funding arrangements for pathologists.

- There is no information about the algorithm used to generate the results.
- The applicant has not undertaken quality assessment of the 2 prognostic modelling studies. The Commentary conducted these assessments and found both studies to be at high risk of bias using the Prediction model Risk Of Bias Assessment Tool (PROBAST) tool.

Relevant discussion about change in management and change in health outcomes are predicated on the prognostic value of PromarkerD being sufficient. The Commentary considered that neither of these prior requirements have been proven based on the evidence reported in the ADAR.

In the pre-ESC response, the applicant addressed these points as follows:

- For information on the incremental benefit of biomarkers to each clinical model for predicting risk of renal outcomes the applicant referred to Appendix E of the ADAR (which compared sensitivities and specificities of PromarkerD against KDIGO risk categories) for more information.
- The applicant acknowledged the low PPV of PromarkerD and argued that the strength of the test is the ability to rule out patients (high NPV) at low-risk, yet still capture the majority of those at highest risk. The applicant also observed that there are several MBS funded tests with a low PPV due to the incidence of the outcome.
- Regarding comorbidities, the applicant stated that the test was developed for people with T2DM, including people with both microvascular and macrovascular comorbidities.
- The applicant did not provide further detail on the practicalities or funding arrangements for pathologists
- Regarding the algorithm, the applicant reiterated that a 'black box' approach had been accepted by PASC but referred to further information in its Pre-ESC response Appendix.
- The applicant disagreed with the Commentary's assessment of a high risk of bias associated with the two prognostic modelling studies and provided its own assessment in a detailed table in the pre-ESC response.

Change in management

The applicant discussed a US-based survey of clinicians (Fusfeld 2022), then conducted their own similar, Australian-based study. From the results of the Fusfeld study that were reported in the ADAR, PromarkerD was not considered to be the most important factor in making a decision for prescribing, increasing or replacing therapy.

Table 6: Key features of the included change in management evidence comparing PromarkerD with standard care

Trial/study	N	Study design Risk of bias	Population	Intervention	Comparator	Key outcome(s)	Result used in economic model
Fusfeld et al. 2022	400 respondents 42 hypothetical patient profiles	Conjoint analysis Low risk of bias	Endocrinologists and primary care doctors	PromarkerD	Standard care	Treatment decisions if PromarkerD was available	N/A

The Australian survey, similar to the Fusfeld study, conducted by the applicant represents changes in clinician *intention* based on the hypothesised use of the PromarkerD tool. The Commentary therefore considered that the survey results did not represent evidence of any actual change in management.

The Commentary noted several methodological issues with the Australian survey, and therefore noted that the results may not be reliable. Clinicians answering the survey were provided with some data about PromarkerD but omitted from the description any discussion about the poor PPV. Clinicians answering the survey were not aware of how many false positives PromarkerD would produce. The Commentary also considered that there were a number of leading questions in the survey; consequently, there are some conclusions that have been drawn about clinicians' attitudes and opinions about PromarkerD that do not seem reasonable. In its pre-ESC response the applicant disputed this, stating that multiple choice questions were used in the survey, as leaving blank fields will likely lead to a low volume of answers, or answers that cannot be standardised in a way to draw overall claims but that options for a respondent to include their own response or to elect a negative response were available.

One important aspect of the survey was the reporting of results when PromarkerD was not used; that is, only the KDIGO risk groups were available. In the low-risk (green) patients, clinicians reported that they would treat 57% of patients with glycaemia-lowering, lipid-lowering or antihypertensive medications, while in the moderate-risk (yellow) patients, clinicians reported that they would treat 84% of patients. If the majority of patients in the yellow risk group are (hypothetically) already receiving treatment to prevent CKD progression from clinicians, then it is unclear why they would be suitable candidates for PromarkerD.

The Commentary noted that in order to verify claims about PromarkerD's ability to change management, the applicants should conduct a study where PromarkerD is used in a cohort of patients and controls, so that outcomes can be followed up over time.

Health outcomes

The applicant reported that 7 trials related to SGLT2 inhibitors, statins and blood-pressure-lowering interventions met the inclusion criteria; however the Commentary noted that there is no information about what those inclusion criteria were and was unable to assess whether the evidence reported is reasonable.

Given the lack of evidence for change in management, the trials that reported health outcomes were not assessed by the Commentary as these could not be linked to the effect of PromarkerD.

In its pre-ESC response, the applicant referred to Appendix A of the ADAR for information on inclusion criteria.

Limitations of the evidence

The Commentary noted several methodological issues regarding how the systematic review was reported in this ADAR; specifically, the search was inadequate to be confident that all relevant studies were identified, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is inaccurate.

The Commentary noted that while the applicants have provided what appear to be GRADE Summary of Findings tables these are not complete or accurate. The Commentary noted that none of the included studies have been assessed for quality, there is no supporting information provided and the applicants have graded all studies as having a low risk of bias, which does not match the assessment group's independent quality assessments. The Commentary's quality assessments on the 2 studies thought to provide the most relevant information for this ADAR (Peters 2019 and Peters 2020) were both found to be at high risk of bias.

The Commentary noted that there are several places in the ADAR where data is missing, especially for the test accuracy section, outcomes for predictive models and safety data.

