Australian Government

68 Medical Services Advisory Committee

Public Summary Document

Application 1632 – PSMA PET/CT imaging for informing treatment of patients with prostate cancer

Applicant: Australian Association of Nuclear Medicine Specialists (AANMS) and Cyclotek (Aust) Pty Ltd

Date of MSAC consideration: MSAC 82nd Meeting, 29-30 July 2021

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

1. Purpose of application

An Applicant Developed Assessment Report (ADAR) requesting Medicare Benefits Schedule (MBS) listing of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) for informing treatment of patients with prostate cancer was received from the Australian Association of Nuclear Medicine Specialists (AANMS) and Cyclotek (AUST) Pty Ltd by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) for informing treatment of patients with prostate cancer. MSAC advised that PSMA PET/CT had at least non-inferior safety and superior effectiveness in terms of superior diagnostic accuracy and clinical utility; in particular, its ability to change management intent compared with conventional imaging in the initial staging and restaging of prostate cancer. In addition, MSAC advised that PSMA PET/CT had acceptable cost-effectiveness and financial impact.

The MSAC-supported MBS items are provided below:

Category 5 – Diagnostic Imaging Services
MBS [item number] Whole body prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computerised tomography (CT) study, performed for the initial staging of intermediate- to high-risk prostate adenocarcinoma, for a previously untreated patient who is otherwise considered suitable for locoregional therapy with curative intent. Applicable only once per lifetime
Fee: $1400

Category 5 – Diagnostic Imaging Services
MBS [item number] Whole body prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computerised tomography (CT) study, performed for the restaging of recurrent prostate adenocarcinoma, for a patient who has undergone prior locoregional therapy and who is otherwise considered suitable for further locoregional therapy to determine appropriate therapeutic pathways and timing of treatment initiation. This includes patients with: • a prostate-specific antigen (PSA) increase of 2 ng/ml above the nadir after external beam radiotherapy (EBRT), or • failure of PSA to fall to undetectable levels or rising serum PSA after radical prostatectomy. Applicable only twice per lifetime
Fee: $1400

Consumer summary

This application is from the Australian Association of Nuclear Medicine Specialists and Cyclotek (Aust) Pty Ltd for listing prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) on the Medicare Benefits Schedule (MBS) for people with prostate cancer.

PSMA PET/CT is a type of whole-body scan that can detect prostate cancer. The patient is injected with molecules that spread around the body and bind to cells affected by prostate cancer. These molecules then show up as bright spots on a scan wherever there is prostate cancer in the body. Knowing where the cancer is and whether it has spread can help doctors and patients make better decisions about treatment.

MSAC concluded that PSMA PET/CT is better at detecting prostate cancer throughout the body than other types of scans. It is also just as safe as other types of scans. MSAC also concluded that the cost of PSMA PET/CT was acceptable.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported MBS funding of PSMA PET/CT for people with prostate cancer because it is comparatively safe and effective and good value for money.

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

MSAC noted the purpose of the application was to request MBS listing of PSMA PET/CT imaging for informing treatment of patients with prostate cancer. MSAC noted that the MBS Review Taskforce recommended that MSAC consider the inclusion of gallium-68 (68Ga)-PSMA PET/CT on the MBS, referring to the modality's superiority over conventional imaging (CVI) for staging and restaging of prostate cancer, and its ability to change management intent for newly diagnosed and recurrent prostate cancer patients.

MSAC noted that the targeted consultation was largely in support of PSMA PET/CT, including the input received from a single consumer.

MSAC noted the proposed item descriptors as presented in the applicant-developed assessment report (ADAR) and considered these to be largely appropriate. MSAC noted the discussion at the Evaluation Sub-Committee (ESC) meeting on whether "CT" could be removed from "PET/CT" in the descriptor to be consistent with all other PET items and the

fee reduced by $100, and allowance of co-claiming with MBS item 61505 where CT is performed. MSAC noted that PET and CT are listed separately on the MBS for historical reasons related to the separate development of the technologies. MSAC noted that, in current clinical practice, PET is never performed without CT (except for PET/MRI, which is rarely done), and that PET/CT is considered to be a single service, with both PET and CT being necessary components of the final scan. MSAC therefore concluded that the item descriptor should state "PET/CT". However, MSAC advised that alignment with existing MBS item descriptors was preferable for the following terms:

- "initial staging" should be used instead of "primary" or "N- and M-" staging
- "whole body" (i.e. specifying that PET/CT is a whole-body scan).

MSAC advised that the item for initial staging should be limited to once per patient, but that the item for restaging may be used multiple times, and potentially extended to be used for monitoring if not otherwise restricted. The Department informed MSAC that a similar application for PSMA PET/CT for monitoring purposes was expected to be made to MSAC in the next 2–3 years. MSAC noted that, given the natural history of the disease, any patient would be unlikely to require more than two restaging scans in the next 2–3 years. MSAC therefore advised that the item for restaging should be restricted to twice per lifetime.

MSAC agreed with the Commentary that the proposed fee was reasonable. MSAC noted the potential for continued out-of-pocket costs for consumers; however, MSAC also noted that most service providers charge zero gap or a small gap for high-cost imaging services. MSAC further noted that, in response to requests from PASC and ESC, the pre-MSAC response provided a summary on the ownership of intellectual property for the radiopharmaceutical tracers.

MSAC accepted the comparators of CT and/or whole-body bone scan (WBBS) and single photon emission computed tomography (SPECT)/CT (referred to as CVI). MSAC also accepted the ADAR's alternative comparator of no imaging which was considered relevant for a subset of restaging patients with PSA levels less than 1.0 ng/mL.

MSAC considered the data on comparative safety and accepted that PSMA PET/CT was at least non-inferior (and possibly superior) to CVI.

MSAC considered the data on comparative effectiveness, including accuracy, clinical validity, clinical utility and therapeutic effectiveness in both populations. For initial staging, MSAC noted that the ADAR's clinical evidence primarily relied on a direct randomised controlled trial (ProPSMA trial). This trial provided convincing evidence of improved performance of PSMA PET/CT over CVI in terms of analytical validity, clinical validity and change in clinical management.

For restaging, MSAC noted there was no comparative study of diagnostic accuracy, so the ADAR presented single-arm studies of PSMA PET/CT only. In addition, MSAC noted that an Australian trial (IMPPORT trial) had been published since the ADAR literature search (but presented in the Commentary and pre-ESC response), which found that PSMA PET/CT had superior accuracy over CVI, notably when both scans were performed during a single session, removing the risk of confounding due to time passing between scans. MSAC also noted the applicant included retrospective studies (in the pre-ESC response) to further validate its claim of superiority of PSMA PET/CT over CVI in restaging. MSAC noted that the pre-MSAC response assessed these additional studies as having a low to moderate risk of bias. MSAC noted the 34% to 77% participants who had a change in clinical management

after PSMA PET/CT, indicating some clinical utility, but noted that these were also not incremental results over the comparator.

For both initial staging and re-staging, MSAC also noted that limited data were presented on long-term oncological outcomes but considered it reasonable to assume that accurately determining whether or not there is metastatic involvement would lead to improved treatment. For initial staging, PSMA PET/CT avoids futile locoregional ablative therapy, and for re-staging, PSMA PET/CT better targets salvage radiotherapy to positive sites. MSAC accepted that these treatment improvements would likely lead to improved cancer outcomes.

Overall, MSAC agreed with ESC and considered that the evidence for comparative effectiveness was more convincing for initial staging than for restaging of prostate cancer, but accepted that PSMA PET/CT had superior effectiveness in terms of superior diagnostic accuracy and clinical utility compared with CVI for both purposes.

MSAC reviewed the information on concordance across Australian radiopharmaceutical tracer options and considered that it was difficult to conclude whether they were clinically equivalent due to the small sample size of or lack of a clear reference standard for the presented studies. However, MSAC noted the applicant's biological arguments in support of clinical equivalence based on the characteristics of the available options being small-molecule glutamate urea-based molecular inhibitors of the PSMA enzymatic site and acknowledged that these options were being used interchangeably in practice. MSAC therefore advised that it would be preferable not to specify any radiopharmaceutical tracers in the MBS item descriptors, to allow clinicians and nuclear medicine physicians the choice of radiopharmaceutical tracer, and to allow for any future improved radiopharmaceutical tracers to be used as well. Current radiopharmaceutical tracers could be mentioned in the explanatory notes for the item.

MSAC noted that the economic evaluation included several outcomes:

- cost per additional accurate diagnosis – incremental cost effectiveness ratio (ICER) of $185.82 for initial staging, weighted ICER[1] of $1,071.80 for restaging
- cost per futile treatment avoided – ICER of $603.46 for initial staging, weighted ICER of $1,386.03 for restaging
- cost per quality-adjusted life year (QALY) gained – PSMA PET/CT was dominant for initial staging, weighted ICER $9,168 for restaging.

ESC had queried whether there would be any difference in test performance and clinical utility in patients with intermediate-risk cancer (included in the proposed MBS initial staging population) compared with patients with high-risk cancer (predominant population included in the proPSMA trial). MSAC noted that sensitivity analyses performed in the pre-MSAC response showed that assuming lower sensitivity of PSMA PET/CT for metastases or nodal involvement, and/or assuming lower frequency of metastases or nodal involvement had little effect on the ICER. ESC had also queried the appropriateness of several utility values in the economic model, in particular the disutility values applied for incorrect diagnoses (false negative and false positive scans) and the duration they were applied. MSAC noted that disutilities had been assigned in the ADAR based on actual disease state and diagnosis-based treatment, with effects lasting for 1 year, but that the pre-MSAC response provided additional sensitivity analyses on these model parameters showing they had little effect on the ICERs.

[1] Weighted by the proportions who received CVI or no imaging in the comparator arm.

MSAC considered that the applicant's pre-MSAC response adequately addressed the areas of concern raised by ESC. Together with the reassurance provided by the other sensitivity analyses presented in the ADAR, MSAC concluded that PSMA PET/CT was acceptably cost-effective for both initial staging (of both intermediate-risk and high-risk patients) and re-staging.

MSAC noted the financial impact, including the cost of PSMA PET/CT services, cost offsets from substituted CVI services and adjustment for the Greatest Permissible Gap. The net cost to the MBS was around $2.6 million to $2.9 million each year over 5 years. MSAC advised that a review be conducted in 2 years to monitor utilisation.

4. Background

This was the first submission for PSMA PET/CT for informing treatment of patients with prostate cancer. MSAC has not previously considered this application.

The MBS Review Taskforce recommended that the Medical Services Advisory Committee (MSAC) consider the inclusion of gallium-68 (68Ga)-PSMA PET/CT on the MBS, referring to the modality's superiority over CVI for staging and restaging of prostate cancer and its ability to change management intent for newly diagnosed and recurrent prostate cancer patients.

5. Prerequisites to implementation of any funding advice

PET/CT
The Ratified PICO noted that PET imaging is now almost always combined with CT, with scans collected using a single, hybrid PET/CT scanner (PICO Confirmation, p. 14). There are several hybrid PET/CT devices listed on the Australian Register of Therapeutic Goods (ARTG) (ARTG numbers: 343270, 324191, 296394, 292543, 271560, 144218 and 118077).

PSMA
PASC reported that the most widely used radiopharmaceutical tracer in PSMA PET/CT imaging for informing treatments of patients with prostate cancer is ^{68}Ga-PSMA-11. Radiopharmaceuticals such as ^{68}Ga-PSMA-11, that are produced extemporaneously in a facility holding a GMP license (license to manufacture therapeutic goods), are exempt from a requirement for ARTG listing under Schedule 5(6) and 8(2) of the Therapeutic Goods Regulations 1990 and part 3-3 of the Therapeutic Goods Act 1989.[2]

6. Proposal for public funding

The ADAR proposed radiopharmaceutical tracer-agnostic MBS item descriptors for PSMA PET/CT in two distinct populations as summarised in Table 1 (Population 1) and Table 2 (Population 2). Changes in the wording of the item descriptors in the ADAR from those used in the PICO Confirmation are marked up in red text.

