



Australian Government

Department of Health

Application 1691

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

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated [Application Form Instructions](#) to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted. The separate [MSAC Guidelines](#) should be used to guide health technology assessment (HTA) content of the Application Form

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/A

Corporation name: Proteomics International Pty Ltd

ABN: 78 096 013 455

Business trading name: Proteomics International Pty Ltd

Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

2. (a) Are you a consultant acting on behalf on an applicant?

- Yes
 No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

Proteomics International Pty Ltd

3. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes
 No

(b) If yes, are you listed on the Register of Lobbyists?

Not applicable

(c) Have you engaged a consultant on your behalf?

Not applicable

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

PromarkerD – A predictive test for diabetic kidney disease risk in people with type 2 diabetes

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Type 2 diabetes mellitus (T2D) is the leading cause of chronic kidney disease (CKD), accounting for up to 50% of cases worldwide (Webster et al. 2017).

The kidneys are the body's filtration system, removing waste and extra water from the blood. They also produce hormones and help to control blood pressure. When the kidneys are damaged, they no longer function effectively causing waste to build up leading to a range of health problems.

Symptoms of diabetes such as high blood glucose and high blood pressure can damage the kidneys causing diabetic nephropathy or diabetic kidney disease (DKD). Around 40% of patients with T2D develop DKD which can eventually lead to end-stage renal disease (ESRD) (Hussain et al. 2021). Individuals with ESRD require haemodialysis and eventually kidney transplantation.

Early detection of DKD and the implementation of intervention measures is important in reducing further kidney damage and hence progression of the disease.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

PromarkerD is an in-vitro quantitative blood test designed to predict incident DKD or progression of DKD in patients with T2D.

The test measures three novel plasma protein biomarkers (ApoA4, CD5L and IBP3) combined with clinical factors (age, HDL-cholesterol, estimated glomerular filtration rate (eGFR)) to generate prognostic risk scores for DKD in patients with T2D. The concentrations of the biomarkers, along with the clinical factors, 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/1.73m²) within 4 years, or a decline in eGFR of ≥30% over 4 years.

Over 95% of patients with kidney damage or reduced kidney function are asymptomatic meaning early detection and treatment of DKD is essential to prevent further kidney injury. PromarkerD can predict the risk of DKD in patients with T2D before kidney damage occurs.

7. (a) Is this a request for MBS funding?

- Yes
 No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

- Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service/technology:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
- No

(g) If yes, please advise:

N/A

8. What is the type of medical service/technology?

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

N/A

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

Sodium-glucose cotransporter-2 (SGLT2) inhibitors which are recommended for treatment of patients with a diagnosed risk of DKD are currently listed on the PBS for patients with type 2 diabetes. Therefore, a co-dependant submission is not required.

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian marketplace which this application is relevant to?

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

13. Please identify any single and / or multi-use consumables delivered as part of the service?

- Single-use consumables: 3 x PromarkerD 96-well microplate **REDACTED**
- Multi-use consumables: None provided.

Required consumables not provided are:

- Polypropylene tubes
- Polypropylene plates
- Aluminium foil

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide details

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: Proteomics International Pty Ltd
Sponsor's name: Proteomics International Pty Ltd

- (b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

TGA application being prepared. See 15c.

Currently registered as a Class I Device for export purposes only.

- (c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

- Class III
 AIMD
 N/A

- (d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

N/A

15. (a) If not listed on the ARTG, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

- Yes (If yes, please provide supporting documentation as an attachment to this application form)
 No

- (b) If the therapeutic good is not ARTG listed, is the therapeutic good in the process of being considered by TGA?

- Yes (if yes, please provide details below)
 No

TGA application being prepared. See 15c.

- (c) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

- Yes (please provide details below)
 No

Estimated date of submission to TGA: **REDACTED**

Proposed indication(s), if applicable: For all T2D patients (*Final indication pending*).

Proposed purpose(s), if applicable: For the prognosis of diabetic kidney disease in patients with T2D (*Final intended purpose pending*).

