NICE advice

PromarkerD for predicting the risk of diabetic kidney disease in people with type 2 diabetes

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is PromarkerD. It is used for predicting the risk of diabetic kidney disease in people with type 2 diabetes.
- The **innovative aspects** are that PromarkerD is designed to allow earlier or more accurate prediction of kidney disease in people with type 2 diabetes, which could lead to more appropriate treatment.
- The intended **place in therapy** would be in addition to the standard care tests to predict renal function based on clinical symptoms of kidney disease in people with type 2 diabetes.
- The **main points from the evidence** summarised in this briefing are from 4 studies (2 validation studies, 1 prospective study and 1 early discovery study) including a total of 5,789 people with type 2 diabetes. They show that PromarkerD is effective at predicting renal function decline in people with type 2 diabetes.

- **Key uncertainties** around the evidence or technology are that the evidence base for PromarkerD is limited. No studies were done in the UK or NHS. Further studies including populations that represent those in NHS practice and that assess how the PromarkerD test leads to subsequent changes in clinical management and patient outcomes would be useful.
- **Experts advised** that the technology is novel and is expected to be used in addition to standard care tests. They said that PromarkerD would cost significantly more than standard care, and long-term cost savings would be materialised only if adopting the test reduces the number of people who need end-stage renal failure treatments.
- The **cost** of PromarkerD is £185 per unit (excluding VAT) and would be in addition to standard care. This cost includes the test and prognostic report for 1 person.

The technology

PromarkerD (Proteomics) is a blood test used to assess the risk of diabetic kidney disease in people with type 2 diabetes. The test combines 3 biomarkers measured by immunoassay (ApoA4, CD5L and IGFBP3) with 3 routine clinical factors (age, high-density lipoprotein [HDL]-cholesterol and estimated glomerular filtration rate [eGFR]). Using an algorithm, the test generates a prognostic risk score for a person developing diabetic kidney disease up to 4 years in advance. For the test, a plasma sample measures the 3 biomarkers and the software then generates a risk report which laboratory staff download and send to the clinician. People are classified according to 1 of 3 risk groups (low risk, moderate risk and high risk) which informs the level of monitoring and management strategies required. People with a high-risk PromarkerD prognostic risk score would be retested every 3 months, moderate risk every 6 months and low risk every 12 months.

Innovations

There is currently no available test to predict renal function decline in people with type 2 diabetes. PromarkerD predicts the likelihood of occurrence of kidney disease in people without symptoms, which may allow earlier or more accurate diagnosis and could lead to more appropriate treatment.

Current care pathway

The current care pathway for diabetes care includes an annual health check for blood glucose, lipid profile and kidney function. The kidney function tests measure eGFR and urine albumin to creatinine ratio (uACR). These results provide a measurement of the current state of a person's kidneys to inform the most appropriate intervention. Based on the physician's assessment, clinical and laboratory risk factors may be monitored every 3, 6 or 12 months.

The following publications have been identified as relevant to this care pathway:

- NICE's guideline on managing type 2 diabetes in adults
- NICE's quality standard on diabetes in adults
- NICE's clinical knowledge summary on type 2 diabetes.

Population, setting and intended user

PromarkerD tests are intended to be used to predict the onset of diabetic kidney disease in people with type 2 diabetes or further decline in kidney function in patients with existing diabetic kidney disease. Tests are likely to be requested by primary care clinicians in GP surgeries, as well as by endocrinologists and nephrologists in secondary care. Plasma samples are sent to the manufacturer's laboratory, where trained personnel test the samples and input data into cloud-based software to generate a report which is sent back to the clinician.

No additional training would be needed for clinicians, other than understanding how to interpret the report.

Costs

Technology costs

The cost of a PromarkerD test is £185 per unit (excluding VAT). This includes the cost of a test and the prognostic report for 1 person.

Costs of standard care

The cost of the standard care diagnostic tests (uACR and eGFR) is less than the cost of a PromarkerD prognostic test.