[2] Supporting documentation provided with the original Application

Table 1 Proposed MBS item descriptor for Population 1 (ADAR-proposed changes from PASC marked in red)

Category 5 – Diagnostic Imaging Services
MBS [item number] Prostate-specific membrane antigen (PSMA) ~~PET study~~ positron emission tomography (PET)/computerised tomography (CT) study, performed for the ~~initial N- and M- staging~~ primary staging of intermediate- to high-risk prostate adenocarcinoma, for a previously untreated patient who is otherwise considered suitable for locoregional therapy with curative intent.
Fee: $1400

Source: Compiled from Table ES 2, p26 of the ADAR

Table 2 Proposed MBS item descriptor for Population 2 (ADAR-proposed changes from PASC marked in red)

Category 5 – Diagnostic Imaging Services
MBS [item number] Prostate-specific membrane antigen (PSMA) ~~PET study~~ positron emission tomography (PET)/computerised tomography (CT) study, performed for the restaging of recurrent prostate adenocarcinoma, for a patient who has undergone prior locoregional therapy and who is otherwise considered suitable for further locoregional therapy to ~~delay systemic therapy~~ determine appropriate therapeutic pathways and timing of treatment initiation. This includes patients with: • a prostate-specific antigen (PSA) increase of 2 ng/ml above the nadir after external beam radiotherapy (EBRT), or • failure of PSA to fall to undetectable levels or rising serum PSA after radical prostatectomy
Fee: $1400

Source: Compiled from Table ES 3, p26 of the ADAR

For population 1, PASC recommended changing the wording of the descriptor from 'performed for the primary staging' to 'performed for the initial (N- and M-) staging'. In the ADAR the applicant notes that 'primary staging' is the terminology used in published evidence and clinical settings.

PASC was concerned that for population 2 there could be leakage to therapy monitoring. To reduce this, PASC suggested adding the phrase 'to delay systemic therapy' to the item descriptor. In the ADAR, the applicant suggests that 'to determine appropriate therapeutic pathways and timing of treatment initiation' is used instead, since the main aim of this service is to localise the site of recurrence and then offer optimal therapy including modalities that may delay disease progression which has the net effect of delaying systemic therapy.

The Commentary advised that it consulted with a clinical expert who suggested that the second dot-point in the ADAR proposed MBS item descriptor for Population 2 be amended to include a minimum PSA level of 0.2 ng/mL as a cut-off to signify biochemical recurrence after radical prostatectomy. However, in the pre-ESC response, the applicant advised that it contacted clinical experts who suggested that this is acceptable for patients treated with radiotherapy alone. After a radical prostatectomy, there should be no prostate tissue left and therefore, any rise is indicative of tumour recurrence. The co-sponsors oppose a threshold in this subgroup.

PASC advised that the applicant would need to demonstrate equivalence among tracers before a generic item descriptor could be considered appropriate, or else the evidence-supported tracers would need to be specified.

The proposed MBS fee for PSMA PET/CT for prostate cancer is $1,400.00. This proposed MBS fee is higher than all other PET items, with MBS fees ranging from $901.00 (item 61538) to $1,053.00 (item 61647), and most PET items having an MBS fee of $953.00.

The applicant suggests that the justification for this higher MBS fee is the higher cost of the PSMA radiopharmaceutical tracers compared with FDG.

7. Summary of public consultation feedback/consumer issues

Targeted consultation feedback was received from eight groups which included:

- The Royal Australasian College of Surgeons (RACS)
- The Prostate Cancer Foundation of Australia (PCFA)
- The Clinical Oncology Society of Australia (COSA) with Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)
- The Australian Society of Medical Imaging and Radiation Therapy (ASMIRT)
- The Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM)
- The Medical Oncology Group if Australia (MOGA)
- The Royal Australian and New Zealand College of Radiologists (RANZCR)
- The Australian and New Zealand Society of Nuclear Medicine Limited (ANZSNM)

The groups were largely in support of the service. Refer to the PICO confirmation (pp. 29-30) for a more comprehensive summary of the targeted consultation.

Consultation feedback was also received from one individual consumer in support of the service. They stated that they have had a historical diagnosis and treatment for prostate cancer, and has subsequently received PSMA PET to identify any additional lesions for treatment. They considered that a more sensitive test that can more accurately diagnose metastatic disease will result in better treatment decisions made for patients. They noted that the significant out-of-pocket cost for this test is a barrier to access for many patients.

Late consultation feedback was received from a radiopharmaceutical manufacturer in support of the benefit of ^{68}Ga-PSMA PET/CT imaging in men with prostate cancer. This feedback agreed with the comparators and the two populations proposed in the application, but did not agree with the proposed item descriptor and fee, indicating that these should be specific to the radiopharmaceutical tracer which are not all equivalent.

8. Proposed intervention's place in clinical management

Description of proposed intervention
PSMA PET/CT is a non-invasive imaging procedure that involves the administration of one of several radiopharmaceutical tracers that share the characteristic of highly specific binding to PSMA. PET imaging measures the biodistribution of an intravenously injected biological tracer labelled with a positron-emitting radionuclide. In this way, PET imaging can detect and quantify a biological process occurring within the body. The most widely used radiopharmaceutical tracer in clinical practice in Australia is 68Ga-PSMA-11. The proposed service included PET in combination with CT.

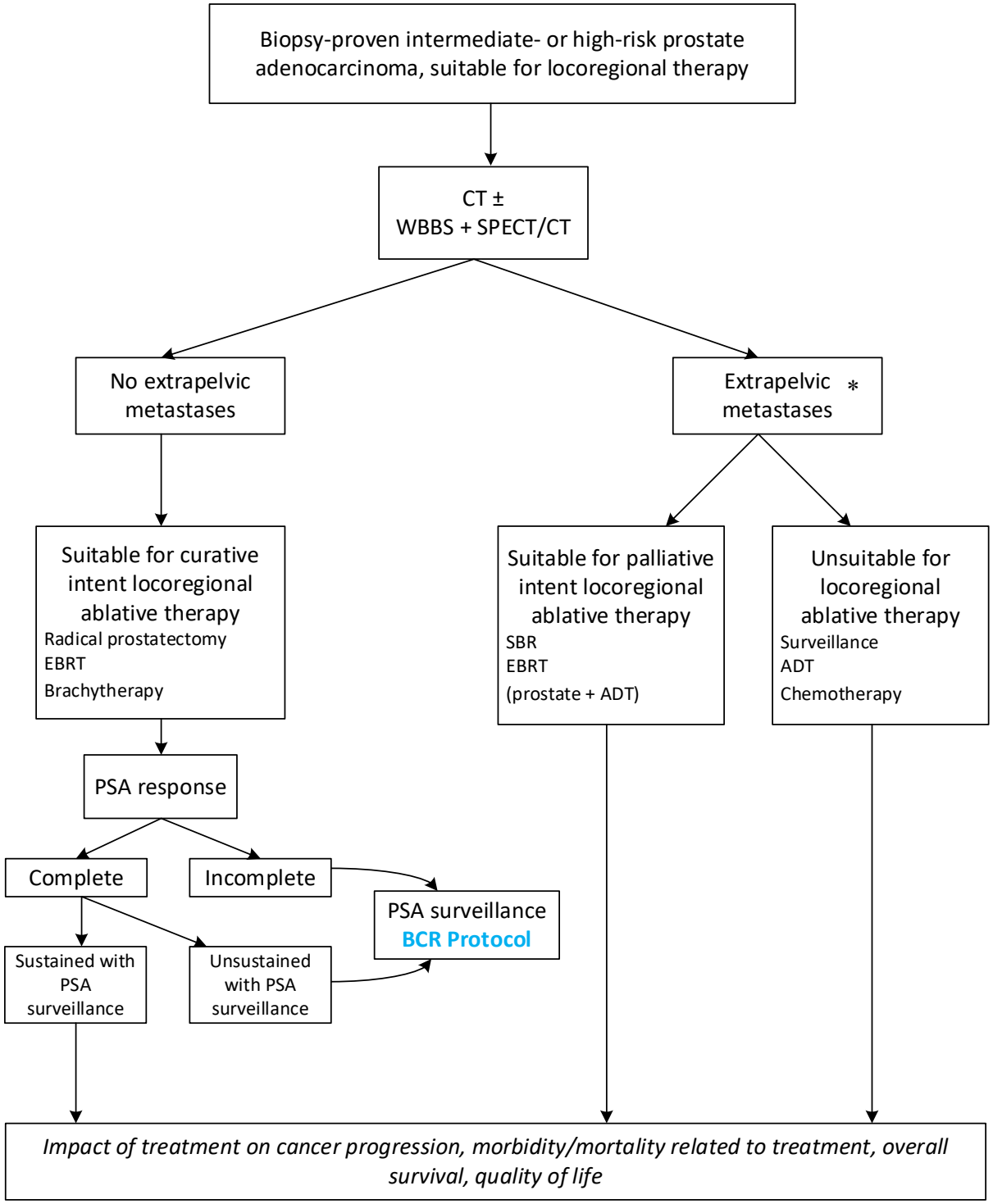
Description of medical condition(s)
There were two proposed populations:

- **Population 1**: as defined in the ADAR, included patients with biopsy-proven prostate adenocarcinoma with intermediate[3]- or high-risk[4] features who have not undergone previous treatment but are considered suitable for locoregional therapy with a curative intent. In this population, PSMA PET/CT is used for primary staging. The ADAR changed the wording from 'performed for the initial N- and M-staging' (used in the PICO Confirmation and considered as the correct wording by PASC) to 'used for primary staging'.
- **Population 2**: as defined in the ADAR, included patients with recurrent prostate adenocarcinoma for whom locoregional therapy is considered suitable to determine appropriate therapeutic pathways and timing of treatment initiation. For these patients, PSMA PET/CT is used to identify the location of the prostate cancer recurrence (e.g. BCR); in particular, for locating sites of metastatic disease to help guide treatment decisions. In the PICO Confirmation, the purpose given for PSMA PET/CT was 'to delay systemic therapy' instead of 'to determine appropriate therapeutic pathways and timing of treatment initiation'.

The current and proposed clinical management algorithms for Population 1 are shown in Figure 1 and Figure 2, respectively; and for Population 2 are shown in Figure 3 and Figure 4, respectively. In the proposed clinical management algorithm for Population 1, patients will undergo PSMA PET/CT to determine nodal involvement or the presence of distant metastases (DM) in place of the comparator tests (CT and/or WBBS with SPECT/CT). In the proposed clinical management algorithm for Population 2 (Figure 2), patients will undergo PSMA PET/CT to determine the presence of extrapelvic metastases, in place of comparator tests (CT and/or WBBS with SPECT/CT).