PART 4 – SUMMARY OF EVIDENCE

16. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At ‘Application Form lodgement’, please do not attach full text articles; just provide a summary.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Biomarker discovery – post-hoc analysis of longitudinal observational study	Comprehensive mass spectrometry-based biomarker discovery and validation platform as applied to diabetic kidney disease	Biomarkers in 572 patients from the Fremantle Diabetes Study Phase II (FDS2) were compared against gold standard tests for evaluating DKD. Protein biomarkers ApoA4, CFHR2, IBP3, and AMBP were significantly associated with DKD, improving true positive (88% vs 73%) and false positive rates (32% vs 88%) against standard tests alone.	https://pubmed.ncbi.nlm.nih.gov/29900119/	January 2017
2.	Biomarker discovery and test development – post-hoc analysis of longitudinal observational study	Identification of Novel Circulating Biomarkers Predicting Rapid Decline in Renal Function in Type 2 Diabetes: The Fremantle Diabetes Study Phase II	Baseline biomarkers in 345 patients from the FDS2 measured by mass spectrometry to determine predictors of rapid eGFR decline over a 4-year follow-up period. Novel plasma biomarkers (ApoA4, CD5L, C1QB, and IBP3) identified that could predict outcomes, independently of recognised clinical risk factors in T2D.	https://pubmed.ncbi.nlm.nih.gov/28851702/	August 2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Test validation – post-hoc analysis of longitudinal observational study	Validation of a protein biomarker test for predicting renal decline in type 2 diabetes: The Fremantle Diabetes Study Phase II	Identified biomarkers assessed for predicting rapid decline in eGFR in 447 patients with T2D. Addition of biomarkers to the clinical model improved model fit, calibration, discrimination, sensitivity, specificity, and risk classification. PromarkerD had 86% sensitivity to predict DKD development within 4 years in individuals who were disease free at baseline.	https://pubmed.ncbi.nlm.nih.gov/31669066/	December 2019
4.	Protocol optimisation	A robust multiplex immunoaffinity mass spectrometry assay (PromarkerD) for clinical prediction of diabetic kidney disease	PromarkerD was optimised to a high throughput multiplex immunoaffinity mass spectrometry assay with applications in pathology practice. Processing time was reduced from seven to two days and test results demonstrated strong correlation (R = 0.96) to the original immunodepletion method used in development of the test.	https://clinicalproteomicsjournal.biomedcentral.com/articles/10.1186/s12014-020-09302-w	October 2020
5.	Protocol optimisation	The New and the Old: Platform Cross-Validation of Immunoaffinity MASS Spectrometry versus ELISA for PromarkerD, a Predictive Test for Diabetic Kidney Disease	PromarkerD developed into a standard ELISA workflow and compared to multiplexed immunoaffinity capture mass spectrometry assay. The performance characteristics of the two technology platforms were compared using a cohort of 100 samples, with PromarkerD test scores demonstrating a high correlation (R = 0.97).	https://pubmed.ncbi.nlm.nih.gov/33126588/	October 2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
6.	Post-hoc analysis of Phase III randomised controlled trial	PromarkerD Predicts Renal Function Decline in Type 2 Diabetes in the Canagliflozin Cardiovascular Assessment Study (CANVAS)	PromarkerD scores were measured at baseline in 3568 CANVAS participants with T2D (n = 1195 placebo arm, n = 2373 canagliflozin) and used to predict incident DKD and eGFR decline $\geq 30\%$ over 4 years. After adjusting for treatment, baseline PromarkerD risk scores were increasingly prognostic for incident DKD.	https://pubmed.ncbi.nlm.nih.gov/33036174/	October 2020

17. Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

	Type of study design	Title of research	Short description of research	Website link to research	Date
1.	Post-hoc analysis of Phase III randomised controlled trial	Canagliflozin attenuates PromarkerD diabetic kidney disease risk prediction scores Poster abstract	PromarkerD scores were measured at baseline and Year 3 in 2008 participants with a baseline eGFR ≥ 60 mL/min/1.73m ² . When stratified by PromarkerD risk category, patients with high-risk scores at baseline who were randomised to canagliflozin had significantly lower scores at Year 3 while those on placebo remained high.	https://www.xcdsystem.com/adc/program/vPZbWzx/index.cfm	Q3 2021
2.	Clinical decision impact/utility	Evaluation of the clinical utility of the PromarkerD in-vitro test in predicting diabetic kidney disease and rapid renal decline through a conjoint analysis	REDACTED	REDACTED	REDACTED

