



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1397 – mpMRI Prostate diagnostic scans

Applicant: **Australian and New Zealand Association of Urological Surgeons and Australian Diagnostic Imaging Association**

Date of MSAC consideration: **MSAC Executive 12 December 2017**
MSAC 70th Meeting, 27 July 2017
MSAC 69th Meeting, 6-7 April 2017

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 two new Medicare Benefit Schedule (MBS) listings for multiparametric magnetic resonance imaging (mpMRI), to diagnose clinically significant cancer in patients suspected to have prostate cancer, and for disease monitoring in patients with known prostate cancer who have undertaken active surveillance, was received from the Australian and New Zealand Association of Urological Surgeons (ANZAUS) and the Australian Diagnostic Imaging Association (ADIA) by the Department of Health (the Department).

2. MSAC Executive Committee – December 2017 consideration

The MSAC Executive Committee supported the listing of mpMRI prostate diagnostic scans for both the diagnosis of prostate cancer and the active surveillance of patients with a proven diagnosis based on acceptable safety, clinical and cost effectiveness.

Summary of consideration and rationale for MSAC Executive Committee advice – December 2017

The MSAC Executive noted that MSAC deferred Application 1397 at its July 2017 meeting pending provision of additional information on the item descriptor, utilisation and financial impact of the listing to the MSAC Executive.

The MSAC Executive noted that the proposed eligible population for the diagnostic MBS item descriptor was modified based on the Prostate Cancer Foundation guidelines and MBS data on Prostate Specific Antigen (PSA) testing in consultation with the applicant and several expert advisers. The MSAC Executive considered that the patient and referring specialist limitations included in the MBS item descriptor were reasonable. The MSAC Executive supported the requirement in the item descriptor that the request specifies that the clinical criteria is met to inform the radiologist that the patient is eligible under the MBS criteria. The

department in consultation with the Royal Australian and New Zealand College of Radiologists (RANZCR) will progress this.

The MSAC Executive noted the results of the department consultation regarding the fee currently charged by Australian diagnostic providers to perform an mpMRI of the prostate, which ranged from \$285.00 to \$585.00. The MSAC Executive considered the proposed MBS item fee was reasonable, however questioned if contrast was included in the fee. The MSAC Executive advised that the MBS item fee should be \$450 if contrast is included, and \$400 if contrast is not included.

The MSAC Executive and the applicant supported the following items descriptors:

Category 5 – Diagnostic Imaging Services
DIAGNOSIS ITEM NUMBER
MBS [item number] Multiparametric Magnetic Resonance Imaging (mpMRI) using a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated); and performed under the professional supervision of an eligible provider at an eligible location; and the patient is referred by an urologist, radiation oncologist, or medical oncologist; and the request specifies that the clinical criteria below are met; and the patient is suspected of having prostate cancer based on: 1. A digital rectal examination (DRE) which is suspicious for prostate cancer; or 2. In a person aged less than 70 years, at least two prostate specific antigen (PSA) tests performed within an interval of 1- 3 months are greater than 3.0 ng/ml, and the free/total PSA ratio is less than 25% or the repeat PSA exceeds 5.5 ng/ml ; or 3. In a person aged less than 70 years, whose risk of developing prostate cancer based on family history is at least double the average risk , at least two PSA tests performed within an interval of 1- 3 months are greater than 2.0 ng/ml, and the free/total PSA ratio is less than 25%.; or 4. In a person aged 70 years or older, at least two PSA tests performed within an interval of 1- 3 months are greater than 5.5ng/ml and the free/total PSA ratio is less than 25%. Scan of the prostate for: – detection of cancer (R) Fee: \$450.00 (incl contrast) [Relevant explanatory notes] Note: Benefits are payable on one occasion only in any 12 month period. Relevant family history is first degree relative with prostate cancer or suspected of carrying a BRCA 1, BRCA 2 mutation.

ACTIVE SURVEILLANCE ITEM NUMBER

MBS [item number]

Multiparametric Magnetic Resonance Imaging (mpMRI) using a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated); and performed under the professional supervision of an eligible provider at an eligible location; where the patient is referred by an urologist, radiation oncologist, or medical oncologist; and where the request specifies that the clinical criteria below are met:

- a) the patient is under active surveillance following a confirmed diagnosis of prostate cancer by biopsy histopathology; and
- b) the patient is not planning or undergoing treatment for prostate cancer.

Scan of the prostate for:

- assessment of cancer (R)

Fee: \$450.00 (incl contrast)

[Relevant explanatory notes]

Note: Benefits are payable at the time of diagnosis of prostate cancer, 12 months following diagnosis and then every 3rd year thereafter or at any time, if there is any concern clinically or with PSA progression. This item is not to be used for the purposes of treatment planning or for monitoring after treatment.

The MSAC Executive noted the financial analysis scenarios provided, and the potential cost impact if the MBS item is requested for additional populations outside the item descriptor. The MSAC Executive was reassured that, even in the worst case scenario, the costs were reasonable. However, the MSAC Executive advised that, once the items are MBS listed, the department should closely monitor the utilisation through the Predicted versus Actual (PvA) reporting process.

The MSAC Executive agreed with the department that usual standards of training and accreditation for provision of this diagnostic imaging service would be required and noted that RANZCR had commenced drafting Prostate MRI Professional Development Guidelines. The MSAC Executive was concerned that these Guidelines should be developed in a timely manner and requested the department write to RANZCR to encourage completion of this within nine months to align with the expected listing date. This would enable a check of compliance with the accreditation standards in any future audit of providers.

In line with MSAC's July 2017 recommendation, the MSAC Executive supported MBS funding for mpMRI prostate diagnostic scans for both the diagnosis of prostate cancer and the active surveillance of patients with a proven diagnosis based on acceptable safety, clinical and cost effectiveness. This recommendation will be tabled at the March 2018 MSAC meeting.

3. MSAC's advice to the Minister – July 2017 consideration

MSAC deferred a decision on the listing of multiparametric magnetic resonance imaging (mpMRI) for the diagnosis of prostate cancer (PCa) pending provision of additional information on the utilisation and financial impact of the listing.

MSAC agreed there was a clinical place for mpMRI and recalled that it had previously accepted its safety and effectiveness compared with ultrasound-guided biopsy. However, MSAC remained uncertain about the financial impact of potential use of mpMRI outside the proposed populations. MSAC noted that potential costs due to leakage may be substantial. MSAC requested further revision of the item descriptors, further assessment of the fee and

new modelling which assumed that all men with incident cases of PCa would receive an mpMRI as a staging procedure. MSAC suggested that the progress of this application be managed via the MSAC Executive to ensure that the appropriate information was provided to the full committee in a timely manner.

Summary of consideration and rationale for MSAC's advice – July 2017

MSAC recalled that it had considered the listing of multiparametric magnetic resonance imaging (mpMRI) for the diagnosis of prostate cancer (PCa) at its April 2017 meeting. MSAC recalled that while it had accepted that mpMRI had superior safety and non-inferior effectiveness if used to diagnose clinically significant disease in men suspected of having PCa (population 1) or men on an active surveillance program (population 2), it had deferred the listing due to concerns about use outside these populations ([MSAC Public Summary Document \(PSD\) Application 1397, April 2017](#)). MSAC recalled that at this meeting it had requested:

- modification of the wording of the item descriptor to prevent additional use;
- reduction of the MBS item fee to \$400; and
- an estimate of the total potential utilisation and financial impact of use outside the two identified patient populations.