[3] At least one of the following risk factors (IRFs) in the absence of any high-risk features: PSA of 10-20 ng/ml, or Gleason score of 7 or ISUP grade group 2 or 3, or Stage T2b or T2c †
[4] At least one of the following risk factors: PSA >20 ng/ml, or Gleason score >7 or ISUP grade group 4 or 5, or Stage T2c or ≥T3 †

Figure 1 Current clinical management algorithm for the primary staging of intermediate- or high-risk patients (Population 1)

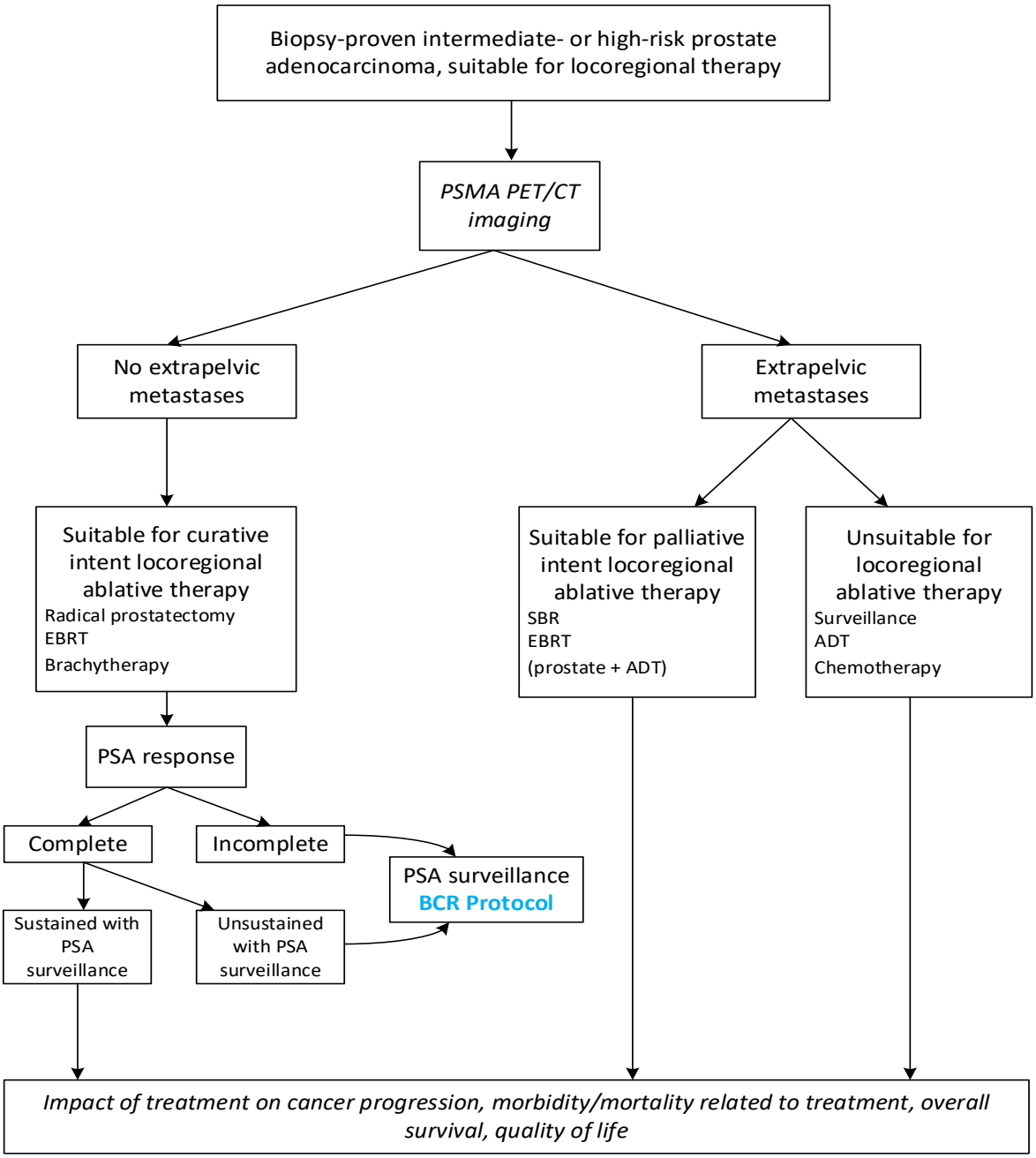


Source: Ratified PICO, Figure 1 p24

Abbreviations: ADT = androgen deprivation therapy; BCR = biochemical recurrence; CT = computed tomography; EBRT = external beam radiotherapy; PSA = prostate-specific antigen; SBR = stereotactic body radiotherapy; SPECT = single photon emission tomography; WBBS = whole body bone scan

*Extrapelvic refers to distant metastases

Figure 2 Proposed clinical management algorithm for the primary staging of intermediate- or high-risk prostate cancer (Population 1)

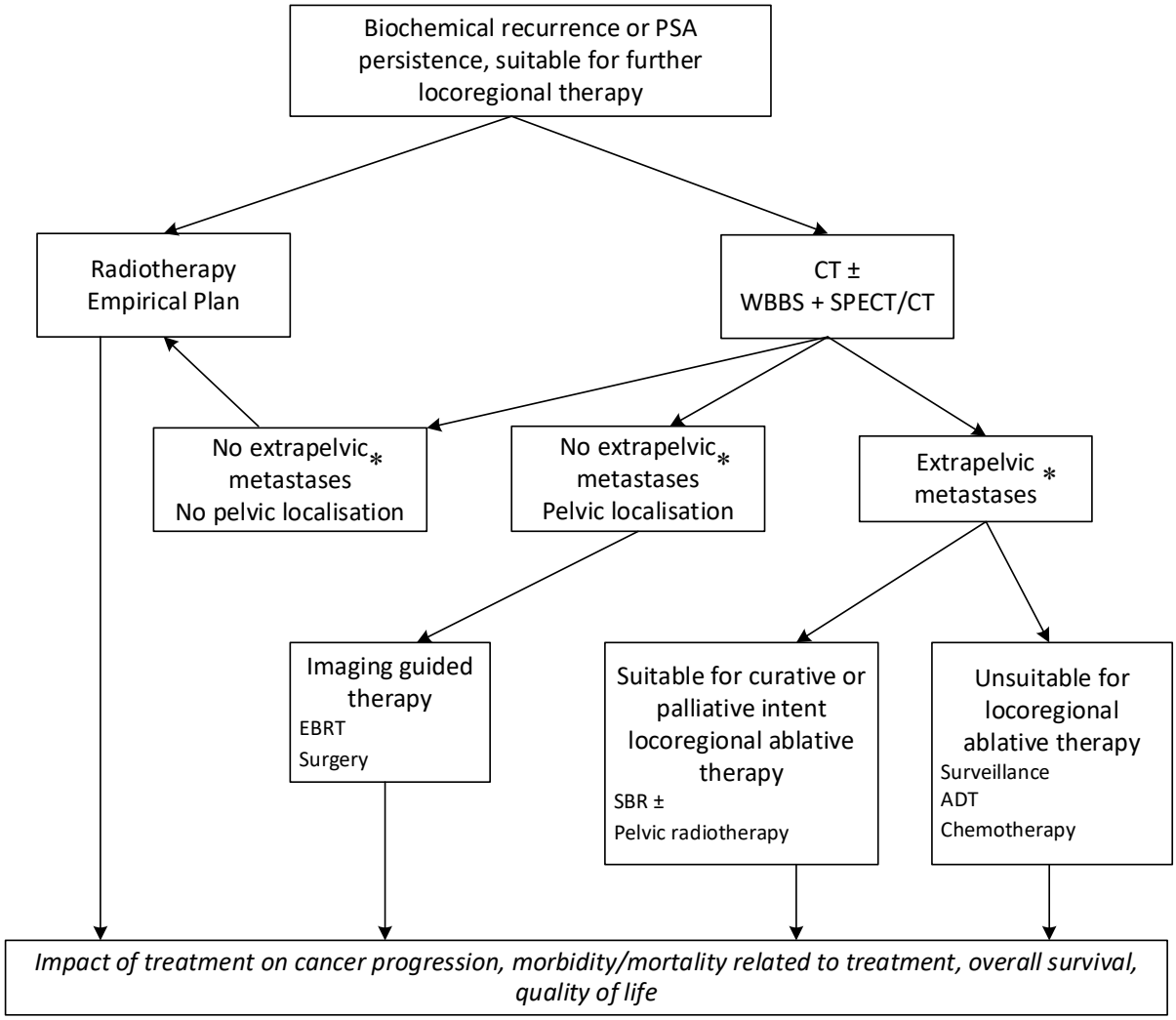


Source: Ratified PICO, Figure 3 p26

Abbreviations: ADT = androgen deprivation therapy; BCR = biochemical recurrence; EBRT = external beam radiotherapy; PSA = prostate-specific antigen; PSMA PET/CT = prostrate specific membrane antigen positron emission tomography/computed tomography; SBR = stereotactic body radiotherapy

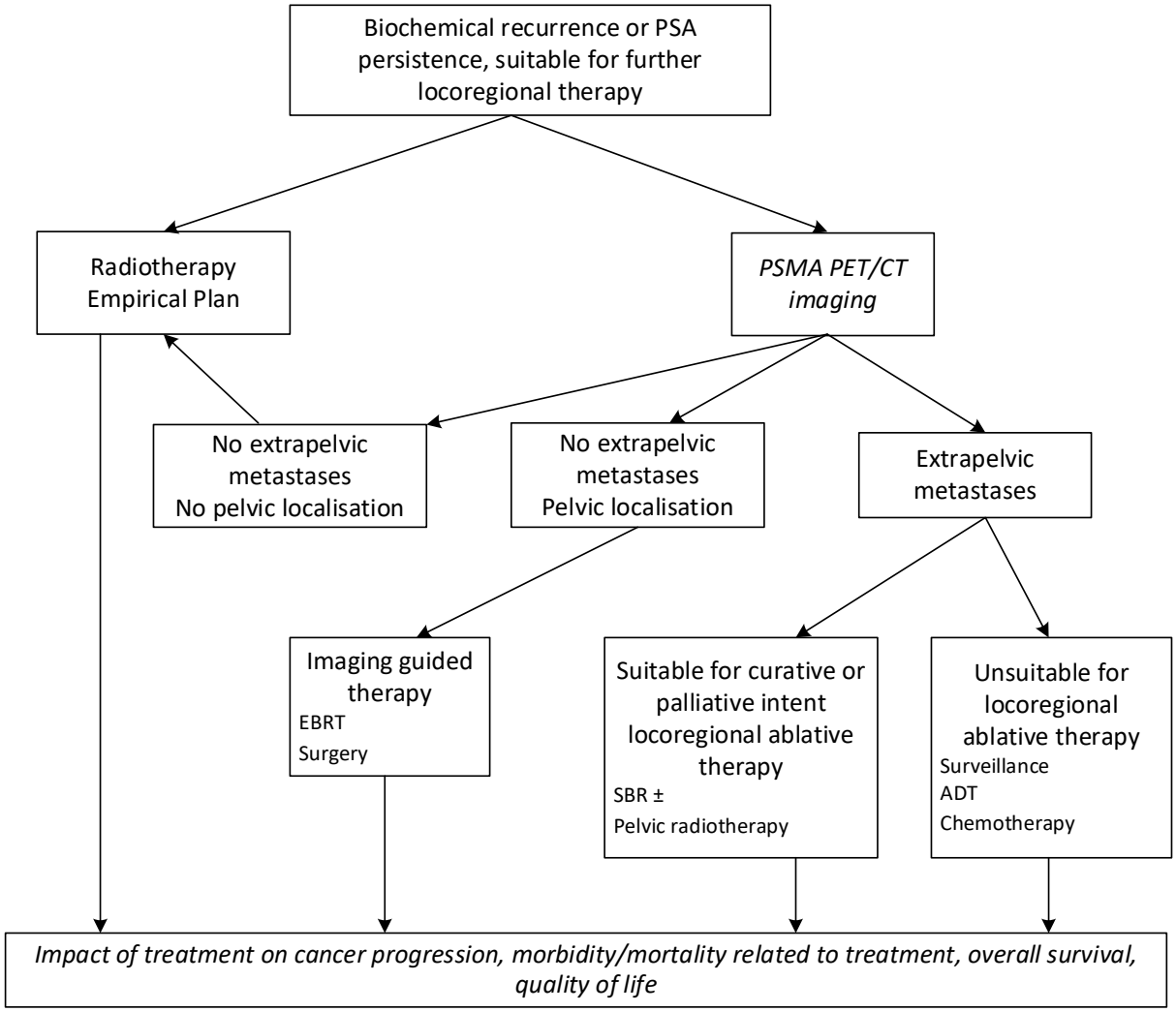
*Extrapelvic refers to distant metastases.

Figure 3 Current clinical management algorithm for the restaging of patients with recurrence (Population 2)



Source: Ratified PICO, Figure 3 p25
Abbreviations: ADT = androgen deprivation therapy; CT = computed tomography; EBRT = external beam radiotherapy; PSA = prostate-specific antigen; SBR = stereotactic body radiotherapy; SPECT = single photon emission tomography; WBBS = whole body bone scan
*Extrapelvic refers to distant metastases

Figure 4 Proposed clinical management algorithm for the restaging of patients with recurrence (Population 2)



Source: Ratified PICO, Figure 4 p27
Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; PSA = prostate-specific antigen; PSMA PET/CT = prostrate specific membrane antigen positron emission tomography/computed tomography; SBR = stereotactic body radiotherapy
*Extrapelvic refers to distant metastases

9. Comparator

The comparators for PSMA PET/CT for Populations 1 and 2, as described in the ADAR and PICO Confirmation, were conventional imaging (CVI): CT and/or whole body bone scan (WBBS) with single photon emission computed tomography (SPECT)/CT. CT scans of the upper abdomen and pelvis or chest, abdomen and pelvis are MBS listed (MBS item 56507), as are WBBS using SPECT (MBS item 61425) and CT scans performed at the same time and covering the same body areas as SPECT for localisation or attenuation correction (MBS item 61505).