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 18. List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief ‘Statement of Clinical Relevance’ from the most relevant college/society.**

The following professional bodies represent the health care professionals responsible for directing treatment of patients with type 2 diabetes, and who are relevant in the provision of renal-protective care:

- Kidney Health Australia
- Australian Diabetes Society (ADS)
- Australian and New Zealand Society of Nephrology (ANZSN)

As PromarkerD is a laboratory test, the Royal College of Pathologists of Australasia (RCPA) are also relevant.

- 19. List any professional bodies / organisations that may be impacted by this medical service (i.e., those who provide the comparator service):**

There are no comparator services.

- 20. List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the ‘Application Lodgement’ stage of the MSAC process):**

Diabetes Australia (formerly the Australian Diabetes Council)

- 21. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

There is no sponsor which produces a similar product in Australia.

- 22. Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:**

REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease (in terms of both morbidity and mortality):

Almost 1 million Australian adults (5.3% of those aged 18 and over) had type 2 diabetes (T2D) in 2017–18, according to self-reported data from the Australian Bureau of Statistics (ABS) 2017–18 National Health Survey. An estimated 1.7 million (10%) Australian adults aged 18 years and over had biomedical signs of chronic kidney disease (CKD) in 2011–12. Type 2 diabetes is the leading cause of CKD globally, accounting for up to 50% of cases worldwide (Webster et al. 2017). Diabetes associated CKD, known as diabetic kidney disease (DKD), develops in 40% of patients with T2D and 30% of patients with type 1 diabetes (Hussain et al. 2021). Diabetes-associated kidney disease is the 16th leading cause of death in the US, accounting for 40,000 deaths per year (Mokdad et al. 2018).

In Australia, CKD contributed to 11% of all deaths in 2018 (around 16,800 deaths), according to the Australian Institute of Health and Welfare (AIHW) National Mortality Database. Chronic kidney disease was the underlying cause of death in around 3,600 deaths (21% of CKD deaths). It was an associated cause of death in a further 13,200 deaths (79% of CKD deaths). Overall, kidney and urinary diseases accounted for 1.4% of Australia’s total burden of disease in 2015. Chronic kidney disease represented the majority of burden from this disease group comprising 1.2% of total burden in 2015 (increasing from 0.8% in 2003 and 0.9% in 2011). Of the total CKD burden, 77% was due to fatal burden and 23% to non-fatal burden (AIHW 2020a).

Diabetic kidney disease refers to specific pathological structural and functional changes seen in the kidneys of people with diabetes that result from consistently high blood sugar levels which damages the blood-filtering capillaries in the kidneys. Clinically, DKD is characterised by progressive kidney damage reflected by increasing albuminuria, impairment in renal function (decline in glomerular filtration rate (GFR)), elevated blood pressure, and excess morbidity and mortality due to cardiovascular complications, and if left unchecked, DKD can progress to end-stage renal disease (ESRD) (Persson and Rossing 2018). Individuals with ESRD require haemodialysis and eventually kidney transplantation. According to the AIHW, diabetes is the leading cause of ESRD among patients commencing kidney replacement therapy (KRT), with 38% of cases attributable to diabetes (AIHW 2020a). Early detection of DKD and the implementation of intervention measures is important in reducing further kidney damage and hence progression of the disease.

Symptoms of DKD include albuminuria (excretion of albumin in the urine), weight gain, swelling of ankles and legs, frequent urination in the night, morning sickness, anaemia, and high blood pressure (Persson and Rossing 2018). Despite this, CKD remains a highly under-diagnosed condition. According to the AIHW, only 10% of people who showed biomedical signs of CKD self-reported that they had the condition (AIHW 2020a). It is referred to as a “silent disease” because 90% of kidney function can be lost before symptoms appear (Bellasi, Di Lullo, and Di Iorio 2019). Further, the asymptomatic nature of the disease in the early stages means the prevalence of the disease is severely under-reported, and many people are not aware they have the disease until they suffer from ESRD when it is too late to undertake preventative treatment. Timely identification of those at risk is an essential part of implementing interventions that can prevent the progression of DKD to ESRD.

24. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

Patient characteristics

The proposed medical service, PromarkerD, is a test designed to predict incident DKD or progression of DKD in patients with T2D before kidney damage or clinical symptoms occur. Patients that would be eligible for the proposed medical service include those who meet the following criteria:

- a. Patients diagnosed with Type 2 diabetes; and
- b. Estimated glomerular filtration rate (eGFR) of greater than or equal to 60ml/min/1.73m²; and
- c. Albumin: Creatinine Ratio (uACR) test results of less than or equal to 30mg/mmol;

Around 1 million Australian adults (5.3% of those aged 18 and over) had type 2 diabetes in 2017–18 (AIHW 2020b). Prevalence was higher in men (6.1%) than women (4.6%) and in those aged over 45 years with the risk increasing with age (AIHW 2020b). However, T2D can also occur in younger age groups including children, adolescents, and young adults.

Diabetes mellitus is a chronic condition caused by relative or absolute insulin deficiency. This insulin deficiency results in hyperglycaemia, which in the long term can affect many organs, in particular the blood vessels, nerves, eyes and kidneys. Type 2 diabetes is a progressive condition in which the body becomes resistant to the normal effects of insulin and/or gradually loses the capacity to produce enough insulin in the pancreas. Epidemiology of T2D is affected by genetic and environmental factors. The risk is greatly increased in people who have high blood pressure, are less physically active, are overweight or obese and have a poor diet.

Investigation, management and referral

Type 2 diabetes is asymptomatic in the early stages. As a result, diagnosis may be delayed and complications associated with diabetes are often present at the time of diagnosis. Therefore, testing is recommended in people at high risk of developing T2D. Diagnostic tests for diabetes include glycated haemoglobin (HbA1c), venous blood glucose concentration and the oral glucose tolerance test.

Initial request for PromarkerD would likely be conducted by general practitioners. Once a patient is diagnosed with T2D a diabetes management plan is prepared. Patients may be referred to a multidisciplinary team for diabetes which can include general practitioners, endocrinologists, diabetes educators, social workers, dietitians, pharmacists, podiatrists, Aboriginal health workers, dentists, exercise physiologists and psychologists (eTG 2019). However, due to the large number of people with T2D in Australia, patient care would be undertaken primarily by general practitioners.

Once a patient is diagnosed with T2D, they are at risk of complications related to their diabetes including DKD. Conventional assessment and monitoring of DKD is by one of two tests; measurement of albuminuria (uACR) and/or, renal function (eGFR) – calculated using serum creatinine level, age, sex, and race. According to the Australian therapeutic guidelines, monitoring for DKD using these tests is recommended annually for patients with T2D and more frequently for those with changing results (eTG 2019).

Diabetic kidney disease is usually diagnosed by reduced eGFR (< 60mL/min/1.73m²) and/or increased uACR (≥3 mg/mmol creatinine), that persists ≥3 months in the presence of longstanding diabetes and exclusion of other causes of CKD. Currently there are no tests that can quantify a patient's risk of developing DKD in those with clinically normal kidney function.

PromarkerD would be recommended in people with T2D, alongside current standard tests, to quantitatively predict a patient's risk of developing, or further decline in, DKD. The testing criteria represent the population of T2D patients who are likely to benefit the most from PromarkerD.

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

Key components:

PromarkerD comprises three enzyme-linked immunosorbent assays (ELISA) that measure the concentration of a panel of three novel protein biomarkers (ApoA4, CD5L and IBP3) combined with results from standard routine tests, including eGFR and HDL-cholesterol, and patient's age. The combined raw data is submitted to the PromarkerD Hub, and a test report is generated. PromarkerD Hub is a software tool **REDACTED** that contains a proprietary algorithm used to calculate the risk of developing, or further progression of, DKD.