The clinical claim made by the applicant is that:

- the use of PromarkerD results in superior effectiveness compared with standard of care (no predictive test)
- the use of PromarkerD results in inferior safety compared with standard of care (no predictive tests) solely as a result of downstream changes in management and these safety implications are not directly related to the use of the PromarkerD test itself.

The Commentary concluded that the body of evidence presented is insufficient to support any clinical claim about the use of PromarkerD in T2DM patients who are at low-risk of developing CKD.

13. Economic evaluation

A cost-utility analysis is presented in the ADAR to quantify the benefits of using PromarkerD to predict DKD incidence among T2DM patients. The selected approach is appropriate given the claim of clinical superiority. A Markov, Monte-Carlo individual patient simulation model was developed in Excel, which aims to capture the costs and clinical benefits of earlier detection of patients at risk of DKD and potentially initiate or intensify treatment to decrease the rate of progression to more severe forms of the disease. The model includes Pre DKD (<DKD Stage 3a), along with pre- and post-kidney-transplant DKD Stages 3a, 3b, 4, 5 and death. Each state was assigned a utility value derived from the literature. The economic analysis includes a base 30-year projection and 1 year cycle length. A summary of the model elements is provided in Table 7.

Table 7 Element of the economic model included in the evaluation

Component	Description
Perspective	Australian health system
Population	Patients with a diagnosis of T2DM; eGFR ≥60 ml/min/1.73m^2; and uACR ≤30 mg/mmol
Prior testing	Diagnostic tests for diabetes: • serum creatinine to determine eGFR • urine albumin and urine creatinine to determine uACR.
Comparator	The Submission refers to standard of care, as no current investigative test to predict onset of DKD is available. eGFR and uACR tests are used to derive Kidney Disease Improving Global Outcomes (KDIGO) risk scores (Levin et al 2013). PromarkerD prognostic accuracy should be compared to these risk profiles.
Type(s) of analysis	Cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years
Time horizon	30 years
Computational method	Markov, Monte-Carlo individual patient simulation model
Generation of the base case	The steps undertaken include: • simulating baseline characteristics of individual patients • assigning patients, the PromarkerD test or no test • assigning patients' treatment • estimating risk of developing DKD using the Nelson et al (2019) risk equation • modelling progression of DKD to kidney events and mortality • assigning costs to each health state.
Health states	Pre DKD (defined as DKD Stage 1 and DKD Stage 2); DKD Stage 3a; DKD Stage 3b; DKD Stage 4; DKD Stage 5/ESRD/dialysis; kidney transplant; post-kidney-transplant DKD Stage 3a; post-kidney-transplant DKD Stage 3b; post-kidney-transplant DKD Stage 4; post-kidney-transplant DKD Stage 5/d ESRD/dialysis; death
Cycle length	1 year
Transition probabilities	The risk equation from Nelson et al (2019) calculates the transition probability for pre-DKD (CKD Stage 1 and CKD Stage 2) to DKD Stage 3a. The transition probabilities for later stages include the use of the Cid Ruzafa et al (2015) study for Stages 3a-5, wait times for transplant from the National Clinical Taskforce on Organ and Tissue Donation (2008) and transition to death from studies such as Lim et al (2017).
Discount rate	5% for both costs and outcomes
Software	Excel

Abbreviations: DKD = diabetic kidney disease, eGFR = estimated glomerular filtration rate, KDIGO = Kidney Disease Improving Global Outcomes, QALY = quality-adjusted life years, T2DM = type 2 diabetes mellitus, uACR = urine albumin creatinine ratio.
Source: Submission, Table 34 (p. 59) and compiled for the commentary.

Incremental costs and effectiveness

The ICER over 30 years was estimated to be $3,615 per quality-adjusted life year (QALY) gained and $4,337 per life year gained for one run of the base case analysis (see Table 8).

Table 8 Results of the economic analysis

Step	PromarkerD	Standard care	Increment	ICER
Step 1 – Comparative diagnostic accuracy, as applied to the prevalence in the eligible Australian population Time horizon: time to reach a diagnosis				
Costs	Not included	Not included	Not included	Not included
Total correct diagnoses	Not included	Not included	Not included	Not included
Step 2 – Incorporation of effectiveness of treatment (e.g. survival benefit) translated to the Australian population and/or setting, and extrapolated to the appropriate time horizon				
Costs Life years gained	███████████████████████████████████████			$4,337
Step 3 – Outcomes transformed into a relevant health outcome (e.g. QALYs)				
Costs QALYs	███████████████████████████████████████			$3,615

The Commentary noted some uncertainties and evidence gaps in the economic model. The model uses the equation of Nelson to derive the transition probability of patient progression from pre-DKD to DKD and this equation is formulated based on US military veterans' cohort data, which may not be generalisable to the Australian population. This results in, among other things, an assumption in the model that 2.4% of the population is African American. No validation of the equation using Australian data was undertaken or comparison with PromarkerD and KDIGO prognostic performance presented. The modelling does not explicitly consider the incremental prognostic accuracy of PromarkerD over current standard care (KDIGO assessment), and no allowance was included for costs and utility impacts on false positive patients who would not benefit from increased medication regimes. False negative prognosis could also falsely reassure the clinician and the patient and potentially delay treatment leading to reduced health outcomes. The Commentary noted that the diagnostic effectiveness of PromarkerD should be compared to the current diagnostic effectiveness of KDIGO assessment and resulting clinical management in the economic model. The modelled prognostic accuracy of PromarkerD compared to KDIGO needs to be described and validated using Australian data. This analysis would provide background as to whether false positive and false negative costs are being captured in the modelling framework. However, in the pre-ESC response the applicant stated that the model does not explicitly consider the incremental prognostic accuracy because PromarkerD and DKD are not directly comparable - PromarkerD assigns a level of risk of developing DKD for a patient, whereas the KDIGO assessment only measures eGFR and uACR and only points at high risk once kidney damage is done.