In the economic evaluation and financial implications sections of the ADAR, the applicant considered a different comparator for a subset of patients within Population 2. Specifically, for patients with BCR after definitive therapy and a PSA level ≥1.0 ng/ml, CVI comprising CT ± WBBS was considered the comparator, whilst for patients with BCR and a PSA level <1.0 ng/ml, the comparator was considered to be no imaging. The rationale for this was CVI may not be used for all patients with BCR because of the low diagnostic yield, particularly in patients with low PSA levels who generally experience asymptomatic recurrence. Patients instead receive radiotherapy (RT) determined empirically directed to the prostate bed and

sometimes pelvic lymph nodes on the assumption that metastases are not present with no imaging assessment.

The reference standard for determining the accuracy of PSMA PET/CT was defined as histopathologic assessment combined with other imaging and clinical and biochemical findings.

10. Comparative safety

The summary of the included studies is provided for primary staging (Table 3) and restaging (Table 4).

Table 3 Overview of primary included study types and numbers: Primary staging

Type of evidence †	Participants	Details
Comparative evidence ‡	k = 1 n = 295	Australian proPSMA RCT (Hofman et al., 2020). Provides evidence of diagnostic accuracy and clinical utility (change in management) ^{68}Ga-PSMA-11 (k = 1)
Diagnostic accuracy studies (level II to III-1) ‡	k = 6 n = 324	Included for radiopharmaceutical tracers other than ^{68}Ga-PSMA-11 to demonstrate equivalence among tracers to support a generic item descriptor ^{18}F-DCFPyL (k = 3), ^{18}F-PSMA-1007 (k = 2), ^{18}F-rhPSMA-7 (k = 1)
Clinical utility (change in management) studies	k = 0	Data extracted from direct comparative evidence (proPSMA trial) ^{68}Ga-PSMA-11 (k = 1)
Therapeutic effectiveness studies	k = 0	Narrative exploration only
Concordance studies	k = 1 § n = 16	Included with the aim of demonstrating equivalence across radiotracers to support a generic (radiopharmaceutical tracer agnostic) MBS item descriptor ^{68}Ga-PSMA-11 vs. ^{18}F-PSMA-1007 (k = 1)

Abbreviations: k = number of studies; n = number of patients across included studies; PSMA = prostate-specific membrane antigen.
Notes: † = Level II evidence = a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation; level III-1 evidence = a study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation; ‡ = In the proPSMA RCT, a composite reference standard comprising available histopathology, imaging, and biochemistry follow up results at 6 months was used. Across the 6 level II to III-1 accuracy studies, the reference standard was either histopathology after RP ± pelvic lymph node dissection (n=5) or a composite reference standard (n=1); § = This study (Kuten et al., 2020) was also an included diagnostic accuracy study (row 2).
Source: Compiled for the Commentary [Table 4, p7]

Table 4 Overview of primary included study types and numbers: Restaging

Type of evidence †	Participants	Details
Comparative evidence	k = 0	No direct head-to-head evidence comparing PSMA PET/CT to the comparator was identified
Diagnostic accuracy studies (level II to III-1) ‡	k = 10 n = 1,231	Two of ten single arm studies required patients to have prior negative or equivocal findings on CVI, providing insight into the incremental impact of PSMA PET/CT over CVI. ^{68}Ga-PSMA-11 (k = 8); ^{18}F-DCFPyL (k = 1); ^{18}F-PSMA-1007 (k = 1)
Clinical utility (change in management) studies	k = 21 n = 2,238	Assessed implemented or intended decision impact of PSMA PET/CT on clinical management. Five of 21 studies required patients to have prior negative or equivocal findings on CVI ^{68}Ga-PSMA-11 (k = 15); ^{18}F-DCFPyL (k = 4); ^{68}Ga-PSMA-I&T (k = 1); ^{68}Ga-THP-PSMA (k = 1)
Therapeutic effectiveness studies	k = 2 n = 314	• SABR vs. observation after ^{18}F-DCFPyL PSMA PET/CT (k = 1) • Salvage RT ± ADT following ^{68}Ga-PSMA-11 PSMA PET/CT (k = 1)
Concordance studies	k = 2 n = 210	Included with the aim of demonstrating equivalence across radiopharmaceutical tracers to a support generic (radiopharmaceutical tracer agnostic) MBS item descriptor ^{68}Ga-PSMA-11 vs. ^{18}F-DCFPyL (k = 1) ^{68}Ga-PSMA-11 vs. ^{68}Ga-PSMA-1&T (k = 1)

Abbreviations: ADT = androgen deprivation therapy; CT = computed tomography; CVI = conventional imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RT = radiotherapy; SABR = stereotactic ablative radiotherapy.
Notes: † = level II evidence: a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation. level III-1 evidence: a study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation; ‡ = Across the 10 accuracy studies, the reference standard was either histopathology or a composite reference standard
Source: Compiled for the Commentary [Table 5, pp7-8]

Evidence on the safety of PSMA PET/CT was considered across both populations together.

Radiation exposure was the only safety outcome for which a comparison between PSMA PET/CT and conventional imaging (CVI) was made. Test adverse events were not compared between PSMA PET/CT and conventional imaging CVI. The ADAR concluded that PSMA PET/CT has superior safety relative to CVI.

The Commentary noted that the conclusion of superior safety appeared to be based on the comparative patient radiation exposure between 68Ga-PSMA-11 PET/CT and CVI. This comparison is only relevant for patients undergoing both WBBS and abdominopelvic CT. The Commentary also noted that some patients with intermediate-risk features (Population 1) or PSA levels <1.0 ng/ml (Population 2) may undergo only one, or neither, comparator scan therefore the superior safety may not be justified based purely on radiation exposure.

Nonetheless, the Commentary notes that no serious safety concerns related to 68Ga-PSMA-11 or 18F-DCFPyL PSMA PET/CT were identified in the ADAR, and suggested PSMA PET/CT is at least non-inferior to CVI across all proposed MBS-eligible patients. The Commentary also noted that included studies reporting on test adverse events were limited to the 68Ga-PSMA-11 and 18F-DCFPyL radiopharmaceutical tracers.

11. Comparative effectiveness

Accuracy
Appropriate reference standards were used in the key accuracy studies.

Primary staging

Direct comparative evidence demonstrates the superior accuracy of PSMA PET/CT over CVI in the primary N- and M-staging of patients with prostate cancer and one or more of the following: PSA ≥20 ng/ml; ISUP grade ≥3; clinical stage ≥T3. In the proPSMA RCT (Hofman et al., 2020[5]), PSMA PET/CT had a statistically significant absolute greater area under the curve (AUC) of the receiver operating characteristics (ROC) curve for accuracy for PSMA PET/CT compared to CVI (difference: 0.27; p <0.0001).

The sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT and CVI – presented as critical outcomes in the ADAR, are summarised in Table 5.

Table 5 Summary of findings for the diagnostic accuracy of PSMA PET/CT relative to CVI: Primary staging

Outcomes	Participants	68Ga-PSMA PET/CT (95% CI)	CVI (95% CI) †	Quality of evidence ‡	Comments
Sensitivity §	k = 1 n = 295	0.85 (0.74, 0.96)	0.38 (0.24, 0.52)	⊕⊕⊕⊕ High quality	Sensitivity is better for 68Ga-PSMA PET/CT compared to CVI, with no overlap in confidence intervals.
Specificity §	k = 1 n = 295	0.98 (0.95, 1.00)	0.91 (0.85, 0.97)	⊕⊕⊕⊕ High quality	Specificity is high for both ^{68}Ga PSMA PET/CT and CVI.

Abbreviations: CI = confidence interval; CT = computed tomography; CVI = conventional imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
Notes: § sensitivity and specificity for any metastases (pelvic nodal or distant); † Conventional imaging used in Hofman et al. (2020) was CT and bone scan; ‡ GRADE Working Group grades of evidence (Guyatt et al., 2013):
⊕⊕⊕⊕ **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.
Source: Adapted from Table B.13, p.121 of the ADAR.

The Commentary considered that it was uncertain whether the comparative evidence is applicable to patients with intermediate-risk features (excluding those with ISUP grade 3 prostate cancer) falling within the proposed MBS population, but outside the inclusion criteria for the proPSMA RCT, because PSMA PET/CT may have better performance at higher grades (Clinical expert 1, 18 March 2021). The proPSMA trial data may overestimate the diagnostic performance (and thereby ability to change patient management) of PSMA PET/CT in the proposed MBS population, however whether this translates to the comparative performance of PSMA PET/CT vs. CVI being potentially overestimated is unclear.

The Commentary considered it was difficult to draw conclusions on the equivalence of radiopharmaceutical tracers based on the non-comparative data presented:

- 68Ga-PSMA-11 and 18F-DCFPyL or 18F-rhPSMA-7 tracers in the primary N-staging of prostate cancer
- 8Ga-PSMA-11 and 18F-PSMA-1007 tracers in the primary M-staging of prostate cancer.

[5] Hofman, M. S., Lawrentschuk, N., Francis, R. J., et al. 2020. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet, 395, 1208-1216.

In addition, the Commentary noted that the European Association of Urology (EAU) guidelines consider at present there are no conclusive data about comparisons across radiopharmaceutical tracers (Mottet et al., 2021)[6].

Restaging

Single-arm studies using PSMA PET/CT in patients with BCR, without the requirement of a prior negative or equivocal CVI result, demonstrate the high sensitivity and specificity of PSMA PET/CT in the setting of BCR (Table 6).

Table 6 Summary of findings for the accuracy of PSMA PET/CT on a per-patient based analysis: Restaging

Outcomes	Participants	PSMA PET/CT (95%CI)	Quality of evidence †	Comments
Sensitivity	*k = 3* *n = 349*	*0.963* *(0.904 to 0.986)*	⊕⊕⊕⊙ *Moderate quality ‡*	*PSMA PET/CT demonstrated high sensitivity in the setting of BCR. A quantitative comparison with CVI was not possible.*
Specificity	k = 2 n = 256	0.99 (0.83 to 1.00)	⊕⊕⊕⊙ *Moderate quality ‡*	*PSMA PET/CT demonstrated high specificity in the setting of BCR. A quantitative comparison with CVI was not possible.*

Abbreviations: CI = confidence interval; CT = computed tomography; k = number of studies; PET = positron emission technology; PSMA = prostate-specific membrane antigen.
Notes:
Red italicised value reflects the pooled sensitivity value derived in the Commentary after excluding the Morigi et al. (2015) study. The impact of this exclusion was minimal (sensitivity changed from 0.966 to 0.963).
† = GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊕⊕⊙ **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.
‡ = Diagnostic accuracy outcomes downgraded for following reasons: small number of single arm studies included in bi-variate meta-analysis (n = 2 – 3), different definitions of positivity across included studies.
Source: Adapted from Table B.34, p.159 of the ADAR.

Despite not presenting a direct quantitative comparison of diagnostic accuracy parameters between PSMA PET/CT and CVI, the ADAR concluded that PSMA PET/CT is superior in the setting of BCR.

A possible basis to conclude that PSMA PET/CT has superior accuracy to CVI in the nodal and metastatic staging of patients with PSA persistence or recurrence is the two studies requiring patients to have prior negative or equivocal findings on CVI (Emmett et al., 2019[7]; Lindenberg et al., 2020[8]). These studies appear to provide evidence that PSMA PET/CT is sensitive to lesions not detectable on CVI, whilst maintaining a high specificity (sensitivity 0.67 and 0.69; specificity 1.00 and 0.91, respectively).