MSAC recalled that it was concerned about leakage in the following populations: 1) men with suspected PCa who have had a negative biopsy; 2) men with a known diagnosis of PCa in whom mpMRI was being used to stage or plan treatment or 3) men with suspected recurrent PCa after curative intent treatment. MSAC noted that while the item descriptors for population 1 and population 2 had been tightened, they were still not sufficient to preclude use in the three additional populations.

. MSAC noted the applicants' comments that it would be exceptional for a patient to receive treatment without having undergone imaging and that treatment planning would be conducted as part of the initial mpMRI. MSAC noted that while T2 weighted (T2W), diffusion weighted image (DWI), and dynamic-contrast enhanced (DCE) pulse sequences were required for accurate diagnosis, only T2W images were essential for staging. Therefore, MSAC noted that while the \$600 fee may be justifiable for full mpMRI to diagnose clinically significant PCa (per the initial application), it would not be justified for staging. MSAC noted that as it was likely that mpMRI would be undertaken for all incident cases of PCa, a lower fee than the proposed \$600 could alleviate the financial impact of the use of mpMRI to stage disease and plan treatment in addition to its diagnostic use.

MSAC noted that no information on the financial impact of reducing the proposed fee from \$600 to \$400 had been provided to the committee. MSAC noted that advice provided to the Department from individual radiologists had indicated that mpMRI was more complex than item 63476 (MRI scan of the pelvis for the initial staging of rectal cancer: MBS fee ~\$403). MSAC noted that these radiologists suggested that undertaking mpMRI of the prostate was comparable to undertaking breast MRI for the detection of cancer (item 63464: MBS fee \$690 for both breasts).

MSAC noted that while the applicants claimed that the number of men diagnosed with incidental cancer and on an active surveillance program (population 2) would fall to minimal levels, no evidence had been presented to support this claim. MSAC also noted that the applicants had suggested that there would be a third population suitable for mpMRI - men identified as having small but visible PCa, that is intermediate risk on biopsy, and who have chosen ongoing observation rather than treatment (population 3). The applicants indicated

that men in population 3 would be monitored with one scan every year. MSAC noted that no evidence had been provided to support the use of mpMRI in population 3.

MSAC recalled that it had recommended modelling of the financial impact of use outside the proposed populations but this had not been provided. MSAC recommended new modelling, which assumes all men with early PCa receive an mpMRI, be undertaken. MSAC noted that in response to its request for further data at the April 2017 meeting, the following information had been provided which could inform the new model:

- [AIHW data on cancer incidence](#) suggest an additional 25,000 to 31,000 men will be diagnosed with PCa in 2020;
- the use of MBS item 66655 (quantitation of PSA once in a 12 month period) has fallen since 2012 (when mpMRI became available privately) and there appeared to be a slight reduction in the ratio of ultrasound-guided biopsies (item 37219) to PSA tests. MSAC noted that it was unknown whether this was because privately funded mpMRIs were ruling out clinically insignificant PCa in some patients or because PSA testing is being used more judiciously;
- Victorian Prostate Cancer Registry data from 2013–15 indicated that 21% of men were categorised as being at very low to low risk and 44% at intermediate risk according to the National Comprehensive Cancer Network (NCCN) risk categories; and
- Victorian Prostate Cancer Registry data from 2013–15 indicated that 65% of men with very low to low risk disease and 16% of men with intermediate risk disease were managed conservatively with either active surveillance or watchful waiting.

MSAC reiterated its previous advice that an accreditation and training program, specific to imaging of the prostate, would need to be implemented before listing.

MSAC suggested that the progress of this application be managed via the MSAC Executive to ensure that the appropriate information was provided to the full committee in a timely manner.

4. MSAC's advice to the Minister – April 2017 consideration

After considering the available evidence regarding comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice for mpMRI for the diagnosis of prostate cancer (PCa).

MSAC accepted that mpMRI had superior safety and non-inferior effectiveness if used to diagnose clinically significant disease in men suspected of having PCa (population 1) or for men diagnosed with low- or intermediate-risk PCa who have undertaken active surveillance (population 2). MSAC noted that mpMRI would be cost saving at the expense of a small reduction in quality adjusted life years (QALYs) if used in these populations. However, MSAC remained concerned that the number of mpMRIs was likely to be much higher than estimated in the application due to use outside these populations. MSAC requested further information on the potential cost implications of higher use before finalising its decision. MSAC also considered that the proposed MBS fee was too high and should be reduced to a similar fee of other MBS-listed MRI items.

MSAC therefore requested the Department to:

- (a) modify the wording of the item descriptor to prevent the additional use,
- (b) reduce the MBS item fee to \$400, and
- (c) estimate the total potential utilisation and financial impact

Summary of consideration and rationale for MSAC's advice – April 2017

MSAC considered the listing of multiparametric magnetic resonance imaging (mpMRI) for the diagnosis of clinically significant prostate cancer (PCa) and for monitoring men with known prostate cancer under active surveillance. MSAC noted that the clinical claim made was that mpMRI of the prostate would be as accurate and safer than the current approach to diagnosis and monitoring.

MSAC noted that approximately 20,000 new cases of PCa were diagnosed in 2012. MSAC noted that while prostate-specific antigen (PSA) levels and/or digital rectal examination (DRE) can raise the suspicion of PCa, a biopsy is required to make the diagnosis. The MBS subsidises transrectal ultrasound guided biopsy (TRUSGB) or transperineal ultrasound guided biopsy (TPUSGB) for diagnosis of PCa under MBS item 37219. MSAC noted that these are invasive tests with associated risks. MSAC noted that the number of services under MBS item 37219 has been falling despite the ageing population. In 2010-2012 there were ~26,500 services provided per year, compared to ~19,800 in 2015. MSAC noted that mpMRI of the prostate became available in Australia after 2012, and suggested that this may indicate that men are already accessing mpMRI to avoid biopsy or declining to undergo biopsy altogether.

MSAC noted that there were two populations under consideration:

- Population 1: men suspected of having PCa on the basis of a high or concerning PSA level - these men had not previously undergone either TRUSGB or TPUSGB. The comparator for this population was PSA/DRE + clinical judgement and TRUSGB/TPUSGB or, in men who choose not to undergo TRUSGB/TPUSGB, PSA/DRE + clinical judgement alone.
- Population 2: men diagnosed with low- or intermediate-risk PCa who have undertaken active surveillance (AS). By definition these men have already undergone biopsy. The comparator for this population was routine TRUSGB/TPUSGB at intervals specified in current guidelines.

MSAC noted that there are no significant safety concerns when using MRI in appropriately selected patients. MSAC noted that mpMRI is a non-invasive imaging technique while TRUSGB/TPUSGB are invasive and expose men to a risk of complications and harms including infection, bleeding and urinary obstruction. While MSAC noted that risks were lower for TPUSGB than TRUSGB, the evidence presented indicated up to 5.5% of patients are re-hospitalised post TRUSGB/TPUSGB while up to 2.4% and up to 6.9% of patients have a major or minor infection, respectively, post TRUSGB. On the basis of these different risk profiles, MSAC accepted that mpMRI had superior safety to TRUSGB/TPUSGB.

MSAC noted that much of the evidence presented in the application to support the clinical effectiveness of mpMRI was of low quality. MSAC noted that there were no studies in either population 1 or population 2 that assessed changes in management due to mpMRI. As a result, a linked evidence approach was undertaken to estimate any change in health outcomes.