The Commentary considered that this validation also needs to consider, among other things, the implications of the demographic assumption in the model that 2.4% of the population is African-American, especially given that the sensitivity analysis (see Table 9) finds that the cost per QALY more than triples with a 20% decrease in the assumed base case population share which is African-American.

The calculated ICERs were sensitive to assumptions such as age, GFR, baseline PromarkerD risk, along with CKD Stage 4 dialysis and lower CKD Stage 1–2 assigned utilities. The ICER direction of some of the sensitivity analyses were not explained in the ADAR. For example, changes in the time horizon (20 and 40 years) both increased cost-effectiveness. These results were presented in the ADAR and outlined in the following table.

Table 9   Submission sensitivity analyses

Sensitivity analysis parameter	Cost/QALY	
Base	**$3,615**	
Sensitivity	**Upper +20%**	**Lower- 20%**
Age (years)		
Duration of diabetes (years)		
Male (%)		
Ever smoker (%)		
Black or African American (%)		
HbA$_{1c}$, %		
BMI, kg/m^2		
SBP, mmHg		
DBP, mmHg		
HDL cholesterol, mmol/l		
ACR, mg/g		
GFR (MDRD), mL/min/1.73m^2		
PromarkerD risk category		
CKD Stage 1–2 utility		
CKD Stage 3a utility		
CKD Stage 3b utility		
CKD Stage 4 utility		
Adjusted dialysis utility		
Kidney transplant utility		
Post-transplant CKD Stage 1–2 utility		
Post-transplant CKD Stage 3a utility		
Post-transplant CKD Stage 3b utility		
Post-transplant CKD Stage 4 utility		
Discount rate		
Time horizon 40/20 years		
HbA$_{1c}$ effect		
BMI effect		
eGFR effect		
uACR effect		
SBP effect		
DBP effect		
HDL effect		
Scenario analysis – cost of MBS item 66500 added to PromarkerD test cost	$4,757	

Abbreviations
ACR = albumin creatinine ratio; BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; eGFR = estimated Glomerular Filtration Rate; HbA1c = glycosylated haemoglobin; HDL = high-density lipoprotein; GFR (MDRD) = glomerular filtration rate (modification of diet in renal disease); ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year; SBP = systolic blood pressure; uACR = urinary albumin creatinine ratio.
Source
Submission, Table 61, p. 106.

A number of additional sensitivity analyses were conducted as part of the commentary. The inclusion of a hypertension threshold of 140/90 aligned with the Nelson study had an impact on the estimated ICER (███████) (the current threshold for hypertension is actually 130/80). It was not clear how SGLT2 eligibility (HbA1c>7%) was included in the model. Omission of SGLT2 inhibitors effects increased the ICER (██████).

Table 10 Commentary sensitivity analyses

Hypertension definition (140/90)	
CKD Stage 4 utility (0.55)	
CKD Stage 5 utility (0.54)	
Haemodialysis utility (0.44)	
Post-transplant CKD Stage 3a utility (0.75)	
Post-transplant CKD Stage 5 utility (0.67)	
No SGLT2 inhibitors effect	
No ACE inhibitors effect	
No ARBs effect	
No statins effect	
No IHD impact on Nelson equation	
No CHF on Nelson equation	

Abreviations
ACE = angiotensin-converting enzyme, ARBs = angiotensin II receptor blockers, CHF = Congestive heart failure, CKD = chronic kidney disease, ICER = incremental cost-effectiveness ratio, IHD = ischaemic heart disease, QALY = quality-adjusted life year.
Source
Calculated as part of the commentary.

Key uncertainties and drivers of the model are summarised in Table 11.

Table 11 Key uncertainties and drivers of the model

Description	Method/value	Impact as assessed by Commentary
No explicit allowance was included for costs and utility impacts on false positive patients.	The positive predictive value of PromarkerD is 54–68% (incident CKD using Peters 2020 placebo arm in CANVAS or lower using FDS2 data), so a substantial proportion of patients are false positive. The safety description in the Submission indicates 'The risk of a false positive will be stricter management of diabetes, which will have minimal risks for the patient, and will likely benefit their overall diabetes health'. Clinical feedback during the evaluation suggested this may not be the case. Prognostic inaccuracy of this nature may lead to unnecessary blood tests and venepuncture discomfort, patient anxiety (which can be considerable) and cost of unnecessary tests and appointments on finite health budget. The clinician suggested that, in some cases, more intrusive scans are likely to be done; if contrast or radiolabelled agents are given, this can also (rarely) cause harm. In addition, if the patient is started on medication, there are the costs of the medication, along with the potential harm of exposing the patient to side effects of the medication There is no discussion about possible unnecessary costs for patients who are false positive or allowance in the model for them to be quantified.	Possibly high, favours intervention. The disutility associated with adverse events and additional costs of unnecessary medicines are not captured in the model. Given the PPV of the intervention, these costs could be significant.
The incremental prognostic accuracy of	The model does not capture incremental prognostic accuracy of PromarkerD over the relevant comparator. The Submission indicates there is no direct comparator as current standard of care diagnoses	Possibly high, favours intervention. The improved accuracy of