Resource consequences

The technology is not currently used in the NHS. The PromarkerD test is expected to be used in addition to the current standard care tests to estimate renal function. PromarkerD is intended to diagnose kidney disease earlier, which allows earlier intervention, potentially slowing down diabetic kidney disease progression. Blood samples may need to be sent to alternative laboratories for processing of results. No infrastructure changes are associated with adopting the technology.

Regulatory information

The PromarkerD immunoassay and the PromarkerD Hub are CE-marked in vitro diagnostic medical devices, regulated under the European Commission's in vitro diagnostic medical devices directive.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

People with type 2 diabetes are considered to have a disability if they have a physical or mental impairment which has a substantial and long-term adverse effect on their ability to carry out normal day-to-day activities as a result of the condition. People from some family backgrounds are at higher risk of developing diabetic kidney disease. Race and disability are protected characteristics under The Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available

published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 4 studies summarised in this briefing, including a total of 5,789 people with type 2 diabetes. The evidence includes 2 validation studies (Peters et al. 2019 and Peters et al. 2020), 1 prospective study (Peters et al. 2021) and 1 early discovery study (Bringans et al. 2017).

In addition, there is a further study assessing the potential of the biomarkers used by PromarkerD to predict rapid decline in renal function in people with type 2 diabetes (Peters et al. 2017). There are also analytical validation studies on PromarkerD (Bringans et al. 2020a) and studies on the stability, reproducibility and precision of the assay (Bringans et al. 2020b).

The clinical evidence and its strengths and limitations are summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for PromarkerD is limited and predominantly comes from validation studies. The studies have relatively large sample sizes and one of the validation studies included people from 30 different countries. Despite this, one of the limitations highlighted by study authors and clinical experts was the lack of generalisability of results. This is because of the relative lack of representation of different family backgrounds across the evidence base, particularly those that are at high risk of developing diabetic kidney disease (DKD). One comparative study is included in the evidence base (Peters et al. 2021) comparing the PromarkerD test to the standard care tests used in clinical practice. Further external validation of the technology through comparative studies in a UK context including a wide range of patient groups would be beneficial. Three of the publications cited in this briefing assessed patients from the same study cohort. The time horizon used in the studies is approximately 4 years, which is a relevant prognostic time horizon for people with type 2 diabetes.

Peters et al. (2020)

Study size, design and location

A multicentre validation study predicting renal function decline in 3,568 people with type 2 diabetes. The study was done at 667 centres in 30 countries.

Intervention and comparator

PromarkerD, no comparator.

Key outcomes

Mean baseline estimated glomerular filtration rate (eGFR) was 77 ml/min/1.73 m^2. 16.5% of people had renal impairment, classified as having an eGFR lower than 60 ml/min/1.73 m^2. 1,351 people (38%) had chronic kidney disease at baseline, defined by a composite of eGFR and urine albumin to creatinine ratio (uACR), eGFR lower than 60 ml/min/1.73 m^2 and/or uACR higher than 30 mg/g. Excluding those with renal impairment, 926 people (31.1%) developed chronic kidney disease during the 4-year follow-up period. During follow up, 564 people (16%) suffered a decline in eGFR of more than 30%.

The prognostic score for PromarkerD was significantly associated with predicting incident chronic kidney disease ($p<2.8\times10^{-47}$). Moderate-risk and high-risk scores were increasingly prognostic for incident chronic kidney disease; odds ratio (OR) 5.29 (4.22 to 6.64) and OR 13.52 (10.69 to 17.11) respectively. The prognostic score was also significantly associated with an eGFR decline of more than 30%; OR 1.13 (1.04 to 1.24). PromarkerD provided 60.6% sensitivity and 82.6% negative predictive value at the 10% cut-off, and 94.0% specificity and 73.9% positive predictive value at the 20% cut-off for predicting 4-year risk of developing chronic kidney disease. The test performed poorly in differentiating people with rapid eGFR decline from those with lesser declines.

Strengths and limitations

A significant strength of the study was the large sample size. The study included people with type 2 diabetes using a global multicentre approach, independent of the Australian population used to develop the test. This study also describes the development of PromarkerD. One of the limitations highlighted by the authors was that 81% of participants were from a white family background, which limits the generalisability of the PromarkerD

test to other family backgrounds. Only baseline clinical and biomarker data was used to predict outcomes; subsequent changes in biomarker concentrations during the follow-up period were not considered.