MSAC considered the diagnostic accuracy of mpMRI for detecting clinically significant PCa (defined as a Prostate Imaging Reporting and Data System [PI-RADS] score of 4 or 5) in population 1. The sensitivity of mpMRI compared with biopsy was 74.4% (95% confidence interval [CI] 51.0–89.1%) and specificity was 84.1% (95% CI 75.0–90.3%). MSAC noted that the wide confidence interval around the sensitivity point estimate reflected uncertainty and heterogeneity in the results. MSAC acknowledged that a recently published meta-

analysis reported a higher pooled sensitivity of 89% with a narrower range (95% CI 86–92%) in studies using the updated PI-RADS v.2 (Woo S et al 2017).

MSAC noted that for the purposes of this application, it was assumed that the introduction of mpMRI would not alter the rest of the clinical treatment algorithm. MSAC noted that if mpMRI indicated that a patient had a PI-RADS score of 4 or 5, he would undergo biopsy. For most men with a PI-RADS score of 1–3, biopsy would be avoided. The exception would be if they were considered to be of high concern because of risk factors such as a family history of PCa or *BRCA* gene mutation, a free/total PSA ratio < 12% or PSA density > 0.15. MSAC noted that the applicants had advised that 20% of men with a PI-RADS score of 1–3 on mpMRI would fall within this group and would receive a biopsy despite the mpMRI result. Therefore, the main impact of mpMRI would be avoidance of biopsy and overtreatment (and its potential associated adverse effects including incontinence, impotence or anorectal problems) in men without significant PCa. MSAC noted that another potential impact would be delayed treatment if the mpMRI wrongly categorised the patient as PI-RADS 1–3 (false negative).

MSAC accepted that if the prevalence of clinically significant PCa in population 1 was 35.5%, use of mpMRI in 1000 men would avoid 505 biopsies and avoid overtreatment of insignificant disease in 94 men. However, it would result in a treatment delay of clinically significant disease in 54 men. MSAC noted that the delayed diagnosis may not impact disease progression and mortality although the quality of evidence to support this was very low. MSAC acknowledged the applicants' claim that the number of men at risk of delayed treatment is likely to be lower than 54 because 20% of men with a PI-RADS score of 1–3 would undergo biopsy due to high concern.

On the basis of the presented evidence, MSAC accepted that mpMRI had superior safety to TRUSGB/TPUSGB and non-inferior effectiveness in population 1. MSAC noted that the economic model suggested use of mpMRI in population 1 would slightly reduce benefits when compared with biopsy (0.039 quality adjusted life years [QALYs] lost [~2.0 weeks]) but was less expensive. Use of mpMRI in population 1 resulted in a saving of \$40,363 per QALY lost. MSAC noted that, in the majority of the sensitivity analyses conducted, use of mpMRI remained cost saving at the expense of a small QALY reduction. The exception was if a shorter time horizon of 5 or 10 years was used instead of a lifetime horizon. In these analyses mpMRI was dominant (more effective and less expensive) than TRUSGB/TPUSGB.

MSAC noted the sensitivity of mpMRI for detecting clinically significant PCa in population 2 was 79.3% (95% CI 74.6–83.3%) and specificity was 55.1% (95% CI 50.4–59.8%). MSAC noted that mpMRI would be used to upgrade disease in patients on an active surveillance program. If mpMRI indicated that a patient in population 2 had a PI-RADS score of 4 or 5, he would undergo biopsy. For most men with a PI-RADS score of 1–3, biopsy would be avoided and they would continue in the active surveillance program — if there were a high clinical concern of upgraded disease, they would still undergo biopsy. MSAC noted that the main impact of mpMRI in population 2 would be avoidance of biopsy in men without higher-grade PCa or delayed diagnosis of upgraded disease if the mpMRI wrongly categorised the patient as PI-RADS 1–3 (false negative).

MSAC accepted that if 30% of men in an active surveillance program had their disease upgraded, use of mpMRI in 1,000 men in population 2 would avoid 358 biopsies but would result in a delay in diagnosing upgraded disease in 31 men. Once again MSAC acknowledged the applicants' claim that the number of men at risk of delayed diagnosis of upgraded disease may be lower if men of high concern are biopsied despite having a PI-RADS score of 1–3.

On the basis of the presented evidence, MSAC accepted that mpMRI had superior safety to TRUSGB/TPUSGB and non-inferior effectiveness in population 2. MSAC noted that the economic model suggested use of mpMRI in population 2 would result in marginally less benefit than biopsy (loss of 0.001 QALY [~0.3 days]) but was less expensive. Use of mpMRI in population 2 resulted in a saving of \$232,269 per QALY lost. MSAC noted that in the majority of the sensitivity analyses conducted, use of mpMRI remained cost saving at the expense of a small QALY reduction. However, mpMRI was dominant (more effective and less expensive) than TRUSGB/TPUSGB if the time horizon was shortened from lifetime to 5 or 10 years; if the disutility associated with TRUSGB/TPUSGB was greater; if the probability of progressing from insignificant to significant PCa was lower; or if the patient was older when he entered the model.

MSAC noted that listing mpMRI in populations 1 and 2 would result in a net cost of approximately \$2.8 million per year to the MBS but a net saving of approximately \$8.1 million to the health system as a whole (including costs to the MBS, other health funders and patient co-payments). These costs were based upon 20,149 mpMRI procedures per year - 13,276 in population 1 and 6,873 in population 2 - at an MBS cost of \$12.1 million per year. These costs were offset by \$9.3 million in avoided TRUSGB/TPUSGB.

MSAC noted that the financial estimates relied upon an assumption that the number of mpMRIs would be similar to the number of TRUGB/TPUSGB biopsies claimed on the MBS (approximately 20,000 per year). However, MSAC noted that using MBS claims for TRUSGB/TPUSGB was likely to underestimate the number of men eligible for mpMRI because some men refuse TRUSGB/TPUSGB; some men are already paying for mpMRI privately; and because of the ageing population. MSAC noted that while sensitivity analyses of the financial impact of listing mpMRI indicated it would be a cost saving for the health system as a whole in most scenarios, increasing the number of patients who had an mpMRI in population 1 from 13,276 men to 20,000 men per year resulted in a net cost to the health system as a whole of \$4.65 million per year.

MSAC noted that the application did not include the following populations: 1) men with suspected PCa who have had a negative biopsy; 2) men with a known diagnosis of PCa in whom mpMRI was being used to stage disease or plan treatment; or 3) men with suspected recurrent PCa after curative intent treatment. However, MSAC acknowledged that leakage to these populations, particularly for staging or treatment planning, was likely. While MSAC considered that some of this leakage could be contained through the item descriptor, the Committee was unable to identify a way to prevent use of the item for these populations. MSAC noted that some newer therapies, in particular partial gland therapy, relied upon imaging of the prostate. MSAC also noted that the Applicants had argued that clinical staging of PCa was inaccurate and that it would be exceptional for a patient to receive treatment without having undergone imaging.

MSAC also noted that the availability of mpMRI could increase the attractiveness of using PSA for screening and therefore increase rates of PSA testing. MSAC suggested that it may be more difficult to deter clinicians from inappropriately using PSA testing for screening purposes if the follow-up test is non-invasive in nature (mpMRI), in contrast to the existing invasive TRUSGB/TPUSGB procedures. MSAC noted that any increase in the use of PSA for screening could therefore further increase the use of mpMRI above that estimated in the application. MSAC indicated that while restricting the authority to request mpMRIs to specialists only and limiting the number of mpMRIs performed per patient over a year may help to prevent this, it was unlikely that such measures would fully address these concerns.