Description	Method/value	Impact as assessed by Commentary
PromarkerD over the relevant comparator is not included in the model	DKD after clinical symptoms appear rather than predicting risk of DKD. Tests are available that quantify risk factors, along with a KDIGO risk assessment framework. KDIGO should be used as a comparator for the intervention.	PromarkerD over KDIGO risk needs to be described and included in the model.
All patients are assumed to be prescribed and adhere to appropriate medicines.	The model assumes a proportion of doctors would start or increase treatment based on PromarkerD risk outcomes. This proportion of patients are assumed to be prescribed and adhere to appropriate medicines. This may not be the case, and no allowance is included in the model for this possibility. Clinician feedback during the evaluation suggests only patients with borderline hypertension or cholesterol would be prescribed intensified treatment and gain clinical benefits. The model does not seem to account for this proportion.	Possibly high, favours intervention
The PromarkerD risk profile for Australia is uncertain.	The background PromarkerD risk category has the largest impact on the estimated ICER. The Fremantle study has been used to generate this profile, but it is difficult to determine applicability to the whole of Australia.	Uncertain. The background PromarkerD risk profile has the largest impact on calculated ICER (e.g. a lower profile increased the ICER ▮▮▮▮▮ per QALY gained).
Prognostic algorithms require validation.	There was limited description of how the PromarkerD algorithm was developed in the Submission, how its prognostic accuracy compares to KDIGO risk assessment, and the Nelson equation included in the economic model. These prognostic approaches and economic modelling results need to be validated using Australian data. Excel workbooks and Annex E included with the Submission include calculations, but they are not described in the main body of the report and referenced in the economic model.	Uncertain. Limited details about how the PromarkerD algorithm has been developed were provided. The model is driven by the transition from pre-DKD to DKD using the Nelson equation.
Specification of hypertension	The economic model uses a 130/80 threshold for hypertension which differs to that used in the Nelson study of 140/90 and forms the basis of the transition equation from pre-DKD to 3a stage DKD in the model. The non-alignment of thresholds (140/90 is high) in the economic model and Nelson equation creates uncertainty. A sensitivity analysis was included in the commentary with the 140/90 threshold definition.	Uncertain. The ICER increased from ▮▮▮▮▮ to more than ▮▮▮▮▮ with a change in definition of 130/80 to 140/90
All patients appear to be eligible for SGLT2 inhibitors, despite requiring HbA1c>7% for Australian PBS eligibility.	The initiation and increase in SGLT2 inhibitor medication because of PromarkerD risk appears to have a large impact on the ICER, as use of this medicine is estimated to reduce HbA1c, BMI, eGFR, SBP and uACR. The Australian PBS requires patients to have an HbA1c>7% for eligibility. It is unclear how this is factored into treatment allocation in the model, or treatment being stopped once HbA1c falls below 7%. Baseline HbA1c in the economic model is 6.90% taken from the VERIFY study.	High, favours intervention. The ICER increased from ▮▮▮▮▮ to ▮▮▮▮▮ with removal of SGLT2 inhibitors effects

Abbreviations
BMI = body mass index, CANVAS = CANagliflozin cardioVascular Assessment Study, CKD = chronic kidney disease, DKD = diabetic kidney disease, eGFR = estimated glomerular filtration rate, FDS2 = Fremantle Diabetes Study Phase II, HDL = high-density lipoprotein, ICER = incremental cost-effectiveness ratio, KDIGO = Kidney Disease Improving Global Outcomes, PBS = Pharmaceutical Benefits Scheme, PPV = positive predictive value, QALY = quality-adjusted life year, SBP = systolic blood pressure, SGLT2 = sodium-glucose cotransporter-2, uACR = Urinary albumin creatinine ratio, VERIFY = Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes.

Source
Compiled during evaluation.

14. Financial/budgetary impacts

The financial implications to the MBS resulting from the proposed listing of PromarkerD are summarised in Table 12. The Commentary noted that the epidemiological approach used is appropriate given that testing would not substitute for a comparator in the market and uptake is estimated as a proportion of T2DM prevalence in Australia, along with the estimated eGFR and uACR defined eligible sub-population.

The proposed MBS eligibility criteria for PromarkerD states that patients with T2DM are only considered eligible if they have both an eGFR of greater than or equal to 60 ml/min/1.73m^2 and uACR test result of less than or equal to 30 mg/mmol. Using this criterion, the ADAR estimated that 84.6% of Australian patients with T2DM met the criteria for PromarkerD. The projected number of eligible patients was 930,715 in 2022 and 674,174 in 2027. Patients re-test after 2 or 4 years, based on risk category. Service volumes and expenditure by financial year is preferred for Governmental implementation purposes. Population for the base calculation and MBS unit costs would not have increased substantially between 2022 and the 2022-23 financial year, so financial cost impact changes would be minor for the current financial year 2022/23.