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[6] Mottet, N., Cornford, P., van den Bergh, R. C. N., Briers, E., De Santis, M., Gillessen, S., Grummet, J., Henry, A. M., van der Kwast, T. H., Lam, T. B., Mason, M. D., O'Hanlon, S., Opera-Lager, D. E., Ploussard, G., van der Poel, H. G., Rouvière, O., Schoots, I. G., Tilki, D. & Wiegel, T. 2021. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer. Available: https://uroweb.org/wp-content/uploads/EAU-EANM-ESTRO_ESUR_ISUP_SIOG-Guidelines-on-Prostate-Cancer-2021.pdf.
[7] Emmett, L., Metser, U., Bauman, G., Hicks, R. J., Weickhardt, A., Davis, I. D., Punwani, S., Pond, G., Chua, S., Ho, B., Johnston, E., Pouliot, F. & Scott, A. M. 2019. Prospective, Multisite, International Comparison of (18)F-Fluoromethylcholine PET/CT, Multiparametric MRI, and (68)Ga-HBED-CC PSMA-11 PET/CT in Men with High-Risk Features and Biochemical Failure After Radical Prostatectomy: Clinical Performance and Patient Outcomes. J Nucl Med, 60, 794-800.
[8] Lindenberg, L., Mena, E., Turkbey, B., Shih, J. H., Reese, S. E., Harmon, S. A., Lim, I., Lin, F., Ton, A., McKinney, Y. L., Eclarinal, P., Citrin, D. E., Dahut, W., Madan, R., Wood, B. J., Krishnasamy, V., Chang, R., Levy, E., Pinto, P., Eary, J. F. & Choyke, P. L. 2020. Evaluating Biochemically Recurrent Prostate Cancer: Histologic Validation of (18)F-DCFPyL PET/CT with Comparison to Multiparametric MRI. Radiology, 296, 564-572.

The Commentary stated that, whilst these results suggest PSMA PET/CT is sensitive to lesions not previously detected on CVI, the time between CVI and PSMA PET/CT imaging is a potential source of confounding. In the time between scans, lesions may have increased in size or new lesions may have developed. The time between CVI and study enrolment was up to 12 weeks in the Emmett et al. (2019) study and 3–4 months in the Lindenberg et al. (2020) study. The significance of these intervals is unclear.

The Commentary stated that, in the setting of BCR, clinical practice guidelines and expert advice indicate that PSMA PET/CT is accepted clinically as the superior choice, given the poor diagnostic yield of CVI.

Evidence presented in EAU guidelines suggests that, in men with PSA-only relapse after radical prostatectomy (RP) and a PSA level <7.0 ng/ml, the diagnostic yield of WBBS is <5%, whilst the diagnostic yield of CT in men with BCR after radical prostatectomy (RP) is 11–14% (Mottet et al., 2021). The diagnostic yield of PSMA PET/CT varied from 33% in men with a PSA <0.2 ng/ml to 95% in men with a PSA level >2.0 ng/ml (Perera et al., 2020)[9].

The IMPPORT trial, published since the ADAR's updated literature search, compared the detection rates (diagnostic yield) of ^{18}F-DCFPyL and diagnostic CT (chest, abdominal, and pelvic) in 97 men with evidence of BCR after RP being considered for salvage radiotherapy (RT) and with PSA between 0.2 – 2.0 ng/ml (Koschel et al., 2021)[10]. Results were presented prior to publication in the ADAR (p.156) following contact with the study authors (ADAR, p.99). Overall, ^{18}F-DCFPyL PET/CT scans were positive in 46.4% of men (n = 45) whilst diagnostic CT was positive in 15.5% of men (n = 15).

The Commentary agreed with the ADAR, which considered that these results validate the finding that PSMA PET/CT is superior to CVI, noting that both scans were performed during a single session, removing the risk of confounding due to time passing between scans.

Concordance studies (both populations)

Available concordance studies provide preliminary evidence to suggest ^{18}F-PSMA-1007 and ^{18}F-DCFPyL may be non-inferior to ^{68}Ga-PSMA-11 (Dietlein et al., 2017[11]; Kuten et al., 2020[12]). In fact, Kuten et al (2020) found ^{18}F-PSMA-1007 may detect additional low-grade lesions of limited clinical relevance, while Dietlien et al. (2017) found ^{18}F-DCFPyL to have improved detection rates at PSA levels between 0.5 and 3.5 ng/ml after RP.

[9] Perera, M., Papa, N., Roberts, M., Williams, M., Udovicich, C., Vela, I., Christidis, D., Bolton, D., Hofman, M. S., Lawrentschuk, N. & Murphy, D. G. 2020. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol, 77, 403-417.

[10] Koschel, S., Taubman, K., Sutherland, T., Yap, K., Chao, M., Guerrieri, M., Benson, A., Starmans, M., Byrne, G., Ong, G., Macleod, C., Foo, M., Wong, L. M., Gyomber, D. & Ng, M. 2021. Patterns of disease detection using [(18)F]DCFPyL PET/CT imaging in patients with detectable PSA post prostatectomy being considered for salvage radiotherapy: a prospective trial. Eur J Nucl Med Mol Imaging.

[11] Dietlein, F., Kobe, C., Neubauer, S., Schmidt, M., Stockter, S., Fischer, T., Schomacker, K., Heidenreich, A., Zlatopolskiy, B. D., Neumaier, B., Drzezga, A. & Dietlein, M. 2017. PSA-Stratified Performance of (18)F- and (68)Ga-PSMA PET in Patients with Biochemical Recurrence of Prostate Cancer. J Nucl Med, 58, 947-952.

[12] Kuten, J., Fahoum, I., Savin, Z., Shamni, O., Gitstein, G., Hershkovitz, D., Mabjeesh, N. J., Yossepowitch, O., Mishani, E. & Even-Sapir, E. 2020. Head-to-Head Comparison of (68)Ga-PSMA-11 with (18)F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. J Nucl Med, 61, 527-532.

However, the Commentary considered it was difficult to draw conclusions given a small sample size [n=16] (Kuten et al., 2020) or lack of reference standard validation to differentiate true positive (TP) and false positive (FP) findings (Dietlein et al., 2017).

Clinical validity

Primary staging

The ADAR reported the positive predictive value (PPV) and negative predictive value (NPV) derived from data presented in the proPSMA trial; however, these were not listed as critical outcomes. Instead, the applicant utilised the sensitivity and specificity data reported above and the pre-test probability of 29.5% to estimate the expected number of patients per 100 men tested having a TP, TN (true negative), FP and FN (false negative) staging outcome on ^{68}Ga-PSMA-11 PET/CT and CVI. The Commentary noted estimates of TP, FP, TN, and FN from the proPSMA trial were similar to the ADAR calculations (Table 7).

Table 7 Summary of findings for the FN and FP rates associated with ^{68}Ga-PSMA PET/CT relative to CVI with assumed pre-test probability of LN or distant metastases of 29.5%: Primary staging

Outcomes	^{68}Ga-PSMA PET/CT		CVI	
	Derived in ADAR n (95% CI)	proPSMA RCT data n (number of patients)	Derived in ADAR n (95% CI)	proPSMA RCT data n (number of patients)
TP per 100 patients tested	25 (22, 28)	23.4 (34)	11 (7, 15)	12.0 (18)
TN per 100 patients tested	69 (67, 71)	71.0 (103)	64 (60, 68)	62.7 (94)
FP per 100 patients tested	2 (1, 4)	1.4 (2)	7 (3, 11)	6.0 (9)
FN per 100 patients tested	5 (2, 8)	4.1 (6)	19 (15, 23)	19.3 (29)
		Total patients = 145		Total patients = 150

Abbreviations: CVI = conventional imaging; FN = false negative; FP = false positive; LN = lymph node; PET/CT = positron emission tomography/computed tomography; PLND = pelvic lymph node dissection; PSMA = prostate-specific membrane antigen; TN = true negative; TP = true positive

Source: Compiled for the Commentary based on outcomes presented in Table B.22, p.132 of the ADAR and data from proPSMA RCT (Hofman et al., 2020) [Table 8, p13 of the Commentary]

The Commentary considered that the reliable identification of distant metastases (DM) was important because local radical therapy cannot achieve cure in the presence of DM and may instead expose patients to treatment-related adverse effects without any therapeutic benefit (Anttinen et al., 2020[13]). The Commentary considered that the increase in TP findings on PSMA PET/CT (vs. CVI) was clinically significant.

Restaging

Ten key studies were included to inform diagnostic accuracy and clinical validity outcomes (PPV, NPV and accuracy) for restaging.

The ADAR utilised pooled sensitivity and specificity results and a pre-test probability of 98.9% (corrected to 88.8% in the Commentary) to estimate the expected number of TP, FP, TN and FN findings per 100 patients tested with ^{68}Ga-PSMA-11 PET/CT (Table 8).

[13] Anttinen, M., Ettala, O., Malaspina, S., et al. 2020. A Prospective Comparison of ¹⁸F-prostate-specific Membrane Antigen-1007 Positron Emission Tomography Computed Tomography, Whole-body 1.5 T Magnetic Resonance Imaging with Diffusion-weighted Imaging, and Single-photon Emission Computed Tomography/Computed Tomography with Traditional Imaging in Primary Distant Metastasis Staging of Prostate Cancer (PROSTAGE). European Urology Oncology, 13, 13.

Table 8 Summary of findings for the FN and FP rates associated with ^{68}Ga-PSMA PET/CT imaging with assumed pre-test probability of recurrence of 88.8%: Restaging

Outcomes	^{68}Ga PSMA-11 PET/CT			
	Derived in ADAR n (95% CI)	Fendler et al. (2019) n (number of patients)	Hamed et al. (2019) n (number of patients)	Zacho et al. (2018) n (number patients)
TP per 100 patients tested	86 (80, 88)	78.5 (73)	87.8 (165)	11.8 (8)
TN per 100 patients tested	11 (9, 11)	NR	11.2 (21)	83.8 (57)
FP per 100 patients tested	0 (0, 2)	15.1 (14)	0 (0)	1.5 (1)
FN per 100 patients tested	3 (1, 9)	6.5 (6)	1.1 (2)	2.9 (2)
		Total patients = 93	Total patients = 188	Total patients = 68

Abbreviations: CI = confidence interval; CT = computed tomography; FN = false negative; FP = false positive; k = number of studies; n = number of participants; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; TN = true negative; TP = true positive.
Source: Compiled for the Commentary based on outcomes presented in Table B.38, p.167 of the ADAR (updated to reflect updated assumed pre-test probability) and data from the primary studies (Fendler et al., 2019; Hamed et al., 2019; Zacho et al., 2018) [Table 9, p14 of the Commentary]

The Commentary noted applicability issues as Hamed et al. (2019)[14]: was a cohort study of Egyptian patients with rising PSA levels after definitive treatment; and it was uncertain whether these patients would have similar PSA levels at the time of PSMA PET/CT to patients in the proposed MBS population. The median PSA level of patients undergoing PSMA PET/CT for BCR in an Australian study (Roach et al [2018][15]) reporting change in management outcomes was lower than the median PSA level of patients in the Hamed et al. (2019) study participants (1.1 ng/ml vs. 2.2 ng/ml, respectively). It was unknown whether this difference was due to chance or due to differences in patient management and clinical decision-making between countries.

The Commentary noted two of the three studies informing pooled sensitivity and specificity estimates referred to the ability of PSMA PET/CT to detect any site of recurrence (vs. no recurrence) (Fendler et al., 2019[16]; Hamed et al., 2019). The third study referred to the ability of PSMA PET/CT to detect/rule out sites of recurrence in the skeletal system (Zacho et al., 2018[17]). Table 8 demonstrates how choice in outcome across the studies impacted on the number of TP and TN outcomes. In Hamed et al. (2019), 87.8% of men had a TP outcome for disease recurrence, whilst in Zacho et al. (2018), only 11.8% of men had a TP outcome for bone metastases.

The Commentary also consider that, given the poor diagnostic yield of CVI in the setting of BCR (as noted above), it was reasonable to expect the number of TP outcomes to be higher with PSMA PET/CT compared with CVI.