MSAC recommended modelling of the financial impact of use outside the proposed populations, using a scenario that assumes all men with early-stage PCa receive an mpMRI. MSAC suggested that information on the use of PSA testing, the proportion of men with a high or concerning PSA levels requiring further investigation, estimates of the number of men diagnosed with early PCa and trends in the use of TRUSGB/TPUSGB would be useful to inform the model. MSAC suggested that such information and modelling could be undertaken by the Department for consideration at the July 2017 MSAC meeting.

MSAC questioned the suggested fee of \$600, which is based upon the current market price, and is higher than the MBS fees for similar MRI procedures (e.g. item 63476 MRI scan of the pelvis for the initial staging of rectal cancer: ~\$403). MSAC noted that the applicants did not provide any justification as to why the market fee of \$600 should be accepted and indicated that the financial impact estimates to be undertaken should use \$400 as the fee.

MSAC noted that there may be issues with inter-reader reliability when using mpMRI to determine PI-RADS scores. In studies in which different readers reviewed the same mpMRI images to separately assign a PI-RADS score, the kappa statistic measuring agreement between the readers ranged from 0.48 to 0.81 (a kappa of 1.0 indicates complete agreement between readers). MSAC noted that the introduction of PI-RADS v.2 may have improved inter-reader reliability. However, MSAC recommended that an accreditation and training program, specific to imaging of the prostate, would need to be implemented. MSAC indicated a preference that this program be in place before mpMRI is listed on the MBS. MSAC noted that the Royal Australian and New Zealand College of Radiologists (RANZCR) had indicated that it was currently working on quality assurance measures for mpMRI.

MSAC noted that men are already accessing mpMRI privately and that this raised issues of equity of access due to an individual's ability to pay out of pocket costs.

5. Background

The initial application (1397: Prostate MRI) was reviewed by the Protocol Advisory Subcommittee (PASC) in April 2015 and August 2015. PASC advised that the initial application should be split into two applications:

1. Intervention for Diagnostic mpMRI; and
2. Intervention for MR-guided biopsy.

There is now a separate application for mpMRI prostate diagnostic scans for diagnosis of prostate cancer (MSAC application 1397) and MR-guided biopsy procedures for diagnosis of prostate cancer (MSAC application 1424).

MSAC also considered Application 1424 at its April 2017 meeting. Further information can be found in the Public Summary Document on the MSAC website.

6. Prerequisites to implementation of any funding advice

MRI systems are registered with the Therapeutic Goods Administration (TGA) on the Australian Register of Therapeutic Goods (ARTG).

7. Proposal for public funding

The proposed MBS item descriptors are summarised in Table 1.

Table 1 Proposed MBS item descriptors

Category 5 – Diagnostic Imaging Services
<p>MBS [item number] Multiparametric Magnetic Resonance Imaging (mpMRI) performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by an urologist, radiation oncologist, or medical oncologist and where:</p> <p>a) a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated) is used; and</p> <p>b) the man is suspected of having prostate cancer on the basis of a high or concerning PSA.</p> <p>Scan of the prostate for:</p> <p>– detection of cancer (R)(Contrast)</p> <p>Fee: [Applicant advises that current fee charged is \$600]</p> <p>[Relevant explanatory notes]</p>
<p>MBS [item number] Multiparametric Magnetic Resonance Imaging (mpMRI) performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by an urologist, radiation oncologist, or medical oncologist and where:</p> <p>a) a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated) is used; and</p> <p>b) the man has an existing diagnosis of low or intermediate risk prostate cancer and is undertaking Active Surveillance.</p> <p>Scan of the prostate for:</p> <p>– assessment of cancer (R)(Contrast)</p> <p>Fee: [Applicant advises that current fee charged is \$600]</p> <p>[Relevant explanatory notes]</p>

The applicant pre-MSAC response suggested amending the first descriptor to include:

Patients who are suspected of having prostate cancer on the basis of any of the following

- a. a PSA level greater than 3mg/L (or lower level in men younger than 50 years); or
- b. a positive family history (includes breast cancer [*BRCA*] gene mutation); or
- c. a free/total PSA ratio less than 25 per cent; or
- d. abnormal DRE.

For the second descriptor, the applicant pre-MSAC response noted that this group will need one scan every 12 months.

8. Summary of Public Consultation Feedback/Consumer Issues

Feedback on the Consultation Protocol was received from peak bodies (seven responses), organisations (three responses), specialists (six responses), a researcher (1 response) and consumers (3 responses).

Issues raised in the responses were:

- The indications should await the final recommendations of the multi-disciplinary national working party (NHMRC / CCA / PCFA / USANZ / RACGP / RCPA). However in general terms: (i) elevated PSA should be confirmed by resampling; (ii) in the range 3.0-5.5 mg/L, free PSA should be considered; (iii) PSA doubling time (velocity) is not recommended at this stage and (iv) digital rectal examination (DRE) is not supported as a screening test.
- Specialist referral should be required from a urologist, radiation oncologist, or medical oncologist.

- The feasibility of measuring change in overall survival and change in prostate cancer specific mortality is very doubtful for a cancer with such a long natural history as prostate cancer (typically >10 years from diagnosis to death).

9. Proposed intervention's place in clinical management

In Population 1, mpMRI is intended to be used as an additional triage tool following an abnormal PSA/DRE, to determine the need for biopsy. Based on the results of the mpMRI scan:

- patients with a PI-RADS score of 4 or 5 will have a biopsy
- low concern patients with a PI-RADS score of 1-3 will avoid biopsy, and either return to primary care with no further follow-up, or remain under observation.
- high concern patients with a PI-RADS score of 1, 2, or 3 will have a systematic biopsy.

In Population 2, mpMRI is proposed as an additional triage test in the AS pathway, to determine the need for prostate biopsy. Based on the results of the mpMRI scan:

- patients with a PI-RADS score of 4 or 5 will have a biopsy
- low concern patients with a PI-RADS score of 1-3 will avoid biopsy and remain on active surveillance.
- high concern patients with a PI-RADS score of 1, 2, or 3 will have a systematic biopsy.

10. Comparator

Within current Australian practice, PCa is usually suspected on the basis of a PSA test and/or a DRE. However, these are not diagnostic tests. The diagnosis of PCa is obtained using either TRUSGB or TPUSGB.

In Population 1, the nominated comparators are:

- PSA/DRE + clinical judgement and TRUSGB or TPUSGB; and
- PSA/DRE + clinical judgement alone, for patients who elect not to undergo TRUSGB or TPUSGB.

In Population 2, the nominated comparator is the current AS protocol with periodic TRUSGB or TPUSGB.

The reference standard for this assessment of mpMRI is histopathology of prostate samples collected via biopsy.

11. Comparative safety

No adverse events associated with mpMRI were identified in the literature.

Adverse events - Trans-rectal biopsy

Patient re-hospitalisation due to trans-rectal biopsy ranged from 0.4 to 5.5 per cent. Major infection ranged from 0.2 to 2.4 per cent. Minor infection ranged from 0.7 to 6.9 per cent. Incidence of bleeding related events (haematuria, hemochezia, or haemospermia) ranged from 0.8 to 88.0 per cent. Urinary obstruction or difficulty voiding ranged from 0.8 to 21.0 per cent. Two deaths due to sepsis resulting from a trans-rectal biopsy-related infection were identified in the literature.