Table12 Net financial implications of PromarkerD to the MBS

Parameter	2021-22	2022-23	2023-24	2024-25	2025-26	2026-27
Estimated use and cost of the proposed health technology						
Eligible population per year	930,715	896,003	866,941	817,647	751,998	674,174
PromarkerD uptake rate						
Total new patients electing treatment per year						
Patients re-testing						
Total PromarkerD services						
MBS cost of PromarkerD (80% benefit)	**$4,653,576**	**$8,960,034**	**$13,956,656**	**$18,186,970**	**$24,433,498**	**$29,294,321**
MBS cost of PromarkerD (revised; 85% benefit)	$4,944,425	$9,520,036	$14,828,947	$19,323,656	$25,960,591	$31,125,216
Change in use and cost of other health technologies						
Increase in MBS Item 104 (professional attendance by a specialist)						
Increased cost to MBS from MBS 104						
Increased cost to MBS from MBS 104 (revised; 85% benefit)						
Net financial impact to the MBS*	**$4,821,909**	**$9,284,143**	**$14,427,050**	**$18,778,500**	**$25,113,542**	**$30,025,922**
Net financial impact to the MBS (revised; 85%)	$5,089,841	$9,800,022	$15,235,302	$19,834,656	$26,548,056	$31,757,219

Abbreviations

MBS = Medical Benefits Scheme.

Source

Compiled during evaluation from Submission Table 71, p. 119.

*Figures in this row assumed that the proposed MBS item for Promarker D is reimbursed at a 80% benefit rate and item 104 for specialist consultations is reimbursed at a 100% benefit rate (but under the pre-indexation rate of $90.35)

**AG revised figures, assuming that both the proposed MBS item for Promarker D and item 104 for specialist consultations are reimbursed at a 85% benefit rate

It was estimated that there would be ▮▮▮▮▮▮▮ PromarkerD services in 2022 and ▮▮▮▮▮▮ in 2027. The Commentary noted that the uptake of the test is highly uncertain. Clinician feedback reported in the Commentary was that the test would be widely used if it were shown to have high

prognostic accuracy, be simple to use (e.g. the risk score was estimated by the pathology service) and the test cost was similar to currently available tests.

The proposed fee for PromarkerD is $250.00. The overall financial impact of the first 6 years post listing was calculated and is shown in the table below. In 2022, the listing of PromarkerD will cost the MBS $4.8M, increasing to $30.0M in 2027 assuming 80% benefit for the test. Assuming 85% benefit for both PromarkerD and specialist services (MBS item 104, 85% benefit) generates a 2027 net MBS financial cost of $31.8 million. The listing of PromarkerD on the MBS was not calculated in the ADAR to impact other health budgets during the first six years of listing. In the short term (6 years), however, use of PromarkerD is expected to increase PBS costs. These costs included SGLT2 inhibitors, statins, ARBS and ACE inhibitors. The Commentary noted that the omission of these costs understates the budget impact of PromarkerD uptake on other health budgets. In its pre-ESC response, the applicant acknowledged that the listing of PromarkerD will increase the usage of certain PBS items in the first six years of listing, due to early diagnosis of DKD risk, generating a minor cost (<$10M) to the PBS in each of the first six years of listing, as a result of introducing new treatment to T2DM patients. However, the applicant contended that improvements in DKD related outcomes because of early diagnosis will generate even greater savings for the PBS beyond the first six years of listing.

The Commentary noted that the prognostic accuracy of developing kidney disease using PromarkerD compared to low- and moderate-risk CKD classifications was not presented in the main body of the ADAR. Establishing that PromarkerD has high predictive accuracy in the KDIGO green risk group is particularly important as low-risk patients account for 71% of the T2DM population and moderate-/high-risk around 29% of the populations. If only moderate-risk patients were eligible to use the test, the 2027 financial cost would be $12 million, rather than $31.8 million for both populations.

15.   Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- There are significant concerns about the clinical utility of this test for patients who fall into the medium-risk category (yellow category) according to KDIGO guidelines (normal eGFR but evidence of microalbuminuria defined as uACR >2.5 mg/mmol in males and 3.5 mg/mmol in females). These patients should already be receiving treatment to prevent DKD progression. Therefore the clinical utility of PromarkerD in this population is uncertain.

- The item descriptor should be amended to restrict PromarkerD use to patients who are currently in the low-risk category (green category) only. This means the eligible population should be restricted to patients with uACR <2.5 mg/mmol if male and 3.5 mg/mmol if female, and eGFR of 60 ml/min/1.73m^2 or greater.

- Retesting for patients identified by PromarkerD as being of medium and high risk for DKD should not be necessary.

- The prognostic evidence for PromarkerD is subject to a high risk of bias. Additionally, the change in management that is claimed would arise from use of this test is only based on a survey of clinicians' intent, not real-world evidence; the evidence regarding change in management is poor and has a high risk of bias.

- The main safety issues which are regarding false positive and false negative results have not been sufficiently addressed by the ADAR. The positive predictive value for this test appears to be low.

- The applicant has not provided sufficient information that is important for MSAC decision-making, including on the effect of individual input variables on the output of prediction models, the incremental benefit of the biomarkers, how comorbidities are accounted for in the PromarkerD algorithm and information about the algorithm used to generate results.

Economic issues:

- Test outcomes have not been accounted for in the economic model. Including test outcomes would allow comparisons with the current clinical approach. Test outcomes should be included as a decision tree component before the state transition model.

- To improve the stability of results, the number of simulated individuals needs to be increased. Stability should then be justified by demonstrating that the variance from multiple runs is much smaller than expected differences between strategies.