[14] Hamed, M. A. G., Basha, M. A. A., Ahmed, H., et al. 2019. ⁶⁸Ga-PSMA PET/CT in Patients with Rising Prostatic-Specific Antigen After Definitive Treatment of Prostate Cancer: Detection Efficacy and Diagnostic accuracy. Academic Radiology, 26, 450-460.
[15] Roach, P. J., Francis, R., Emmett, L., et al. 2018. The impact of⁶⁸Ga-PSMA PET/CT on management intent in prostate cancer: Results of an australian prospective multicenter study. Journal of Nuclear Medicine, 59, 82-88.
[16] Fendler, W. P., Calais, J., Eiber, M., et al. 2019. Assessment of ⁶⁸Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncology, 5, 856-863.
[17] Zacho, H. D., Nielsen, J. B., Afshar-Oromieh, A., Haberkorn, U., deSouza, N., De Paepe, K., Dettmann, K., Langkilde, N. C., Haarmark, C., Fisker, R. V., Arp, D. T., Carl, J., Jensen, J. B. & Petersen, L. J. 2018. Prospective comparison of (68)Ga-PSMA PET/CT, (18)F-sodium fluoride PET/CT and diffusion weighted-MRI at for the detection of bone metastases in biochemically recurrent prostate cancer. Eur J Nucl Med Mol Imaging, 45, 1884-1897.

The Commentary considered a high number of TP outcomes is important, as such outcomes can allow treatment for BCR to be better targeted to positive sites (than empirically defined salvage radiotherapy [RT]), particularly when PSMA PET/CT is positive for oligometastatic disease (Clinical expert 5, 1 April 2021).

Clinical utility (change in clinical management)

Primary staging

Direct comparative evidence demonstrated that, in the primary N- and M-staging of high-risk or ISUP grade 3 prostate cancer, ^{68}Ga-PSMA-11 PET/CT confers a management change in significantly more men than does CVI (28% vs. 15%; p = 0.008) (Hofman et al., 2020).

The Commentary noted these findings were applicable to the Australian context; however, were obtained in a study population that is narrower than the proposed MBS population. Nonetheless, a single-arm Australian study found that in the primary N- and M-staging of 108 men with intermediate- to high-risk disease, ^{68}Ga-PSMA-11 PET/CT conferred a management change in 21.3% of men (Roach et al., 2018). The percentage of men having a change in management did not differ significantly between men with intermediate vs. high-risk features, although the point estimate was lower in the former (16% vs. 22%, respectively; p = not significant [NS]).

Restaging

The ADAR suggested that 21 studies – described as non-randomised comparative studies provide evidence on the change in management impact of PSMA PET/CT compared with CVI. According to the ADAR, PSMA PET/CT may confer an overall implemented or intended management change in 34% to 77% of men compared to CVI.

However, the Commentary noted these studies were non-comparative, single-arm PSMA PET/CT studies in which CVI, where mentioned, was performed prior to PSMA PET/CT imaging. Prior negative or equivocal findings on CVI was an inclusion criterion in five of the included studies. In the remaining studies, patients underwent prior CVI without the need for an equivocal or negative finding being specified for PSMA PET/CT.

The Commentary noted that the ADAR presented the 34% to 77% range as a comparative result, based on the outcomes of second line PSMA PET/CT after prior CVI. Accordingly, the basis for considering the superiority of PSMA PET/CT relative to CVI was that PSMA PET/CT is better able to (appropriately) inform treatment decisions than prior CVI. However, the Commentary considered there is a potential that the time between CVI and PSMA PET/CT imaging had a confounding effect on this comparison. In addition, some studies specified need for prior negative or equivocal findings (k=5) on CVI while others did not, suggesting potential differences across the included populations. The Commentary considered that the range of results provided was relatively wide (i.e. imprecise) but suggested appreciable benefit, nonetheless.

As an exploration of the Australian context, the ADAR focused on one of the included clinical utility studies (Roach et al., 2018). In Roach et al. (2018), PSMA PET/CT led to a change in planned management in 61.5% of patients in the setting of BCR. The Commentary noted that this result of 61.5% falls within the range (albeit towards the upper end) provided by the ADAR. This result is applicable to the Australian setting; however, patients were required to have prior negative or equivocal findings on CVI (i.e. second line PSMA PET/CT) rather than first line PSMA PET/CT as per the proposed MBS population.

Accordingly, it seems that, in Australia practice, PSMA PET/CT can provide new information to better inform management decisions in a large proportion of patients.

The 61.5% estimate was used in the ADAR's cost consequence analysis (CCA), where it was inferred as the incremental impact of PSMA PET/CT over CVI (a value of 0% was assigned to the CVI arm).

However, the Commentary noted inferring an incremental impact of 61.5% inherently assumed the time between CVI and PSMA PET/CT had no confounding effect. The time interval was not specified in the Roach et al. (2018) study, therefore this was unclear.

Therapeutic effectiveness (health benefit from change in management)

Primary staging

The Commentary noted there was no evidence (comparative or single-arm) on the impact of PSMA PET/CT on commonly used metrics of overall long-term oncological outcomes

Restaging

In the Emmett et al. (2020)[18] study, the use of more extensive salvage RT fields and the use of androgen deprivation therapy (ADT) were significantly more likely in men with PSMA PET/CT findings positive (vs. negative) for disease recurrence (42% vs. 23%, p <0.03; 31% vs. 11%, p <0.001, respectively).

Freedom from progression (FFP) at 3 years was reported in 64.5% (120/186) of men who received salvage RT. Of men receiving salvage RT, those with negative PSMA PET/CT results or disease identified as still confined to the prostatic fossa, reported significantly higher FFP at 3 years than men with PSMA PET-positive disease identified outside the prostatic fossa (81.0% vs. 45.3%, p <0.0001).

In the Phillips et al. (2020)[19] RCT, participants randomised to stereotactic ablative radiotherapy (SABR) underwent ^{18}F-DCFPyL PET/CT at baseline and again at day 180; however, the investigative team was blinded to PSMA PET/CT data during SABR treatment planning. Thus, SABR treatment fields were based on CT, not PSMA PET/CT, providing the basis for analyses provided. Overall, 16 of the 36 patients (45%) receiving SABR had baseline PET-positive lesions that were not included in the SABR treatment field because they were undetected on treatment-planning CT.

At 6 months, a significantly higher proportion of patients with any untreated lesions experienced progression compared with patients with no untreated lesions (38% vs. 5%, p = 0.03). Progression-free survival (PFS) and distant metastases-free survival (DMFS) were reduced in patients with any untreated lesions compared with patients in whom all detectable lesions were ablated (hazard ratio [HR] 0.26, p = 0.006; HR 0.19, p <0.001, PFS and DMFS, respectively).

As noted by the ADAR, CT did not detect all metastases compared to PSMA PET/CT, impacting on treatment planning for SABR and resulting in poorer PFS and DMFS. The

[18] Emmett, L., Tang, R., Nandurkar, R., et al. 2020. 3-Year Freedom from Progression After 68Ga-PSMA PET/CT–Triaged Management in Men with Biochemical Recurrence After Radical Prostatectomy: Results of a Prospective Multicenter Trial. Journal of Nuclear Medicine, 61, 866-872.

[19] Phillips, R., Shi, W. Y., Deek, M., et al. 2020. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncology, 6, 650-659.

ADAR inferred that the results suggested that change in management following PSMA PET/CT is associated with improved metastases-free survival and PFS compared to conventional imaging. However, the Commentary noted this is based on speculation rather than evidence linking PSMA PET/CT to improved oncologic outcomes. Nonetheless, the Commentary considered it is possible that, if untreated PSMA-positive lesions had been included in SABR treatment fields, patients may have experienced improved PFS and DMFS. Therefore, the inference made by the applicant seemed reasonable.

Summary in relation to clinical claim
Based on the benefits and harms reported in the evidence base (summarised above), the ADAR suggested that, relative to CVI, PSMA PET/CT (using any radiopharmaceutical tracer) has superior safety and superior effectiveness.

The Commentary considered that the evidence presented in the ADAR supported the claim that PSMA PET/CT has superior safety when both WBBS and abdominopelvic CT are used. When only one, or neither, comparator modality is used, the comparative safety of PSMA PET/CT was unclear, although likely to be at least non-inferior, as no serious safety concerns related to PSMA PET/CT use were identified. Safety data was limited to the 68Ga-PSMA-11 and 18F-DCFPyL radiopharmaceutical tracers.

The Commentary also considered it seemed reasonable to conclude that PSMA PET/CT is superior to CVI in terms of analytical validity, clinical validity and clinical utility. Insufficient evidence was available to conclude that PSMA PET/CT is superior in terms of therapeutic effectiveness.

The Commentary noted that equivalence across PSMA radiopharmaceutical tracers was uncertain. According to EAU guidelines, at present there are no conclusive data about comparisons across radiopharmaceutical tracers (Mottet et al., 2021).

12. Economic evaluation

The economic evaluation was undertaken in three steps:

- Step 1 was a trial-based cost consequence analysis (CCA) taking into account costs of imaging and outcomes of diagnostic PPV and NPV, change in management and equivocal findings.
- Step 2 was a trial-based cost-effectiveness analysis (CEA) presented as cost per accurate diagnosis and cost per harmful treatment avoided.
- Step 3 was a cost-utility analysis (CUA) in which diagnostic accuracy and subsequent management was linked to long-term survival and quality of life over a 10-year time horizon.

The structure of the model is a hybrid decision tree-Markov model based on the economic evaluations of PSMA PET in Australia by de Feria Cardet et al. (2020) and Gordon et al. (2020).

The subsequent treatments resulting from the test results were taken from clinical guidelines (EAU).

A summary of the key characteristics of the economic evaluation is given in Table 9. CVI is the comparator considered for primary staging; the comparator for restaging is also CVI, except for a subgroup of patients with PSA <1.0 ng/ml where usually no imaging is undertaken.

Table 9 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	Primary staging: conventional imaging Restaging for BCR: conventional imaging, no imaging
Type of economic evaluation	cost-effectiveness, cost-utility, cost consequences
Sources of evidence	Primary staging: proPSMA RCT Restaging: meta-analysis of diagnostic accuracy studies and derivation of long-term outcomes from the literature and guidelines
Time horizon	10 years in the model base case
Outcomes	CEA: cost/accurate diagnosis and cost/futile treatment avoided CUA: cost/QALY
Methods used to generate results	Hybrid decision tree–Markov model
Health states	Local disease, pelvic nodal disease, distant metastases, prostate cancer death, natural death
Cycle length	1 year
Discount rate	5% for both costs and effects/benefits/outcomes
Software packages used	Excel, TreeAge Pro Suite

Abbreviations: BCR = biochemical recurrence; PSMA = prostate-specific membrane antigen; QALY = quality-adjusted life year; RCT = randomised controlled trial.
Source: Table ES9, p40 of the ADAR

Cost consequence analysis

The result of the CCA for primary staging is presented in Table 10; for restaging is presented in Table 11 (vs. CVI) and Table 12 (vs. no imaging).