Clinical Steps:

- 1) A patient with T2D would be seen by their managing clinician regularly for general monitoring and annual standard of care tests including eGFR and uACR to assess their kidney function.
- 2) The managing clinician would request PromarkerD for patients with a recent history of eGFR and uACR results who meet the eligibility criteria (see 24).
- 3) Patients would be referred to pathology for a blood draw.
- 4) Blood samples would be sent to accredited pathology laboratories where the PromarkerD kit would be used to prepare blood samples for biomarker testing via ELISA.
- 5) Test results would be interpreted and uploaded into the PromarkerD hub by pathologists to produce a risk score.
- 6) The PromarkerD risk score would be provided to managing clinicians who would then relay that information to patients.
- 7) The test risk score would inform further patient care e.g., monitoring frequency, lifestyle modification, initiation of more aggressive treatment measures, patient education on risk factors etc.

26. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

The product name "Promarker" is a registered trademark belonging to the applicant.

27. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

28. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e., accessibility, dosage, quantity, duration, or frequency)?

Patients with a low-risk PromarkerD score will be limited to one test every 4 years, the length of the predictive period of PromarkerD. Patients who receive a moderate- or high-risk PromarkerD result would be eligible for retesting every 2 years.

29. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Alongside the PromarkerD blood test for the 3 novel plasma protein biomarkers, a standard blood test to determine serum creatinine (for eGFR) and HDL-cholesterol would need to be undertaken or results recently available.

MBS item number: 66500

As part of usual standard of care for patients with T2D, eGFR should be tested annually or more frequently if the patient's results are changing.

Testing would be conducted in appropriately accredited pathology laboratories.

30. If applicable, advise which health professionals will primarily deliver the proposed service:

A request for testing with PromarkerD would be initiated by the patient's managing clinician. Most likely, general practitioners will primarily initiate requests for the service for patients, as they would request routine pathology tests for diabetic patients monitoring lipids, glucose control, etc.

Pathologists will conduct the tests at appropriately accredited laboratories. Results will then be relayed back to general practitioners to communicate with patients.

31. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Testing should only be conducted by qualified and trained pathologists.

32. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Only pathologists may conduct the service, and only a patient's managing clinician may provide a referral.

33. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Testing will be performed by qualified and trained pathologists in laboratories that are accredited by the National Association of Testing Authorities (NATA)/RCPA Laboratory Accreditation Program.

34. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

35. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

- 36. Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):**

There is no comparator test to PromarkerD. The test would be added to the current testing regimen. Patients with T2D currently should have laboratory risk factors (e.g., eGFR, uACR, lipids, HbA1c, etc) measured annually as part of usual monitoring. Should abnormalities in renal function be found and tracked properly by primary care and pathologists – e.g., decreasing eGFR over time, increasing uACR over time – primary care clinicians can elevate interventions. If renal function is declining rapidly or has passed a threshold of 30 ml/min eGFR, the patient is referred to a specialist for maximal intervention.

However, there is currently no test which quantifies the risk a patient may develop DKD in a discrete time period (4 years) and therefore provide a clear indication on the level and details of the intervention/s a patient requires before requiring maximal intervention and specialist care.

In this way, PromarkerD is proposed as an add-on to usual care.

- 37. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?**

- Yes (please list all relevant MBS item numbers below)
 No

- 38. (a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?**

- In addition to (i.e., it is an add-on service)
 Instead of (i.e., it is a replacement or alternative)

- (b) If yes, please outline the extent to which the current service/comparator is expected to be substituted**

Not applicable, proposed service is an add-on.

PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)

- 39. Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e., the landscape before the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current clinical management pathway, but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g., pharmaceuticals, diagnostics, and investigative services, etc.).**

The comparator for the PromarkerD test is “Standard of Care” where PromarkerD is an add-on test to the existing test regimen. Therefore, the clinical management is depicted in Figure 1. As part of regular monitoring, clinical and laboratory risk factors are monitored every 12 months. If renal decline is found to be over 2 mL/min/1.73m² eGFR between two measurements, or if total eGFR below 60 mL/min/1.73m², increased monitoring and intervention is enacted. This still largely takes place within general practice. If patients are at higher risk of ESRD and rapid renal decline (eGFR >4mL/min/1.73m² per year), they are referred to a specialist (e.g., nephrologist, endocrinologist, etc) for maximal intervention.