Adverse events - Trans-perineal biopsy

Re-hospitalisation after TPUSGB ranged from 0.7 to 2.1 per cent. Minor infection was reported in 0.03 per cent of patients; no major infection was reported. Other adverse events reported were urinary obstruction (in 0.4 to 38 per cent of patients), and bleeding in 0.1 to 6.1 per cent. The majority of studies reported that no infection occurred. No reports of deaths related to trans-perineal prostate biopsy were identified.

Based on avoidance of harms associated with biopsy under the proposed algorithms, it is suggested mpMRI has superior safety to TRUSGB or TPUSGB.

Based on avoidance of harms associated with biopsy under the proposed algorithms, it is suggested mpMRI has superior safety to TRUSGB.

12. Comparative effectiveness

No studies were identified that assessed the direct evidence of mpMRI in either population; therefore, a linked evidence analysis was performed.

Accuracy

Biopsy (including TRUSGB, TPUSGB or cognitive MRIGB with TRUSGB) was used as the reference standard in all of the included diagnostic accuracy studies. Summary statistics for Population 1 and Population 2 are provided in Table 2 and Table 3. In Population 1, the point estimates for sensitivity were associated with wide confidence intervals, reflecting uncertainty in the results. Heterogeneity was high, particularly for sensitivity. Subgroup analysis to identify the cause of the heterogeneity could not be performed due to the small number of included studies. Five of the key diagnostic accuracy studies reported Cohen's kappa (κ) to describe inter-reader reliability. The kappa values range from 0.48-0.81, with a median of 0.63. (Including 4 additional studies range 0.34-0.81.). The results suggest reliability may be an issue with mpMRI and this may therefore explain the observed heterogeneity in the estimates of sensitivity and specificity. The quality for the diagnostic accuracy outcomes was rated as 'low' using the GRADE tool. This reflects the issues with imprecision and inconsistency in the evidence base.

The applicant pre-MSAC response noted that with the introduction of the PIRADS v.2 in 2015, the pooled sensitivity has increased and the confidence intervals have narrowed, but specificity is unaltered. PIRADS v.2 was introduced jointly by the European Society of Urogenital Radiologists (ESUR) and the American College of Radiologists (ACR). Woo et al, European Urology January 2107, is a systematic review and a diagnostic meta-analysis which includes 3857 patients and the pooled sensitivity was 0.89 (95% CI 0.86-0.92).

Table .

Table 2 Summary statistics for mpMRI against biopsy (TRUSGB, TPUSGB or cognitive MRIGB) in Population 1 (assumed disease prevalence of 35.5% for clinically significant PCa)

Accuracy	mpMRI (n=1,024, k=4)
Sensitivity, % [95% CI]	74.4% [51.0, 89.1]
Specificity, % [95% CI]	84.1% [75.0, 90.3]
PPV, % [95% CI]	73.0 % [64.2, 80.4]
NPV, % [95% CI]	85.2% [77.6, 90.5]

PPV = positive predictive value, NPV = negative predictive value, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, CI = confidence interval.

In Population 1, the point estimates for sensitivity were associated with wide confidence intervals, reflecting uncertainty in the results. Heterogeneity was high, particularly for sensitivity. Subgroup analysis to identify the cause of the heterogeneity could not be performed due to the small number of included studies. Five of the key diagnostic accuracy studies reported Cohen's kappa (k) to describe inter-reader reliability. The kappa values range from 0.48-0.81, with a median of 0.63. (Including 4 additional studies range 0.34-0.81.). The results suggest reliability may be an issue with mpMRI and this may therefore explain the observed heterogeneity in the estimates of sensitivity and specificity. The quality for the diagnostic accuracy outcomes was rated as 'low' using the GRADE tool. This reflects the issues with imprecision and inconsistency in the evidence base.

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Table 3 Summary statistics for mpMRI against biopsy (TRUGB, TPUSGB or cognitive MRIGB) in Population 2 (assumed prevalence of disease upgrade of 30%)

Accuracy	mpMRI (n=820, k=6)
Sensitivity, % [95% CI]	79.3 [74.6, 83.3]
Specificity, % [95% CI]	55.1 [50.4, 59.8]
PPV	59.4 [53.5, 65.0]
NPV	76.2 [70.1, 81.4]

PPV = positive predictive value, NPV = negative predictive value, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, CI = confidence interval.

In Population 2, results for mpMRI are consistent and there is no apparent heterogeneity. The quality of the diagnostic accuracy outcomes for Population 2 was rated as ‘high’ using the GRADE tool.

There were no applicability issues identified between the included studies and the proposed population in the Protocol. Only studies that used a consistent threshold for PI-RADS scoring as stated in the Protocol (\geq PI-RADS 4 for a positive result), and that stratified results for clinically significant and insignificant PCa, were included in this analysis.

Therapeutic efficacy (change in management)

There was no evidence identified assessing a change in management due to mpMRI. The proposed changes to management due to mpMRI are:

- Avoidance of biopsy in most patients with a negative mpMRI
- Avoidance of treatment of insignificant PCa for some patients
- Delay to the diagnosis and treatment of clinically significant disease

Therapeutic effectiveness (health benefit from change in management)

A selection of the key health outcomes associated with mpMRI in Population 1 are summarised in Table 4.

Patients who have clinically insignificant cancer who have a PI-RADS 1-3 on mpMRI may avoid overtreatment of their disease as data shows that approximately half of patients in this group currently receive treatment in Australia despite being eligible for active surveillance programs. Prostate cancer treatment exposes the patient both to immediate complications due to the procedures (surgical complications and/or radiation toxicity). In addition some patients experience long term adverse outcomes following treatment, mostly urinary incontinence, erectile dysfunction and bowel urgency. Avoidance of overtreatment of insignificant disease will reduce the incidence of these complications and improve quality of life for these patients.

Patients who receive a false negative mpMRI will experience a delay to treatment for clinically significant disease. It is not clear that this delay is associated with any adverse outcomes for patients (Subsection B5). The evidence base to inform patient outcomes following delayed treatment is considered very low quality and is based on observational evidence.

Overall, it is expected that for every 1,000 patients in Population 1 the proposed mpMRI pathway will enable 505 patients to avoid a biopsy and 94 patients to avoid overtreatment of insignificant disease, but result in a delay to treatment of clinically significant disease in 54 patients.

Table 4 Population 1: Selected findings for the linked evidence comparison of mpMRI, relative to TRUSGB or TPUSGB, in patients with suspected prostate cancer with assumed pre-test probability (prevalence) of 35.5% for clinically significant PCa.