Table 10 Key results of the cost consequence analysis: Primary staging

Health state	PSMA PET/CT	Conventional imaging	Increment
Costs			
Cost of initial testing	$1,400	$1,187.95	$212.05
Cost of repeat imaging for equivocal results	$98	$273.23	-$175.23
Total	$1,498	$1,461.18	$36.82
Outcomes			
Overall accurate diagnoses	94%	75%	19%
Futile treatments avoided in patients with DM	15%	9%	6%
Cost of futile treatments avoided	-$2,690.08	-$1,589.59	-$1,100.49
Equivocal results	7%	23%	-16%
% change in management	28%	15%	13%

Abbreviations: CT = computed tomography; DM = distant metastases; NPV = negative predictive value; PET = positron emission tomography; PN = pelvic nodal; PPV = positive predictive value; PSMA = prostate-specific membrane antigen
Source: Table 11, p22 of the Commentary

Table 11 Key results of the cost consequence analysis: Restaging, PSMA PET/CT vs. conventional imaging

Health state	PSMA PET/CT	Conventional imaging	Increment
Costs			
Cost of primary imaging	$1,400.00	$1,187.95	$212.05
Cost of repeat imaging over 5 years	$211.77	$467.44	-$255.67
Total	$1,611.77	$1,655.39	-$43.62
Outcomes			
Overall accurate diagnoses	97%	55%	42%
Futile treatments avoided in patients with DM	52%	29%	23%
Cost of futile treatments avoided	-$6,729.01	-$3,769.27	-$2,959.74
Repeat imaging over 5 years	3%	10%	-7%
Overall % change in management	59%	NR	NR
% change in management in patients with negative/ equivocal conventional imaging	61.5%	0% †	61.5%

Abbreviations: CT = computed tomography; DM = distant metastases; NPV = negative predictive value; NR = not reported; PET = positron emission tomography; PN = pelvic nodal; PPV = positive predictive value; PSMA = prostate-specific membrane antigen
† = The % change in management in patients with negative/equivocal findings having conventional imaging is 0%. The reference by the Applicant for this number is Roach et al. (2018) according to Attachment D1 PSMA PET Model Inputs, tab 'Decision Tree Probabilities Pop 2'.
Source: Table 12, p23 of the Commentary

Table 12 Key results of the cost consequence analysis: Restaging, PSMA PET/CT vs. no imaging

Health state	PSMA PET/CT	No imaging	Increment
Costs			
Cost of primary	$1,400.00	$0.00	$1,400.00
Cost of repeat imaging over 5 years	$403.29	$0.00	$403.29
Total	$1,803.29	$0.00	$1,803.29
Outcomes			
Overall accurate diagnoses	98%	64%	34%
Futile treatments avoided in patients with DM	19%	0%	NE
Cost of futile treatments avoided	-$2,448.05	$0.00	-$2,448.05
Repeat imaging over 5 years †	7%	0%	NE

Abbreviations: CT = computed tomography; DM = distant metastases; NE = not estimable; NPV = negative predictive value; PET = positron emission tomography; PN = pelvic nodal; PPV = positive predictive value; PSMA = prostate-specific membrane antigen.
† = assumes no repeat imaging in no imaging arm.
Source: Table 13, p24 of the Commentary

Cost-effectiveness analysis

The cost per additional accurate diagnosis and cost per futile treatment avoided for primary staging is presented in Table 13.

Table 13 Cost per additional accurate diagnosis / cost per futile treatment avoided: Primary staging

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Cost per additional accurate diagnosis					
PSMA PET/CT	$1,498.00	$36.82	94%	20%	$185.82
Conventional imaging	$1,461.18		75%		
Cost per futile treatment avoided					
PSMA PET/CT	$1,498.00	$36.82	15%	6%	$603.46
Conventional imaging	$1,461.18		9%		

Abbreviations: CT = computed tomography; ICER = Incremental Cost-Effectiveness Ratio; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
Source. MSAC ADAR 1632, Table ES 13, p.43.

The cost per additional accurate diagnosis and cost per futile treatment avoided for restaging is presented in Table 14, according to PSA subgroups as presented by the ADAR. The weighted costs and effects were based on the estimated relative proportion of patients currently receiving CVI (PSA ≥1.0 ng/ml) or no imaging (PSA <1.0 ng/ml), which PSMA PET/CT is likely to replace. The Commentary noted this weighting was based on the proportion of patients that fall into each group based on Fendler et al. (2019). Those with PSA ≥1.0 ng/ml represented 66.1% of patients enrolled in the single-arm prospective study and those with PSA <1.0 ng/ml represented the balance of patients in the study (33.9%).

Table 14 Cost per additional accurate diagnosis / cost per futile treatment avoided: Restaging

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Cost per additional accurate diagnosis					
PSA ≥1.0 ng/ml					
PSMA PET/CT	$1,611.77		97%		
Conventional imaging	$1,655.39	-$43.62	55%	43%	-$101.66
PSA <1.0 ng/ml					
PSMA PET/CT	$1,803.29		97%		
No imaging	$0.00	$1,803.29	64%	34%	$5,356.17
Weighted	$1,180.29	$431.48	57%	40%	$1,071.80
Cost per futile treatment avoided					
PSA ≥1.0 ng/ml					
PSMA PET/CT	$1,611.77		52%		
Conventional imaging	$1,655.39	-$43.62	29%	23%	-$191.33
PSA <1.0 ng/ml					
PSMA PET/CT	$1,803.29		19%		
No imaging	$0.00	$1,803.29	0%	19%	$9,563.23
Weighted (PSA ≥1.0 ng/ml and PSA <1.0 ng/ml)	$1,180.29	$431.48	21%	31%	$1,386.03

Abbreviations: CT = computed tomography; ICER = incremental cost-effectiveness ratio; PET = positron emission tomography; PSA = prostate specific antigen; PSMA = prostate-specific membrane antigen.
Source: MSAC ADAR 1632 Table D22 p.256.

Cost-utility analysis

The overall costs and effectiveness, and incremental costs and effectiveness with resulting ICERs, are displayed in Table 15. Consistent with the CEA, the same weighting is used from Fendler et al. (2019) to estimate a weighted cost per quality-adjusted life year (QALY).

Table 15 Base case incremental costs, effectiveness and ICERs: both populations

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Primary staging					
PSMA PET/CT	$37,746		4.49		
Conventional imaging	$38,057	-$312	4.39	0.11	Dominant
Restaging					
PSA ≥1.0 ng/ml					
PSMA PET/CT	$46,154 *$46,877*		2.71 *2.87*		
Conventional imaging	$46,877 *$46,154*	$723	2.87 *2.71*	0.16	$4,574
PSA <1.0 ng/ml					
PSMA PET/CT	$32,257 *$35,802*		4.07 *4.24*		
No imaging	$35,802 *$32,257*	$3,546	4.24 *4.07*	0.17	$20,414
Weighted (PSA ≥1.0 ng/ml and PSA <1.0 ng/ml)		**$1,542**		**0.16**	**$9,168**

Abbreviations: CT = computed tomography; ICER = incremental cost-effectiveness ratio; PET = positron emission tomography; PSA = prostate specific antigen; PSMA = prostate-specific membrane antigen; QALY = quality-adjusted life year
Source: MSAC ADAR Table D.29, p.264.
Note, italicised represents ADAR transcription errors corrected in the Commentary

The key drivers of the economic model are summarised in Table 16. For primary staging, PSMA PET/CT remained dominant in all scenarios except when the time horizon increased to 30 years. For restaging, several additional sensitivity analyses were performed for the Commentary, varying the proportion of patients with DM, pelvic nodal (PN) and local disease at baseline, given the uncertainty in these numbers. Of these, two in particular affected the results of PSMA PET/CT compared with no imaging: varying the proportions of patients with DM and local disease at baseline, although neither increased the ICER above when the time horizon was shortened to 5 years (~$34,000 per QALY).

Table 16 Sensitivity analyses

Description	Method/Value	Impact of ICER compared to base case
Primary staging, base case of -$2,945		
Time horizon	Increased from 10 years to 30 years	Moderate: $489/QALY
Restaging vs. conventional imaging (PSA ≥1.0 ng/ml), base case of $4,574		
Cost of PSMA PET/CT same as FDG PET/CT	Decreased from $1,400 to $1,053	Moderate: $1,091/QALY
Specificity of PSMA PET/CT	Decreased from 0.992 to 0.897	Moderate: $7,918/QALY
Restaging vs. no imaging (PSA <1.0 ng/ml), base case of $20,414		
Cost of PSMA PET/CT	Decreased from $1,400 to $1,053	Moderate: $17,570/QALY
Time horizon	Decreased from 10 years to 5 years	High: $33,643/QALY
Percentage DM at baseline (additional analysis for Commentary)	Increased from 0.195 to 0.466	High: $11,775/QALY
Percentage local disease at baseline (additional analysis for Commentary)	Decreased from 0.638 to 0.185	High: $12,299/QALY

Abbreviations: CT = computed tomography; DM = distant metastases; PET = positron emission tomography; PSA = prostate specific antigen; PSMA = prostate-specific membrane antigen; QALY = quality-adjusted life year.
Source: Table 17, p27 of the Commentary

13. Financial/budgetary impacts

The ADAR used a market share and epidemiological approach to estimate the financial implications of the introduction of PSMA PET/CT in the staging of prostate cancer for the two proposed populations. For primary staging, this approach was based on the projected number of new cases of prostate cancer and then estimating the proportion of intermediate- to high-risk prostate cancer patients. For restaging, the 5-year prevalence of prostate cancer was used, and relevant data and assumptions applied to identify the number of patients eligible each year. The 10-year rate of BCR in Jones et al. (2011[20]) was used to estimate the annual rate and probability of patients who have a recurrence in a given year. Consistent with the economic evaluation, the proportion of patients with PSA ≥1.0 ng/ml and who undergo CVI was estimated from Fendler et al. (2019). It was assumed that all patients who receive CVI in current clinical practice will receive PSMA PET/CT if listed and approximately one-quarter of patients who currently receive no imaging will receive PSMA PET/CT if listed. The repeat test rates were also applied to identify the number of patients eligible each year. Net costs were calculated based on the absolute reduction in the use of conventional imaging.

Financial implications to the MBS that would result from listing PSMA PET/CT are summarised in Table 17.

[20] Jones, C. U., Hunt, D., McGowan, D. G., et al. 2011. Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer. New England Journal of Medicine, 365, 107-118.

Table 17 Total costs to the MBS associated with listing PSMA PET/CT for prostate cancer *(ESC values added in)*

	2021	2022	2023	2024	2025
Cost of PSMA PET/CT services					
Total number of services					
Primary staging	14,141	14,368	14,592	14,813	15,031
Restaging	4,478	4,528	4,786	5,032	5,274
Total	**18,619**	**18,896**	**19,378**	**19,845**	**20,305**
Cost to MBS					
Primary staging	$16,828,210	$17,098,374	$17,364,914	$17,628,051	$17,886,826
Restaging	$5,328,938	$5,388,159	$5,695,834	$5,987,781	$6,276,157
Total	**$22,157,148**	**$22,486,533**	**$23,060,748**	**$23,615,832**	**$24,162,983**
ESC values GPG adjustment	***$24,490,165***	***$24,854,233***	***$25,488,908***	***$26,102,441***	***$26,707,203***
Savings to the MBS from avoided conventional imaging services					
Number of services					
Primary staging	16,256	16,517	16,774	17,029	17,279
Restaging	3,289	3,540	3,900	4,235	4,550
Total	**19,545**	**20,057**	**20,674**	**21,264**	**21,829**
Cost to MBS					
Primary staging	$16,414,565	$16,678,089	$16,938,076	$17,194,746	$17,447,160
Restaging	$3,321,006	$3,574,720	$3,938,270	$4,276,684	$4,594,218
Total	**$19,735,571**	**$20,252,809**	**$20,876,346**	**$21,471,430**	**$22,041,378**
ESC values GPG adjustment	***$21,562,870***	***$22,127,997***	***$22,809,268***	***$23,459,449***	***$24,082,169***
Net cost to the MBS (cost of PSMA PET/CT minus savings from conventional imaging services avoided)					
Primary staging	$413,645	$420,286	$426,837	$433,305	$439,666
Restaging	$2,007,931	$1,813,439	$1,757,563	$1,711,097	$1,681,939
Total	**$2,421,576**	**$2,233,724**	**$2,184,401**	**$2,144,403**	**$2,121,605**
ESC values GPG adjustment	***$2,927,295***	***$2,726,235***	***$2,679,640***	***$2,642,991***	***$2,625,034***

Abbreviations: CT = computed tomography; GPG = Greatest Permissible Gap; MBS = Medicare Benefits Schedule; PET = positron emission tomography; PSMA = prostate-specific membrane antigen
Source: MSAC ADAR 1632 Table E11, p. 279. **Original Source:** Attachment E1_Financial estimates, worksheets 'MBS costs'.