- The sensitivity of the ICER to the mean PromarkerD risk category score is high. However it may be more appropriate to estimate the impact to the ICER of changes in the PromarkerD risk category score by changes to the risk categories of proportions of the test population rather than basing the sensitivity analysis on changes in the overall mean risk category score of the entire population.

Financial issues:

- The all-encompassing fee is high compared to other MBS items in Group P2 – Chemical. A breakdown of component costs to justify the proposed fee was not provided.

- The potential uptake of the test is highly uncertain. Additionally, the impact on PBS costs in the first 6 years of listing was not included in the financial analysis, and should be included as the amount is not insubstantial (approximately $10 million annually).

ESC discussion

ESC noted that this application from Proteomics International is requesting Medicare Benefits Schedule (MBS) listing of PromarkerD, a prognostic test predicting the risk of patients with type 2 diabetes mellitus (T2DM) developing diabetic kidney disease (DKD) over the next 4 years. This test is proposed for people who have T2DM, a urine albumin:creatinine ratio (uACR) of 30 mg/mmol or less, and an estimated glomerular filtration rate (eGFR) of at least 60 ml/min/1.73m^2. ESC noted that PromarkerD measures three protein biomarkers in human plasma (ApoA4, CD5L and IBP3), which are entered into a proprietary software along with age, high-density lipoprotein (HDL) cholesterol level and eGFR. The software then characterises a patient as having a low, moderate or high risk of developing DKD within the next 4 years.

ESC advised that this would be an outpatient service.

ESC noted the current best practice guidelines from Diabetes Australia recommend that people with type 2 diabetes should be screened annually for DKD using eGFR and uACR. ESC noted that uACR above 2.5–3.0 mg/mmol is indicative of microalbuminuria. Patients who initially demonstrate microalbuminuria should have their uACR tests repeated several times over at least three months to confirm that the elevated uACR is not transient, prior to assigning the patient's risk of DKD. ESC noted that an uACR of 25–30 mg/mmol is indicative of macroalbuminuria. Patients with type 2 diabetes and DKD with either hypertension and/or albuminuria should receive either an ACE inhibitor or an angiotensin receptor blocker (ARB) to delay progression of DKD and treat hypertension if present. The current clinical guidelines recommend that treatment should be started early to prevent progression.

ESC noted the current algorithm for the initial detection of chronic kidney disease, which was based on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines. ESC noted that, according to the guidelines, one of the proposed populations for this application would fall into the "medium-risk" category requiring treatment and intensive management (the yellow category). Therefore, ESC questioned the clinical utility of this application for the medium-risk category of patients.

ESC noted the proposed changes to the item descriptor suggested by the policy paper, which relate to when PromarkerD testing and retesting should be done. ESC considered that as the test predicts a patient's risk of developing DKD, it should be restricted to use in patients who are currently in the low-risk category i.e. those with eGFR greater than or equal to 60mL/min/1.73m^2 and/or uACR <2.5 mg/mmol if male and 3.5 mg/mmol if female. Therefore, ESC questioned whether the uACR limit of 30 mg/mmol should be accordingly amended to reflect these new proposed thresholds. Regarding frequency of re-testing, ESC considered that, for patients deemed to be at low risk of developing DKD as determined by their PromarkerD result, a minimum of 4 years before retesting is reasonable and evidence-based. ESC considered that retesting patients deemed to be at medium to high risk of DKD as determined by their PromarkerD result, may not be necessary. ESC advised that if the re-testing population is limited to avoid frequent retesting, then the economic model would need to be amended.

ESC noted concerns that there is a risk of leakage due to the non-specific nature of the item descriptor which may result in it being utilised for any service that claims to quantify the risk of diabetic kidney disease. ESC considered that because this test is so specific, with a proprietary and "black box" software algorithm, the item descriptor should explicitly state that the ApoA4, CD5L, and IBP3 biomarkers must be quantified and that the proprietary PromarkerD algorithm must be used to quantify the risk of developing DKD to avoid leakage to other tests.

ESC also noted that the ADAR did not adequately address implementation concerns around the capability of pathologists to access the PromarkerD test kits, and the need for extra consultations and blood collection for repeat testing (and the costs associated with these).

ESC noted that some patients consider the self-management regimes for T2DM to be burdensome and difficult to manage at times, which can lead to distress and feelings of regret when they develop DKD. However, the feedback from public consultation expressed uncertainty about whether this test would change clinical management, as there are already tests that predict the risk of developing DKD. In particular ESC noted the feedback from the Endocrine Society of Australia that the test may have limited additional value to clinicians. Feedback also noted that the application did not provide analysis comparing the performance of this test against other proteomic-derived biomarkers, and questioned why PromarkerD biomarkers should be funded over other biomarkers being studied and developed. Other feedback noted that the software and associated proprietary algorithm required further independent validation, as several authors declared conflicts of interest as stakeholders of the patent relating to the biomarkers used in PromarkerD. ESC noted that there were no consumer responses for this application.

ESC noted that the clinical trial data were based on linked evidence. The prognostic evidence on longitudinal accuracy centred on two studies of prognostic models, one of which was a development and temporal validation study and the other an external validation study. ESC agreed with the Commentary that both these studies were subject to a high risk of bias. ESC also agreed that the evidence base for the claimed change in patient management which was based on the applicant's survey of clinicians has a high risk of bias. ESC noted that the linked evidence for health outcomes comprised seven studies reporting the outcomes of different interventions including SGLT2, statins and blood-pressure-lowering regimens. ESC considered the effect on health outcomes reported in these studies to be well-established in literature but noted that this evidence was not assessed in the Commentary for risk of bias because of the lack of evidence that a change in patient management could be linked to the use of PromarkerD.