Outcomes Meaning PI-RADS score	Patients/ Studies	Quality of evidence ^a	No. per 1000 patients with mpMRI ^b	No. per 1000 patients results of biopsy after mpMRI	No. per 1000 patients with comparator (all patients get biopsy) ^c	Comments
True positives Clinically significant PCa PI-RADS 4/5	1,024 patients (4 studies)	⊕⊕⊙⊙	264	215	270	Will undergo biopsy under both proposed and current pathways
False positives No PCa PI-RADS 4/5	1,024 patients (4 studies)	⊕⊕⊙⊙	32	0	0	Will undergo biopsy under both proposed and current pathways
False positives Insignificant PCa PI-RADS 4/5	1,024 patients (4 studies)	⊕⊕⊙⊙	70	80	174	Will undergo biopsy under both proposed and current pathways
True negatives No PCa PI-RADS 1-3	1,024 patients (4 studies)	⊕⊕⊙⊙	403	435	435	Potential to avoid biopsy
True negatives Insignificant PCa PI-RADS 1-3	1,024 patients (4 studies)	⊕⊕⊙⊙	140	131	36	Potential to avoid biopsy and adverse effects of overtreatment.
False negatives Clinically significant PCa PI-RADS 1-3	1,024 patients (4 studies)	⊕⊕⊙⊙	91	139	85	Potential to avoid biopsy. These patients will experience a delay to treatment.
Major infection	45,492 patients (8 studies)	⊕⊕⊙⊙	0	NA	TRUSGB: Range 0-20 TPUSGB: 0	Adverse event associated with biopsy
Overall survival	41,146 (5 studies)	⊕⊙⊙⊙	NA	NA	NA	Treatment delay did not impact overall survival (results from 5 studies).
24 month impotence	1 systematic review, 2,365 patients	⊕⊕⊙⊙	4-11 patients	5-13 patients	11-27 patients	Erectile dysfunction experience by an additional 11-28% of patients following PCa treatment compared to those undergoing watchful waiting.
24 month incontinence	1 systematic review, 2,365 patients	⊕⊕⊕⊙	5-16 patients	6-18 patients	12-39 patients	Urinary incontinence experience by an additional 12-40% of patients following PCa treatment compared to those undergoing watchful waiting.

^a GRADE Working Group grades of evidence (Guyatt et al. 2013).

Note the full version of this table is presented in Subsection B8

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^b A prevalence of clinically significant PCa of 35.5% was sourced from Pokorny et al. For the detection of insignificant PCa mpMRI has a sensitivity of 0.332 (95% CI [0.195, 0.504])

^c Calculated using the reported sensitivity of TRUSGB biopsy for detection of significant PCa of 0.76 (95% CI [0.64, 0.84]), a sensitivity of 0.83 (95% CI [0.77, 0.87]) for the detection of insignificant disease and assuming TRUSGB had a specificity of 100%.

TRUSGB = trans-rectal ultrasound-guided biopsy, TPUSGB = trans-perineal ultrasound-guided biopsy, NA = not applicable, CI = confidence interval.

A selection of the health outcomes associated mpMRI in Population 2 are summarised in Table 5.

Patients who have a false negative mpMRI will have their treatment delayed and remain on AS. One observational study was identified that assessed the impact of delayed treatment in this population and the quality of evidence was rated very low using the GRADE tool.

Overall, assuming 30 per cent of patients in active surveillance programs will have their disease upgraded to require treatment, then for every 1,000 patients on surveillance programs, 358 patients will avoid a biopsy under the proposed mpMRI monitoring pathway. A total of 31 additional patients will experience a delay to disease upgrade being diagnosed under the proposed management. These numbers account for 20 per cent of patients with a negative mpMRI will have a biopsy due to meeting the criteria for 'high concern', as estimated by the applicant. If, as the applicant advises, the incidence of disease upgrade decreases over time with better targeting of patients for active surveillance, then the number of avoided biopsies would be expected to increase.

The relative safety of mpMRI and biopsy are discussed above for Population 1. There is no evidence that the relative harms associated with mpMRI and biopsy will be any different in Population 2 than those described above for Population 1, therefore mpMRI is suggested to have superior safety than TRUSGB and/or TPUSGB.

Table 5 Population 2: Summary of findings for the linked evidence comparison of mpMRI, relative to TRUSGB or TPUSGB, in patients on active surveillance with assumed pre-test probability (prevalence) for upgraded disease of 30%

Outcomes	Patients/Studies	Quality of evidence ^a	No. per 1000 patients with mpMRI ^b	No. per 1000 patients with biopsy following mpMRI	No. per 1000 patients with biopsy only ^c	Comments
True positives	820 patients (6 studies).	⊕⊕⊕⊕	238	190	280	Will undergo biopsy as under current management.
False positives	820 patients (6 studies).	⊕⊕⊕⊕	314	0	0	Will undergo biopsy as under current management.
True negatives	820 patients (6 studies).	⊕⊕⊕⊕	386	386	655	Potential to avoid biopsy
False negatives	820 patients (6 studies).	⊕⊕⊕⊕	62	101	70	Potential to avoid biopsy but possible detriment due to delayed treatment.
Positive surgical margins	219 patients (1 study).	⊕⊙⊙⊙	NA	NA	NA	There is no evidence that delayed treatment increases the rate of positive surgical margins.

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

Note this is a summary of key outcomes, for the full table of outcomes see Subsection B8 of the report

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^b: A prevalence of PCa upgrade of 30% was provided by the Applicant. Only low-concern patients have been included in this assessment as there is no change in management for patients at high-concern, regardless of mpMRI results.

^c: Calculated using the reported sensitivity of TRUSGB biopsy of 0.81 (95% CI [0.70, 0.88]) and assuming TRUSGB had a specificity of 100%

TRUSGB = trans-rectal ultrasound-guided biopsy, TPUSGB = trans-perineal ultrasound-guided biopsy, NA = not applicable, CI = confidence interval.

Clinical Claim

Prostate mpMRI is claimed to have equivalent diagnostic accuracy and an improved safety profile compared to the current approach. More accurate selection of patients for biopsy will reduce diagnosis and overtreatment of low-risk disease.

13. Economic evaluation

The application presented a cost-utility analysis to quantify the trade-off between mpMRI costs and benefits. A summary of the economic evaluation is shown in Table 6.

Table 6 Summary of the economic evaluation

Perspective	Health care perspective (Australia); Out of pocket costs for patients.
Comparator	TRUSGB/TPUSGB
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Systematic review and meta-analysis of clinical trials [Section B] Targeted review for utility parameters [Section C] Expert opinion was elicited where no data were available
Time horizon	Lifetime time horizon (25 years) in the model base-case
Outcomes	QALYG
Methods used to generate results	Combined decision tree and Markov model using cohort expected value analysis
Health states	No prostate cancer Insignificant prostate cancer, undiagnosed Insignificant prostate cancer, diagnosed: active surveillance Insignificant prostate cancer, diagnosed: treated Significant prostate cancer, undiagnosed Significant prostate cancer, diagnosed Advanced prostate cancer Death
Cycle length	1 year
Discount rate	5% for costs and outcomes
Software packages used	TreeAge Pro 2015

MBS = Medical Benefit Schedule, TRUSGB = Trans-rectal ultrasound guided biopsy, TPUSGB = Trans-perineal ultrasound guided biopsy; QALYG = Quality-adjusted life-years gained.

The mpMRI can either be introduced in Population 1, or in Population 2, or in both. For each of these options, Table 6 provides the overall costs, outcomes, incremental costs and incremental outcomes for mpMRI and prostate biopsy as per the model. The table also provides the mean number of biopsies per patient in the model, for each of the strategies. A comparison of the findings from Gordon et al. (2016) and this assessment for Population 1 are also presented.