14. Key issues from ESC to MSAC

ESC key issue	ESC advice to MSAC
Clinical effectiveness- more certain for the primary staging population than the restaging population	There is evidence of clinical utility from improved sensitivity in both populations, although the evidence is more robust for the primary staging population than the restaging population. There is limited evidence on therapeutic effectiveness in both populations, but it may be reasonable to infer likely clinical benefit from metastasis directed therapy or avoiding futile locoregional ablative therapy (primary staging) and better targeting of salvage radiotherapy to positive sites (restaging).
Safety	At least non-inferior to the accepted comparators.
Equivalence between radiopharmaceutical tracers	The evidence of equivalence across different radiopharmaceutical tracers is uncertain, but a non-specific radiopharmaceutical tracer in the item descriptor is probably justified.
Item descriptors and fee	ESC noted the Department's suggestions to remove CT from the item descriptor, reduce the fee by $100, allow co-claiming with MBS item 61505 (CT alongside PET with a fee of $100), and specify that PSMA PET is a whole-body scan. However, ESC queried whether all PET items include a CT component, and requested that the Department provide advice on this matter before changing the item descriptors.
Limited evidence for patients with intermediate-risk disease (primary staging population)	The population in the proPSMA trial was narrower than the proposed MBS population, which also affects the interpretation of the economic evaluation. In particular, ESC queried whether there was any reason to believe that the extent of clinical effectiveness would be different in intermediate-risk patients (included in the MBS population) compared with high-risk patients (predominant population in the proPSMA trial). ESC considered that this issue would benefit from further sensitivity analysis in the economic evaluation.
Model inputs more uncertain for the restaging population	The clinical data informing the economic models for the restaging population are less robust and come from several sources. However, the data reflect Australian and international clinical guidelines use of PSMA PET in this population. ICERs remain below $34,000 per QALY gained in this population.
Utility values decrements (i.e. disutilities) associated with treatment	ESC noted several potential issues with the assumptions regarding the derivation of the utility values in the models: • disutilities associated with treatments may last longer than 1 year • disutilities associated with false positive and false negative scans seem counterintuitive. ESC considered that these issues would benefit from further sensitivity analysis in the economic evaluations.
Intellectual property issues	Information about ownership of intellectual property relating to radiopharmaceutical tracers was requested by PASC but not included in the ADAR. ESC noted that MSAC has previously made recommendations in relation to proprietary technology, but that more information should be sought to clarify any issues.

ESC discussion
ESC noted that the purpose of this application was for Medicare Benefits Schedule (MBS) listing of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) imaging for informing treatment of patients with prostate cancer.

ESC noted the input from targeted consultation, which was largely in support of PSMA PET/CT. ESC also noted that this feedback included the perspective from an individual consumer highlighting that PSMA PET/CT makes a substantial difference to patients; however, out-of-pocket costs are a barrier for many patients.

ESC noted the two populations in the application, as defined in the ratified PICO confirmation:

- Population 1 – PSMA PET/CT for the initial (N- and M-) staging of intermediate to high-risk prostate adenocarcinoma, for previously untreated patients considered suitable for locoregional therapy with curative intent
- Population 2 – PSMA PET/CT for restaging recurrent prostate adenocarcinoma, for patients considered suitable for locoregional therapy to delay systemic therapy.

However, ESC noted that the populations described in the proposed MBS item descriptors and throughout the applicant-developed assessment report (ADAR) differed from the PICO confirmation:

- Population 1 – reason for intervention changed from "for the initial (N- and M-) staging" to "performed for primary staging"; in the item descriptor, "PSMA PET study" changed to "PSMA PET/CT study" (see Table 1)
- Population 2 – reason for intervention changed from "to delay systemic therapy" to "to determine appropriate therapeutic pathways and timing of treatment initiation"; in the item descriptor, "PSMA PET study" changed to 'PSMA PET/CT study, and text added (as recommended by a clinical expert) to define that the population includes patients with a prostate-specific antigen (PSA) increase of 2 ng/mL above the nadir after external beam radiotherapy, or failure of PSA to fall to undetectable levels or rising PSA after radical prostatectomy (RP) (see Table 2).

ESC also noted the pre-ESC response opposed the suggestion in the Commentary to include a minimum PSA threshold to signify biochemical recurrence (BCR) after radical prostatectomy (RP) in the item descriptor for the restaging population because any rise in PSA is indicative of tumour recurrence.

ESC noted the justifications for these changes provided in the ADAR and pre-ESC response, and considered that these changes may be reasonable. For the item descriptors, ESC noted advice from the Department that "CT" could be removed from the descriptor to be consistent with all other PET items and the fee reduced by $100, and allow co-claiming with item 61505 where CT is performed. However, ESC queried whether all PET items include a CT component, and requested that the Department provide advice on this matter before changing the item descriptors. ESC considered that it was reasonable to also specify that PSMA PET is a whole-body scan. ESC also identified potential inconsistencies in language between similar applications (e.g. "primary staging" in this application vs. "initial staging" in Application 1562), and with existing MBS items for FDG PET (61620 and 61640).

ESC confirmed the proposed clinical management algorithms, where PSMA PET/CT would replace CT and/or whole-body bone scan (WBBS) and single photon emission computed tomography (SPECT)/CT (referred to as conventional imaging [CVI]).

ESC noted that an alternative comparator of no imaging was considered for a subset of restaging patients with PSA levels less than 1.0 ng/mL. ESC noted this additional comparator was included in the ADAR's economic evaluation and financial impact. ESC raised no concerns with this alternative comparator.

ESC noted the clinical evidence presented in the ADAR. For primary staging, this included a recent Australian randomised controlled trial (RCT) (proPSMA trial; Hofman et al. 2020), as well as non-comparative studies to demonstrate equivalence across different radiopharmaceutical tracers to support a generic MBS item descriptor. For restaging, there were no comparative studies of diagnostic accuracy, so the ADAR presented single-arm studies of PSMA PET/CT only.

For comparative safety, ESC noted that radiation exposure was the only safety outcome compared between the intervention and the comparator; other test adverse events were not compared. ESC noted that no serious safety concerns were identified, suggesting that PSMA PET/CT is at least non-inferior to CVI.

For comparative diagnostic accuracy in primary staging, ESC noted that sensitivity was statistically higher for PSMA PET/CT compared with CVI. This was also clinically significant, as local radical therapy cannot achieve a cure state if distant metastases are present – if undetected, patients with metastases may be exposed to treatment-related adverse effects without therapeutic benefit. However, ESC also noted that the proposed MBS population includes all patients with intermediate- to high-risk newly diagnosed prostate cancer, whereas the proPSMA trial was limited to patients with high-risk or International Society of Urological Pathology (ISUP) grade group 3 (unfavourable intermediate-risk feature) disease. Estimated sensitivity may therefore be lower in patients with intermediate-risk features in the proposed MBS population who have lower-grade disease than those in the proPSMA trial. ESC therefore considered that there was uncertainty about test performance (and clinical utility) in intermediate risk cancers, and that this would benefit from further sensitivity analysis in the economic evaluation.

For the restaging population, the meta-analysis of single-arm studies showed that PSMA PET/CT had high sensitivity and specificity for BCR, but there was no quantitative comparison with CVI. ESC noted that an Australian trial (IMPPORT; Koschel et al., 2021) had been published since the ADAR literature search. This study, cited in the pre-ESC response, was in 97 men with evidence of BCR after RP being considered for salvage radiotherapy and with PSA between 0.2 ng/mL and 2.0 ng/mL. The study found PSMA PET/CT scans were positive in 46.4% of men (n = 45) compared with diagnostic CT positive in 15.5% of men (n = 15). Both scans were performed during a single session, removing the risk of confounding due to time passing between scans. ESC requested that this study undergo formal assessment, including risk of bias. ESC also requested that retrospective studies (Eiber et al., 2015; Rauscher et al., 2016) claimed by the applicant to further validate the superiority of PSMA PET/CT compared with CVI in the pre-ESC response should also undergo formal assessment, including risk of bias.

Overall, ESC considered that the evidence for superior diagnostic accuracy and clinical utility was more certain for primary staging than for restaging.

ESC noted the limited evidence on the therapeutic effectiveness of PSMA PET/CT in both populations, but considered that it may be reasonable to infer a likely clinical benefit from metastasis-directed therapy or avoiding futile locoregional ablative therapy (primary staging), and better targeting of salvage radiotherapy to positive sites (restaging).

ESC noted that concordance studies for both populations had small sample sizes or lacked a reference standard, making it difficult to draw conclusions on comparative analytical performance across PSMA radiopharmaceutical tracers. In its pre-ESC response, the applicant supported a generic MBS item descriptor for PSMA PET/CT, noting this should be only applicable to all small-molecule glutamate urea-based molecular inhibitors of the PSMA enzymatic site. The applicant acknowledged the European Association of Urology (EAU) guidelines statement that at present there are no conclusive data for comparisons across PSMA radiopharmaceutical tracers. However, the applicant highlighted that: a generic item was also supported by multiple Australian stakeholder organisations (Ratified PICO, pp31-32), PSMA tracers are generally superior to CVI, clinicians should have the flexibility to choose from a range of available radiopharmaceutical tracers, and it may ensure equitable patient access. ESC considered that these were relevant matters for MSAC to consider regarding a generic MBS item for PSMA PET/CT in the absence of conclusive comparative analytical evidence.

ESC noted that issues relating to ownership of intellectual property for radiopharmaceutical tracers were not discussed in the ADAR, although this had been requested by PASC.

ESC reviewed the ADAR's cost-utility analyses presented for both populations and noted some key translation issues:

- For primary staging, the trial population was narrower than the proposed MBS population, leading to uncertainty if the results of the economic model are applicable to patients at intermediate risk
- For re-staging, the lack of comparative studies and numerous data sources used in the economic model resulted in a number of assumptions in the model which introduced uncertainty in interpreting the model results.

ESC noted the Commentary identified a number of modelling uncertainties. ESC noted the pre-ESC response largely addressed these issues; the applicant identified the correct source (Prostate Cancer Outcomes registry 2018 annual report) used to estimate model probabilities for patients undergoing RP or radiotherapy at model entry; clarified the method used to estimate the proportion of patients with local, nodal and distant metastases; and clarified the method used to estimate the total cost of a scan (which included repeat imaging for PSMA PET/CT and CVI).

However, ESC noted several potential issues with the assumptions regarding derivation of utility values in the model. Specifically, ESC queried the logic of the utility values assigned to false positives and false negatives in the model over time. False positive and false negative patients were assigned the utility related to their condition, not the condition they were incorrectly diagnosed as, which seemed counterintuitive. For example, patients who were false negative for pelvic nodal disease in the first cycle were assigned a utility value of 0.369, which was lower than the true positive utility of 0.400; this then increased to 0.670 after 1 year (to their correct diagnosis). ESC considered that this issue would benefit from further sensitivity analysis in the economic evaluation.

ESC noted the incremental cost-effectiveness ratios (ICERs) presented in the base case model, where PSMA PET/CT was dominant for primary staging and weighted at $9,168 per QALY gained for restaging ($4,574 for patients with PSA ≥1.0 ng/mL, and $20,414 for patients with PSA <1.0 ng/mL). Presented sensitivity analyses showed that the model for primary staging is robust, with PSMA PET/CT remaining dominant in all scenarios except where the time horizon was extended to 30 years. For restaging, the ICERs remained below $34,000 per QALY gained.

ESC noted the Department's advice that the ADAR did not include adjustments for the Greatest Permissible Gap. ESC noted including this adjustment resulted in small variations in the net costs to the MBS (see Table 17).

15. Other significant factors

The Commentary stated that the two item descriptors listed above differ slightly from those in the PICO Confirmation (p. 28). In the PICO Confirmation, for both Population 1 and 2 MBS item descriptors, the intervention is described as "Prostate specific membrane antigen (PSMA) PET study" whilst in the ADAR, the intervention is referred to as "Prostate-specific membrane (PSMA) positron emission tomography (PET)/computerised tomography (CT) study". The ADAR did not discuss these differences. In the PICO Confirmation, PASC stated that the proposed item descriptors did not align with other MBS items for PET which specify 'PET' only whilst the proposed descriptors specify 'PET/CT'. PASC advised that alignment with other PET items should be considered further; however, the applicant noted that all the current MBS descriptors follow from the 2000 PET review process before PET/CT was available. The applicant further stated that the accuracy of PET alone has not been estimated but claimed that the rate of false positives (FPs) would be higher with PET alone.

16. Applicant comments on MSAC's Public Summary Document

We thank you for the opportunity to comment and welcome the positive response to our application and advise we have no suggested changes or edits to the information within the PSD. The co-applicants hope the Minister accepts MSAC's positive recommendation. Medicare funding for PSMA PET/CT scanning will benefit many patients who are currently struggling with the out of pocket expenses to obtain what has become standard of care management of their prostate cancer.

17. Further information on MSAC

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