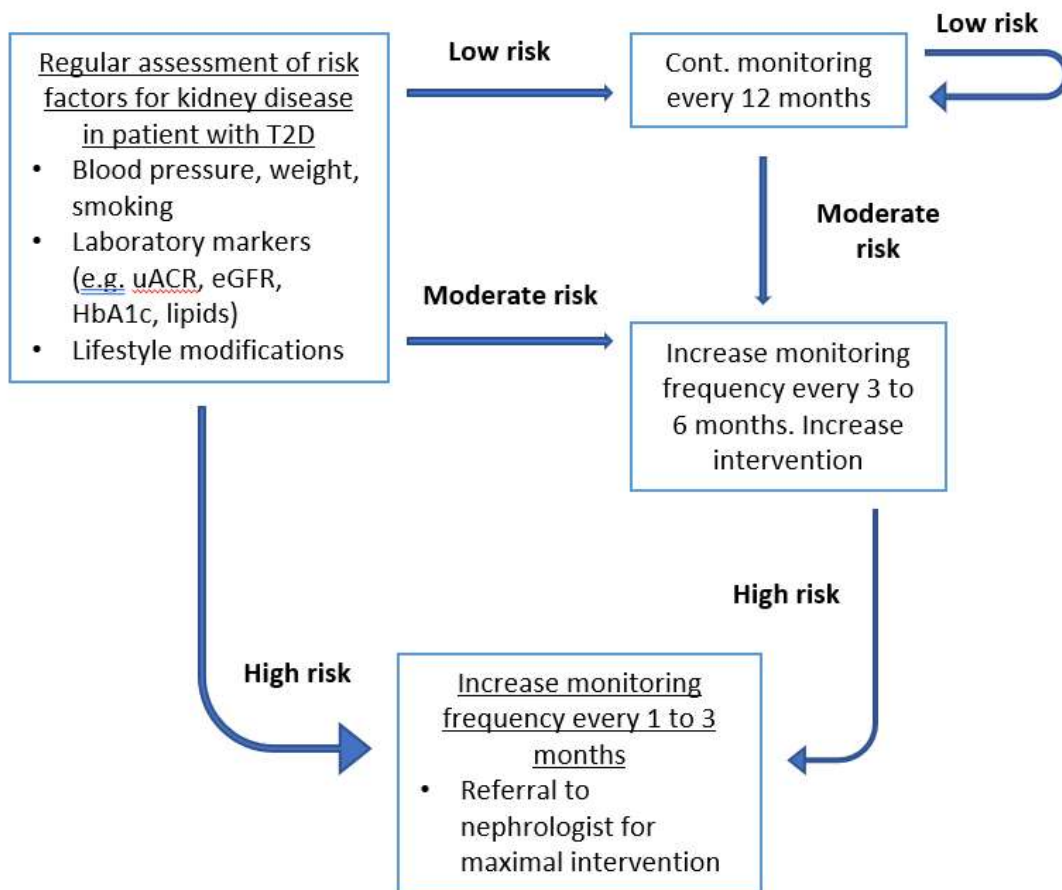


Figure 1. Current clinical management algorithm for monitoring kidney disease in patients with T2D

Risk is defined as risk of developing kidney disease outcomes, as estimated using renal marker tests eGFR, uACR, and other clinical and laboratory markers relevant to T2D disease progression.

Kidney Health Australia provides a table of kidney function stages per eGFR and uACR as shown in Table 1 (see 40). Green squares indicate lowest risk, yellow and orange squares indicate degrees of moderate risk, and red squares indicate high risk of developing negative renal outcomes. These categories are identical to those published by the globally recognised Kidney Disease Improving Global Outcomes (KDIGO) guidelines for evaluation and management of chronic kidney disease (Levin et al. 2013).

40. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow after the proposed service/technology is introduced, including variation in health care resources.

Based on the KDIGO definitions of kidney function, patients with type 2 diabetes whose renal marker measurements fall in the green boxes and the kidney function stage 1/2 yellow boxes in table 1 will be eligible for a PromarkerD test.

If PromarkerD results suggest a requirement for interventions beyond their position in the table below, i.e., patients in low-risk category by Kidney Health Australia guidelines fall into moderate- or high-risk categories by the PromarkerD test, treatment can be escalated before irreversible kidney damage.