Table 7 Results of the economic evaluation

		Cost	Effectiveness (QALYs)	ICER	Mean number of biopsies per patient		
					population 1	population 2	population 1 and 2
Population 1 only							
Intervention	mpMRI in Population 1, prostate biopsy in Population 2	\$16,947	7.237	\$40,363 saved per QALY lost with mpMRI in population 1	0.52	3.02	1.07
Comparator	Prostate biopsy in Population 1 and 2.	\$18,521	7.276		1.00	3.15	1.70
Increment		-\$1,574	-0.039		0.48 biopsies avoided	0.13 biopsies avoided	0.63 biopsies avoided
Population 2 only							
Intervention	Prostate biopsy in Population 1, mpMRI in Population 2.	\$18,289	7.275	\$232,269 saved per QALY lost with mpMRI in population 2	1.00	1.96	1.44
Comparator	Prostate biopsy in Population 1 and 2.	\$18,521	7.276		1.00	3.15	1.70
Increment		-\$232	-0.001		0 No biopsies avoided	1.19 biopsies avoided	0.26 biopsies avoided
Both populations							
Intervention	mpMRI in Population 1 and 2.	\$16,774	7.236	\$43,684 saved per QALY lost with mpMRI in both populations	0.52	1.87	0.86
Comparator	Prostate biopsy in Population 1 and 2.	\$18,521	7.276		1.00	3.15	1.70
Increment		-\$1,747	-0.040		0.48 biopsies avoided	1.28 biopsies avoided	0.84 biopsies avoided
Gordon et al. (2016): Population 1							
Intervention	Strategy 2: mpMRI ≠ MRIGB	\$24,943	7.7		1.14		
Comparator	Strategy 1: TRUSGB	\$24,203	7.82		1.44		
Increment		\$740	-0.12	Dominated	0.3 biopsies avoided		
Intervention	Strategy 3: mpMRI ≠ TRUSGB/ TPUSGB or MRIGB	\$24,337	7.77		1.10		
Comparator	Strategy 1: TRUSGB	\$24,203	7.82		1.44		
Increment		\$134	-0.05	Dominated	0.34 biopsies avoided		

ICER = incremental cost-effectiveness ratio, mpMRI = multiparametric MRI, MRIGB = magnetic resonance guided biopsy, QALY = Quality adjusted life-year, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

Source: CA 1397 base model; Table 12 p33 Gordon et al. (2016)

The results in Table 7 show that the strategies with mpMRI are less expensive than the strategies without mpMRI. This is predominantly due to the avoided biopsies, which were assumed to cost substantially more (\$2400) than an mpMRI (\$600), and associated services (e.g., hospitalisation, anaesthesia, pathology), based on data provided by the Department of Health and in the DAP. The introduction of mpMRI in Population 1 as well as Population 2 slightly reduces the overall number of QALYs. When mpMRI would be listed for use in both populations, this would save on average \$43,684 per QALY lost in the base case.

For each of the strategies, mpMRI reduces the average number of biopsies needed per patient. This reduction is largest where mpMRI is introduced for both Population 1 and 2, resulting in an average of 0.84 biopsies avoided per patient. Key drivers of the economic model are provided in Table .

Table 8 Key drivers of the economic model

Description	Method/Value	Impact
Time horizon	5 and 10 years instead of 25	High, favours intervention
Cost and disutility associated with prostate biopsies	\$600 instead of \$2,400.00 -0.05 instead of -0.035	Moderate, favours intervention Moderate, favours comparator
Probability of progression from insignificant to significant prostate cancer	0.05 instead of 0.088 per year	Moderate, favours comparator

MRIGB = magnetic resonance imaging guided biopsy; mpMRI = multiparametric MRI; PI-RADS = Prostate Imaging Reporting and Data System.

Similar to the current assessment, Gordon et al. (2016) found a reduction in the number of QALYs associated with using mpMRI in Population 1. Gordon et al. (2016) did not evaluate the use of mpMRI in population 2. Contrary to the current assessment, Gordon et al. (2016) found that the use of mpMRI was associated with higher costs than prostate biopsy. Gordon et al. (2016) assumed an average cost of \$600 instead of \$2400 per TRUS-guided biopsy. The modelled mean numbers of biopsies avoided in Population 1 are higher (0.48) in the current assessment compared to in Gordon et al. 2016 (0.34).

14. Financial/budgetary impacts

A combination of the market share approach (in Population 1 and 2) and the epidemiological approach (in Population 2) were used to estimate the financial implications of the introduction of mpMRI. The additional costs of mpMRI are offset by a reduction in prostate biopsies.

The financial implications to the MBS resulting from the proposed listing of mpMRI for prostate cancer are summarised in Table 9.

Table 9 Total costs to the MBS and other health care funders associated with mpMRI for prostate cancer.

Costs of listing mpMRI	Yearly costs (Year 1 to Year 5)			Over 5 years (Total, Year 1-5)		
	Population 1	Population 2	Total	Population 1	Population 2	Total
Number of services (mpMRI)	13,276	6,873	20,149	66,380	34,365	100,745
Number of services (prostate biopsy, sig. PCa)	6,904	4,080	10,984	34,518	20,401	54,918
Total MBS cost per year (mpMRI +prostate biopsy, significant PCa)	\$14,958,866	\$8,257,004	\$23,215,870	\$74,794,329	\$41,285,020	\$116,079,349
Total costs for other healthcare funders	\$6,972,332	\$4,120,831	\$11,093,163	\$34,861,658	\$20,604,157	\$55,465,815
Total co-payments per year	\$3,797,691	\$2,156,923	\$5,954,614	\$18,988,453	\$10,784,616	\$29,773,069
Total direct costs	\$25,728,888	\$14,534,759	\$40,263,647	\$128,644,440	\$72,673,793	\$201,318,233

Cost of prostate biopsies minus cost of listing mpMRI

Cost to the MBS	\$1,510,278	\$1,294,655	\$2,804,933	\$7,551,389	\$6,473,275	\$14,024,664
Cost savings to other health care funders	-\$6,435,998	-\$2,820,676	-\$9,256,675	-\$32,179,992	-\$14,103,380	-\$46,283,373
Costs savings of total direct costs	-\$6,133,512	-\$1,960,441	-\$8,093,953	-\$30,667,560	-\$9,802,207	-\$40,469,767

mpMRI = multiparametric MRI, MBS = Medicare Benefits Schedule, PCa = prostate cancer.

The assessment report stated that listing mpMRI for Population 1 and 2 would result in a reduced number of biopsies and an estimated total savings of all direct costs of \$8.1 million per year, which includes those borne by the MBS, other health care funders and patient co-payments.

The total cost to the MBS of listing mpMRI for both populations was estimated to be \$23 million per year (\$15 million and \$8.3 million per year for Population 1 and 2 respectively). The financial implications are based on the assumption that 20,149 services for mpMRI would be claimed each year which is likely to be an underestimation.

The Applicant's pre-MSAC response queried whether the economic analysis may have underestimated the cost savings to the community and provided estimates of the yearly savings to the community to be between \$24 million and \$92 million per year.

15. Key issues from ESC for MSAC

ESC noted that there are no significant safety concerns when using MRI in appropriately selected patients. ESC noted that transrectal ultrasound guided biopsy (TRUSGB) or transperineal ultrasound guided biopsy (TPUSGB) exposed men to risk of harms including infection, bleeding and urinary obstruction and that infection rates were lower for TPUSGB than TRUSGB.

ESC noted that TRUSGB/TPUSGB are imperfect reference standards and that the impact this has upon the evaluation of mpMRI is uncertain.

ESC noted that there are two populations included in this application:

- Population 1 who are men suspected of having PCa on the basis of a high or concerning prostate-specific antigen (PSA) level. ESC noted that by definition these men had not previously undergone either TRUSGB or TPUSGB; and
- Population 2 who are men diagnosed with low or intermediate risk PCa on an active surveillance (AS) program. ESC noted that these men are a subset of population 1.