Peters et al. (2019)

Study size, design and location

A development and validation study of PromarkerD for predicting renal function decline in 792 people with type 2 diabetes. The study was done in Australia.

Intervention and comparator

PromarkerD, no comparator.

Key outcomes

The study population was separated into 2 groups: the development cohort (n=345) and the validation cohort (n=447). During a mean follow up of 4.2 years, 39 people (9.8%) in the validation cohort developed DKD and 24 people (5.4%) experienced more than a 30% decline in eGFR.

The predictive performance of PromarkerD was assessed. The model for incident DKD had the highest predictive ability to discriminate between people who did and did not develop DKD during follow up. In the development and validation cohorts, the concordance was 0.89 and 0.88, respectively. PromarkerD provided 86.1% sensitivity at the 10% cut-off, and 84.7% specificity at the 20% cut-off to predict 4-year risk of developing DKD. For an eGFR decline of 30% or more, the concordance was 0.81 and 0.73 in the development and validation cohorts, respectively.

Strengths and limitations

The study employed a prognostic time horizon of over 4 years that is relevant to people with type 2 diabetes. A limitation of the study was that baseline clinical and biomarker data was used to predict outcomes, but subsequent changes in biomarker concentrations or diabetes management were not considered. The authors stated that additional external validation across different clinical settings and populations is needed to fully realise the generalisability of the predictive models.

Peters et al. (2021)

Study size, design and location

A prospective study comparing PromarkerD to standard care tests for predicting renal function decline in 857 community-based people with type 2 diabetes, with 4-year follow-up. The study was done in Australia.

Intervention and comparators

PromarkerD, compared with eGFR and uACR (standard care).

Key outcomes

The study incorporated the Kidney Disease: Improving Global Outcomes (KDIGO) risk classes for adverse outcomes, which are based on eGFR and albuminuria measurements. The KDIGO categories give the risk of chronic kidney disease progression, morbidity and mortality. At baseline, participants were classified by PromarkerD as low (63%), moderate (13%) or high risk (24%), and by KDIGO as low (58%), moderate (31%), high (7%) or very high risk (4%) for renal decline within 4 years. Of the 497 people in KDIGO low-risk category with normal kidney function, 45 (9%) developed incident DKD within 4 years and would have been missed by standard care tests. PromarkerD classified 38 (84%) of these people as moderate or high risk, flagging them for early intervention and closer monitoring of disease. In addition, 354 out of 361 (98%) people with low-risk PromarkerD results did not develop incident DKD. Of the people who developed the outcome, 84% had moderate or high-risk PromarkerD scores.

During 4.2 years of follow up, 107 people (12.5%) experienced a decline in renal function. Higher PromarkerD risk scores had a stronger association with renal decline (OR 3.26) compared with lower eGFR and higher uACR (OR 2.63 and 1.21, respectively). PromarkerD moderate and high-risk scores were increasingly prognostic for renal decline (OR 8.11 and 21.34, respectively) compared with low-risk scores ($p<0.001$). PromarkerD has significantly higher predictive performance (concordance of 0.88) compared with standard care tests (eGFR only, concordance of 0.82, uACR only, concordance of 0.63, eGFR + ACR, concordance of 0.82) for predicting decline in renal function within 4 years ($p<0.001$).

Strengths and limitations

The study used a follow-up period of 4 years, which was useful to compare baseline risk scores with outcomes seen at the end of the follow-up period. As well as comparing PromarkerD directly with eGFR and uACR tests, both individually and combined, test scores were also compared with the KDIGO risk classifications. The study was funded by the manufacturer.

Bringans et al. (2017)

Study size, design and location

An early discovery study in 572 people with type 2 diabetes to produce a panel of plasma biomarkers specific to diabetic kidney disease. The study was done in Australia.

Intervention and comparator

PromarkerD, no comparator.