ESC acknowledged that there were no safety issues arising from drawing blood for the test but noted that the main issues identified by the Commentary were around the impact of false positive and false negative results. Some patients may commence treatment or have their treatment increased based on a falsely positive risk score, putting them at risk of subsequent harms from the treatment. Conversely, some patients and clinicians may "feel relaxed" about a falsely negative score, possibly leading to complacency in future management. ESC considered that these issues were not adequately addressed by the applicant. ESC noted the conclusion from the ADAR was that "the use of PromarkerD results in inferior safety compared with standard of care (no predictive tests) solely as a result of downstream changes in management and these safety implications are not directly related to the use of the PromarkerD test itself", which was not supported by the Commentary given the safety issues associated with the impact of false positive and false negative results.

Regarding comparative effectiveness, ESC noted that the evidence for test accuracy relied on two studies (Peters at al. 2019[8] and 2020[9]). ESC considered that although the methodology used to determine test accuracy seemed appropriate, ESC agreed with the Commentary that issues remain around the external validity study of the Peters et al 2020. ESC noted that the

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[8] Peters KE, Davis WA, Ito J, et al. (2019). Validation of a protein biomarker test for predicting renal decline in type 2 diabetes: The Fremantle Diabetes Study Phase II. *Journal of Diabetes and its Complications*, 33, 107406.

[9] Peters KE, Xu J, Bringans SD, et al. (2020). PromarkerD Predicts Renal Function Decline in Type 2 Diabetes in the Canagliflozin Cardiovascular Assessment Study (CANVAS). *Journal of clinical medicine*, 9, 3212.

Commentary calculated the following additional measures based on data extracted from this study:

- C-statistic (area under the curve, concordance index) for test discrimination, which was found to be adequate.
- calibration as a measure of accuracy of predicted risk probabilities, which showed moderate to poor calibration.
- positive and negative predictive values (PPVs and NPVs) – the PPV appeared to be low. In response to this observation the applicant stated that a low PPV is common with tests but that this test may still be useful due to its high NPV.
- ability to predict a decline in eGFR over 4 years, which was shown to be poor.

On the evidence for a change in management, ESC noted the claim from the applicant that the test would affect clinician intent to treat, as currently half of patients do not get treated in accordance with the guidelines. However, ESC noted that this claim was based solely on a survey of intentions conducted by the applicant rather than from observed changes in management from use of PromarkerD. The pre-ESC response stated that real-world evidence for change in management was not necessary. However, ESC agreed with the Commentary that the ADAR does not adequately demonstrate the benefit of the PromarkerD test. ESC also noted that there are many other factors that may lead to a patient starting on treatment like an ACE-I or ARB, irrespective of the urine ACR. These factors include the patient's blood pressure and other cardiovascular risk factors.

ESC noted that the Commentary identified several other key limitations and missing data including insufficient information about

- the effect of individual input variables on the output of prediction models,
- the incremental benefit of the biomarkers,
- how comorbidities are accounted for in the PromarkerD algorithm and
- information about the algorithm used to generate results.

ESC noted that in its pre-ESC response, the applicant had supplied further information on these matters and in particular on the incremental value for the test over and above the KDIGO guidelines while also noting that the algorithm for the test is a "black box". ESC noted that "black box" algorithms are acceptable according to MSAC guidelines. However ESC considered that the pre-ESC response had not sufficiently addressed all the issues as identified by the Commentary above.

ESC noted that the economic evaluation was a cost-utility analysis, with outcomes of life years gained and quality-adjusted life years (QALYs), and a time horizon of 30 years. An individual Monte Carlo simulation state transition model was used, which aggregates individual costs and outcomes (in this case, from 10,000 patients) and averages these to determine the base case result. ESC noted that the economic model did not include test outcomes, the accuracy of tests or the frequency of retesting. ESC considered that including test outcomes as a decision tree component before the state transition model as recommended by guidelines from the International Society for Pharmacoeconomics and Outcomes Research–Society for Medical Decision Making (ISPOR-SMDM) on good modelling practices would improve the model, as it would allow comparisons with the current clinical approach based on KDIGO guidelines. Test outcomes could be incorporated with the prognostic accuracy of developing DKD using PromarkerD compared to low- and moderate-risk classifications in the KDIGO guidelines. ESC considered that this would be appropriate for this application, given the high rate of false positive results. ESC also noted that in the current model, non-DKD clinical events only figure into the risk of DKD, not the costs or outcomes.