ESC noted that the primary outcome for population 1 was changed from diagnosis of PCa to diagnosis of clinically significant PCa after consultation with the Applicant and the Department.

ESC noted the sensitivity (74.4%; 95% confidence interval [CI] 51.0–89.1%) and specificity (84.1%; 95% CI 75.0–90.3%) of mpMRI for detecting clinically significant PCa in population 1 compared with biopsy. ESC noted that the confidence interval around the sensitivity point estimate was wide reflecting uncertainty and heterogeneity in the results.

ESC noted that mpMRI had superior safety when compared with TRUSGB/TPUSGB in population 1. For every 1,000 men, use of mpMRI would avoid 505 biopsies and avoid overtreatment of insignificant disease in 94 men. However, it would result in a treatment delay of clinically significant disease in 54 men. ESC noted that the delayed diagnosis may not impact disease progression and mortality although the quality of evidence to support this was very low.

ESC noted that the economic model suggested use of mpMRI in population 1 would be slightly less effective than biopsy (0.039 QALY lost [\sim 2.0 wk]) but less expensive. Use of mpMRI in population 1 saved \$40,363 per QALY lost. ESC noted that listing mpMRI in population 1 would result in a net cost of approximately \$1.5 million per year to the MBS but a net saving of approximately \$6.1 million to the health system as a whole (including costs to the MBS, other health funders and patient co-payments).

ESC noted that the economic model for population 1 relied on the assumptions that there will be a reduction in biopsies as a result of mpMRI and that there will be no repeat mpMRI. ESC noted that while the prevalence of PCa has increased as the Australian population ages, the number of prostate biopsies has remained steady. ESC discussed whether this indicated that men were already accessing mpMRI to avoid biopsy or refusing biopsy altogether.

ESC noted that there was greater certainty around the diagnostic accuracy of mpMRI in population 2 than in population 1, as evidenced by narrower confidence intervals. When compared with biopsy, sensitivity was 79.3% (95% CI 74.6–83.3%) and specificity 55.1% (95% CI 50.4–59.8%) for mpMRI in detecting any upgrade in PCa. While ESC noted that mpMRI was less accurate than TRUSGB/TPUSGB in population 2, there was limited evidence that this would not adversely affect patient outcomes.

ESC suggested that mpMRI had superior safety compared to TRUSGB/TPUSGB in population 2. The applicant had indicated that 30% of men in an AS program will have their disease upgraded by mpMRI. ESC noted that this meant that for every 1,000 men in an AS program, use of mpMRI would avoid 358 biopsies but would result in a delay in diagnosing upgraded disease in 31 men.

ESC noted that the economic model suggested use of mpMRI in population 2 would be slightly less effective than biopsy (loss of 0.001 QALY [\sim 0.3 day]) but less expensive. Use of mpMRI in population 2 saved \$232,269 per QALY lost. ESC noted that listing mpMRI in population 2 would result in a net cost of approximately \$1.3 million per year to the MBS but a net saving of approximately \$2.0 million to the health system as a whole (including costs to the MBS, other health funders and patient co-payments).

ESC noted the modelling for population 2 was based upon the assumption that 30% of men would have their disease upgraded by mpMRI. ESC noted that if mpMRI is used in a broader population than currently, the proportion of men who are upgraded on mpMRI may fall. ESC suggested that a sensitivity analysis incorporating a 15% prevalence of upgrading would be helpful for decision making.

ESC noted that the economic modelling for both population 1 and 2 was based upon a linked evidence approach.

ESC questioned the suggested fee of \$600, which is based upon the current market price, and is higher than the MBS fees for similar MRI procedures (e.g. item 63476 MRI scan of the pelvis for the initial staging of rectal cancer: ~\$403).

ESC noted that listing mpMRI for diagnosis of PCa could lead to its use outside these two populations. ESC noted that international and Australian guidelines suggest consideration of mpMRI in men after a negative biopsy to determine if another biopsy is required ([NICE 2014](#) and [PCFA/CCA 2016](#)) or if there is continuing suspicion that the patient has PCa ([AUA/SAR 2016](#)). ESC advised that incorporating a limitation on the use of mpMRI after biopsy in the item descriptor may prevent such leakage.

Similarly, ESC expressed concern that mpMRI may be used to stage PCa even if a decision to biopsy and treat has already been made after clinical examination.

In addition, ESC noted that the availability of mpMRI could increase the attractiveness of using PSA for screening and increase rates of PSA testing. ESC suggested that clinicians and men are less likely to be deterred from using PSA inappropriately as a screening test if the follow-up test is a non-invasive mpMRI instead of the invasive TRUSGB/TPUSGB. ESC noted that any increase in the use of PSA for screening could therefore increase the use of mpMRI over and above that estimated in the application.

ESC noted there may be issues with inter-reader reliability when using mpMRI to determine Prostate Imaging Reporting and Data System (PI-RADS) scores. In studies in which different readers reviewed the same mpMRI images and separately assigned a PI-RADS score, agreement as measured by the kappa statistic ranged from 0.48 to 0.81 (a kappa of 1.0 indicates complete agreement between readers). ESC considered that radiologists and centres offering mpMRI should participate in rigorous training and ongoing quality assurance.

ESC suggested including a limit on the number of mpMRI scans claimed per patient per year in the item descriptor. ESC also noted that if mpMRI were MBS-listed, the item descriptors would need to accurately describe the populations of men who could benefit from use of mpMRI.

From a consumer perspective, ESC noted that mpMRI was likely to be more acceptable to patients than biopsy and that some consumers were already paying for the procedure privately. ESC noted that there is potential for mpMRI to be used to reassure clinicians and men that they do not have significant PCa rather than for diagnostic purposes.

16. Other significant factors

Nil

17. Applicant's comments on MSAC's Public Summary Document

Australian men with financial resources are undergoing imaging of the prostate in increasing numbers, and those without financial resources are still undergoing blind TRUS biopsy of the

prostate. Australian men should have equity of access to state of the art diagnostic imaging in prostate cancer. In relation to MSAC's concern that the number of mpMRIs would likely be higher than estimated in the application due to use outside the proposed populations, it is agreed that a small cohort of men with treatment failure (after radiation or surgery) may need mpMRI to assess the presence or absence of local recurrence. Currently, PSMAGa68 Nuclear Scanning is evolving as the first line imaging investigation of recurrence. These numbers would be predicted to be very small compared to the two defined populations. In relation to MSAC's concern that the proposed fee of \$600 is too high and should be reduced to \$400, we consider that \$600 is an appropriate fee for this service. We consider the comparison to rectal MRI is questionable as the sequences for mpMRI prostate are more time consuming to perform and to read. The applicants also respectfully question the methodology on the cost evaluation. It appears that an assumption made in assessing the comparator (TRUSGB) was that the number of biopsies equated to the number of new diagnoses per year. In this historical comparison, the positive diagnosis rate or "hit rate" is not 100%. If only TRUS were being done, the estimate for the number of biopsies needed to diagnose 20,000 cases would be about 50,000 biopsies, based on detection rates (39-42%) reported in a systematic review of 11 997 participants. Thus, at the cost of \$600/mpMRI and \$2,400 per TRUGB, the overall savings in health costs would be projected to be around \$80million over 5 years instead of the calculated saving of \$40million over 5 years.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)