Table 1. Kidney Health Australia risk categories of kidney function and disease in patients with T2D. Patients who stand to receive most benefit are marked in boxes below.

Kidney function stage	eGFR (mL/min/1.73m ²)	Normal uACR (mg/mmol)		Microalbuminuria (mg/mmol)		Macroalbuminuria (mg/mmol)	
		Male: <2.5	Female: <3.5	Male: <2.5	Female: <3.5	Male: <2.5	Female: <3.5
1	≥90	PromarkerD		PromarkerD			
2	60-89	PromarkerD		PromarkerD			
3a	45-59						
3b	30-44						
4	15-29						
5	<15 or on dialysis						

Patients who fall into higher risk PromarkerD categories who would not be flagged for interventions beyond standard monitoring and lifestyle management under currently available classifications, can be started on renoprotective treatment to reduce risk of kidney damage and onset of DKD. Treatments such as SGLT2 inhibitors are associated with reduced outcomes as a result of ESRD in patients with eGFR ≥60 mL/min/1.73 m² (Giorgino et al. 2020).

PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES

41. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

PromarkerD quantifies the risk of DKD development for up to four years after testing in patients with T2D. PromarkerD predicts whether a patient’s eGFR will decline to below 60 mL/min/1.73m² or decline by 30% or greater in this four-year period. Declines in eGFR are strongly associated with end-stage renal disease (ESRD) and mortality (Coresh et al. 2014). Predicting which patients will experience declines in eGFR ahead of time will allow maximal interventions early to mitigate, delay, or altogether avoid the dire outcomes associated with renal decline and ESRD – including kidney failure, transplantation, dialysis, and death.

There is currently no way to predict which patients will experience renal decline beyond intermittent measurement of kidney function. Once a significant enough decline is observed, such as a drop in eGFR below 60 mL/min/1.73m², DKD treatment can be instigated. However, at this stage, irreversible damage to the kidneys has already occurred.

A cohort of patients from the FDS2 database (n=857) have been analysed in and assigned to their respective KDIGO risk categories as per their eGFR (≥60 mL/min/1.73m²) and uACR (≤30 mg/mmol) measurements. A total of 725 patients were assigned to the categories (**REDACTED**).

The 725 patients were then categorised under their PromarkerD risk score at baseline – low, moderate, or high. Whether patients progressed to DKD, defined as eGFR <60 mL/min/1.73m²) was assessed after four years. A total of 69/81 patients were correctly classified as moderate- or high-risk – a sensitivity of 85.2% - and a total of 501/644 were correctly classified as low-risk – a specificity of 77.8%. This compares favourably to the sensitivity and specificity of using simply KDIGO (and Kidney Health Australia) risk categories prognostically, at 44.4% and 70.2% respectively.

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

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

PromarkerD will allow primary care clinicians to identify patients most in need of renoprotective therapy in increased monitoring and reduce the downstream burden of costly ESRD outcomes on the health budget.

42. Please state what the overall clinical claim is:

PromarkerD can quantify the risk of incident diabetic kidney disease in an individual with type 2 diabetes up to 4 years before clinical symptoms develop. Additionally, it can predict rapid renal decline of $\geq 30\%$ eGFR over 4 years.

43. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Clinical Effectiveness Outcomes:

- Life Years Saved
- End Stage Renal Disease (ESRD)
- Quality Adjusted Life Years (QALYs)

Test outcomes:

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

Clinical utility of test:

- Predictive effect of testing of patients to detect DKD

Other test-related considerations:

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

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

44. Estimate the prevalence and/or incidence of the condition in the proposed population:

The prevalence rate of type 2 diabetes in Australia is 5.3%, resulting in 1.1 million Australian adults expected to be diagnosed in 2022.

In order to be eligible for PromarkerD, patients with type 2 diabetes must meet the following criteria:

- Estimated glomerular filtration rate (eGFR) of greater than or equal to 60ml/min/1.73m²; and
- Albumin: Creatinine Ratio (uACR) test results of less than or equal to 30mg/mmol.

According to the Fremantle Diabetes Study, it was reported that:

- 84.6% of patients with type 2 diabetes have an eGFR of greater than or equal to 60ml/min/1.73m² and uACR test result of less than or equal to 30mg/mmol.
- 30% of eligible patients have a moderate to high-risk PromarkerD test score.

45. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

Patients will be limited to one test every 4 years, however, patients with a moderate to high-risk score are eligible for the test once every 2 years. Additional clinical decision impact/ clinical utility data (manuscript submitted, see upcoming publications in Question 17) will support the basis for future testing depending on other treatments clinicians recommend for patients to mitigate risks after receiving PromarkerD results.

46. How many years would the proposed medical service/technology be required for the patient?

Only one test per 4 years per eligible patient is necessary, however, patients with a moderate to high-risk score are eligible for the test once every 2 years. Clinicians should increase interventions on the basis of PromarkerD risk. Data is soon to be published which will support the basis for future testing (see upcoming publications in Question 17).

47. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Applying a prevalence rate of 5.3% to the Australian adult population in 2022, results in an estimated 1.1 million adults with type 2 diabetes. From this prevalent population, **REDACTED** of patients are expected to have both an eGFR of greater than or equal to 60ml/min/1.73m² and uACR test result of less than or equal to 30mg/mmol (**REDACTED**).

With patients limited to one test every four years, the eligible population must therefore be divided by four, in order to estimate the annual eligible population. This results in approximately **REDACTED** patients eligible for PromarkerD in **REDACTED**.

From this eligible population, clinical experts expect an uptake rate of **REDACTED** in the first year of listing, resulting in approximately **REDACTED** patients expected to utilise PromarkerD in **REDACTED**.

The PromarkerD test predicts DKD up to 4 years in advance, hence four-year utilisation numbers are provided to reflect this time frame (Table 3).

REDACTED of eligible patients will have a moderate to high-risk score and will therefore be eligible for one test every two years as opposed to four years. This value was divided by two (one test per two years) and added to the annual PromarkerD population to calculate the total number of PromarkerD services.

Table 3. The estimated utilisation of PromarkerD across the first four years of listing.

	2022	2023	2024	2025
Australian Adult Population (aged 18+)	20,757,917	21,082,471	21,411,852	21,744,502
Prevalence of Type 2 Diabetes	5.3%	5.3%	5.3%	5.3%
Total Prevalent Patients with Type 2 Diabetes	1,100,170	1,117,371	1,134,828	1,152,459
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
REDACTED	REDACTED	REDACTED	REDACTED	REDACTED

48. Estimate the anticipated uptake of the proposed medical service/technology over the next three years, factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors), as well as provide commentary on risk of ‘leakage’ to populations not targeted by the service.

It is estimated that the uptake rate will start at **REDACTED** in the first year of listing and is projected to gradually increase to **REDACTED** by the fourth year. This reflects expert opinion given by nephrologists experienced in the management of DKD and understanding of primary care practices for T2D in Australia.

Estimated uptake of the test over the next three years is approximately **REDACTED** patients (**REDACTED**).

Supply constraints are not expected to be relevant, and leakage will be low given the quantifiable biochemical measures required to qualify for the test.

PART 8 – COST INFORMATION

49. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The proposed price for PromarkerD is \$250 AUD. This price is however subject to change based on the PICO assessment and the economic evaluation submitted in the application to MSAC.

50. Specify how long the proposed medical service/technology typically takes to perform:

4 hours to run the ELISA + uploading and getting results from online hub. Time does not include time to process other blood measures (HDL-cholesterol & eGFR) which are not conducted as part of the PromarkerD kit.

Including these other measures which are part of standard T2D monitoring may increase time by an hour or longer depending on pathology turnaround time.

51. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

Category 6 – Pathology Services
Proposed item descriptor: A test to quantify the risk of diabetic kidney disease incidence in proceeding 4 years in: a. Patients diagnosed with Type 2 Diabetes; and b. Estimated glomerular filtration rate (eGFR) of greater than or equal to 60ml/min/1.73m ² ; and c. Albumin: Creatinine Ratio (uACR) test results of less than or equal to 30mg/mmol. For any patient with a low-risk score, performed once every 4 years. For patients with a moderate- to high-risk score, performed once every 2 years. Fee: \$250 Benefit: 75% = \$187.50 85% = \$212.50

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