Key outcomes

The diagnostic performance of the biomarker model was assessed alongside the standard care uACR and eGFR diagnostic tests. uACR data was found to have a true positive rate of 73% and a false positive rate of 40% when diagnosing eGFR of less than 60 ml/min/1.73 m^2. In the opposite analysis, eGFR data had a true positive rate of 26% and a false positive rate of 8% when used to diagnose uACR less than 3 mg/mmol. The biomarker eGFR model had an improved true positive rate (88% versus 73%) and a reduced false positive rate (32% versus 40%) over the standard care uACR test for diagnosing eGFR of less than 60 ml/min/1.73 m^2. The biomarker uACR model had an improved true positive rate (52% versus 26%) but a poorer false positive rate (15% versus 8%). The diagnostic odds ratios for the eGFR and uACR biomarker models were significantly better than those of the standard care tests (eGFR 14.9 versus 4.0, uACR 6.0 versus 4.0).

Strengths and limitations

The study provides an outline of the methods used to determine the final biomarkers for the PromarkerD test. A significant strength of the study is that the biomarker tests were compared with standard care tests in a large sample of people with type 2 diabetes.

Sustainability

The company does not claim any sustainability benefits of this technology.

Recent and ongoing studies

No ongoing or in-development trials were identified.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

One out of 4 experts was familiar with or had used this technology before.

Level of innovation

Three of the experts agreed that the technology is novel compared with standard care and is expected to be used in addition to established tests such as estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (uACR). The other expert stated that PromarkerD offers an incremental advancement of current biomarkers used to predict renal dysfunction but is unlikely to significantly alter efficacy or safety. One of the experts highlighted that there has been a long-standing search for biomarkers that better predict the development of diabetic kidney disease (DKD) in people with type 2 diabetes. However, before PromarkerD, no established biomarker has been developed that provides more information than the uACR, a test which demonstrates ongoing damage rather than predicting DKD.

Potential patient impact

Two of the clinical experts commented that PromarkerD has the potential to allow earlier identification of people with type 2 diabetes who are at high risk of developing cardiovascular and renal complications. This could allow a more intensive approach to reduce risk of both cardiovascular and kidney damage early on after diagnosis of type 2 diabetes. Another expert stated that PromarkerD could allow for 1 test to be taken instead

of the blood and urine tests done in current practice. The expert highlighted that urine tests tend to score poorly in the national diabetes audit. One expert said that diabetes is the most common cause of end-stage renal disease. People from high-risk family backgrounds are at particular risk of developing DKD, so PromarkerD may prove to be an effective option for these people.

Potential system impact

All of the experts agreed that the technology would cost significantly more than standard care, while the effect on long-term outcomes is unclear. Two of the clinical experts explained that PromarkerD may allow the identification of high-risk patients earlier, which would alter the treatment they receive. So, this could lead to a decrease in the number of people developing end-stage renal disease, reducing hospitalisation and need for dialysis. One expert outlined that long-term cost savings depend on the ability of the test to alter management strategies, such that fewer people need end-stage renal failure treatments. Three of the experts added that a training programme would need to be introduced alongside the technology, so healthcare professionals understand how to use the tests and respond to test results. This would mitigate the risk of further increased costs from unnecessary testing, and provide clinicians and patients with clarity on test outcomes.

General comments

One expert stated that the test carries a false positive rate, which could mean that some people who are not at risk of developing DKD are treated. The false negative rate also means that some people who are at risk are not treated. Two experts highlighted that the key efficacy outcome must be a reduction in the incidence of people with advanced kidney disease in the context of diabetes, otherwise the technology will not provide any significant advantage. Three of the experts felt that more evidence is needed on the technology using larger cohorts to confirm its efficacy before adoption across the healthcare system.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Andrew Frankel, consultant nephrologist at Imperial College Healthcare NHS Trust. Did not declare any interests.

- Dr Peter Winocour, consultant diabetologist at East and North Herts Institute of Diabetes and Endocrinology. Did not declare any interests.
- Professor Stephen Charles Bain, professor of medicine and diabetes at Swansea Bay University Health Board. Did not declare any interests.
- Professor Tahseen Ahmad Chowdhury, consultant in diabetes at Barts Health NHS Trust. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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