ESC noted other recommendations from the ISPOR-SMDM guidelines that, to generate stable results, a sufficient number of individuals needs to be simulated so that variance from multiple runs is much smaller than expected differences between strategies. This was not the case for this application. ESC noted that the models used in this application sometimes require millions of simulated individuals for stable results, but this analysis only used 10,000 individuals. ESC noted from data provided from 25 runs that instability in the incremental cost-effectiveness ratio (ICER) is mostly driven by instability in costs. ESC noted that the ICER over 30 years was estimated to be $3,615 per quality-adjusted life year (QALY),

ESC noted that the Commentary raised concerns about the applicability of the Nelson equation (used to inform transition probabilities) to the Australian population, as it was modelled off an American population with a different ethnic profile. ESC noted that the trial data population's mean for PromarkerD risk category scores (0= low, 1 = moderate, 2 = high) was used as an input in the simulation. The sensitivity analysis for PromarkerD risk then simply adjusted this mean of the categorical variable up and down by 20%. ESC noted that according to the sensitivity analysis, a change of 20% (upwards or downwards) changes the ICER substantially (in particular a 20% decrease in the mean score resulted in an ICER of ▮▮▮▮▮ while a 20% increase in the mean score resulted in an ICER of ▮▮▮▮▮). ESC questioned the appropriateness of this approach in accounting for changes in risk scores in the population and considered it would be more appropriate to estimate the impact of modelling a change in risk categories of set proportions of the population.

ESC noted from the clinician survey undertaken by the applicant that the use of PromarkerD is predicted to increase the use of sodium–glucose co-transporter-2 (SGLT2) inhibitors for glucose control. ESC noted that Pharmaceutical Benefits Scheme (PBS) eligibility for SGLT2 inhibitors depends on blood glucose levels being greater than 7.0%. Because of this, ESC considered that only patients with a high risk of developing DKD would be eligible for SGLT2 inhibitors through the PBS. ESC noted that if eligibility for PromarkerD is excluded for patients with blood glucose levels of less than 7%, the ICER increased from ▮▮▮▮▮ to ▮▮▮▮▮.

ESC considered that the model may overestimate prescription as well as compliance with treatment which would result in a bias towards a lower ICER. ESC noted that the frequency of re-testing also has an impact on the ICER and therefore if the frequency of retesting were to be revisited (in particular re-considering whether retesting of medium to high-risk patients is required) the model would need to be re-estimated.

ESC noted that the inclusion of impact for the KDIGO medium-risk (yellow) group (in increased treatment, assessment and referral) was based on the clinician survey. ESC noted that no scenario or stepped analysis was provided to show the impact of including this group in the economic model.

ESC noted that only a small range of utility values were covered in the sensitivity analyses in the ADAR with the utility weights based on the EQ-5D-3L instrument favoured, but also noted from the Commentary that sensitivity analyses using lower-range utility weights had only a minor impact on the ICER.

ESC noted that only one-way sensitivity analyses were presented in the ADAR, and considered that a multi-way sensitivity analysis may be more helpful.

ESC noted that as there are no tests similar to PromarkerD currently listed on the MBS, the proposed service would likely be listed in Group P2 – Chemical, given it involves a blood test for the quantification of biomarker concentrations. ESC therefore noted concerns about the all-encompassing fee of $250, which exceeds the schedule fees of other MBS items in Group P2 – Chemical (all less than $100). ESC noted that a breakdown of component costs was not provided

by the applicant; the ADAR stated that the fee was determined by costs of the developing technology, the ongoing supply of kits, and an "industry standard profit margin". The fee did not include the costs of associated tests for the PromarkerD risk score, which were assumed to be covered by MBS item 66500. However, ESC noted from the Commentary that adding the cost of these tests ($9.70, from 66500) had little impact on the ICER, even if they were repeated.

ESC noted the estimated net cost to the MBS of listing Promarker D is $4.8 million in year 1 increasing to $30.0 million in year 6. ESC noted that in the short term after listing, there is likely to be an increase in PBS use for low-risk patients (the green risk category) who are predicted to have an increased DKD risk and therefore will require medication to manage their risk. These costs were not included in the financial analysis. ESC noted that although the ADAR stated the test was "not expected to impact other health budgets during the first 6 years of listing", the pre-ESC response acknowledged that "the listing of PromarkerD will generate a minor cost (<$10 million) to the PBS in each of the first 6 years of listing, as a result of introducing new treatment to T2DM patients". ESC considered that these were not insubstantial costs when compared against the reported net costs to the MBS (from $4.8 million in year 1 to $30 million in year 6). In the long term (likely greater than 6 years), the use of PromarkerD was predicted to lead to lower PBS and MBS costs due to the prevention or delay of onset of DKD, primarily through the avoidance of procedures such as dialysis and kidney transplants along with associated medication costs.

ESC noted that the Commentary identified a wider range of potential uptake of the test (up to 30% by year 6) as opposed to 15% estimated by the applicant. This increases the estimated net cost to the MBS to $45 million in year 6.

17.   Applicant comments on MSAC's Public Summary Document

Proteomics International thanks the MSAC for its consideration but is disappointed in the decision to not support PromarkerD funding. Diabetic kidney disease is a significant and growing issue in Australia, and as noted in the commentary there was likely to be significant uptake of the test. With this decision there will remain no publicly funded option for predicting and therefore mitigating DKD risk for individuals with diabetes. Proteomics International also notes the costs per quality-of-life year (QALY) gained for introducing PromarkerD are well below accepted thresholds, with longer term (>6 years) benefits in PBS/MBS costs likely as earlier detection of DKD will reduce the need for dialysis and kidney transplant. Proteomics International is confident in the strength of its published clinical evidence demonstrating the performance of PromarkerD and looks forward to re-engaging with MSAC to address concerns and to clarify any misunderstandings which may have detracted from the Committee making a positive decision.

18.   Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website