Australian Government

Department of Health

RATIFIED PICO

Application 1632:

PSMA PET/CT imaging for informing treatment of patients with Prostate Cancer

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A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
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Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	Two populations are included in this application: *Population 1* Prostate specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) imaging performed 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 imaging performed for restaging of recurrent prostate adenocarcinoma, for patients considered suitable for locoregional therapy to delay systemic therapy. *Intermediate-risk localised prostate cancer is defined by:* • *PSA of 10-20ng/ml, or* • *Gleason score of 7 or ISUP grade group 2 or 3, or* • *Stage T2b or T2c (depending on guideline) [1].* *High-risk localised (or locally advanced) prostate cancer is defined by:* • *PSA of >20ng/ml, or* • *Gleason score >7 or ISUP grade group 4 or 5, or* • *Stage T2c (depending on guideline), or ≥T3.* *Recurrent prostate cancer is defined by PSA levels after locoregional therapy. Population 2 includes patients with PSA persistence/recurrence, which is defined by:* • *PSA increase of 2ng/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.*

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[1] Stage T2c appears in the high-risk group in EAU guidelines, however it appears in the intermediate-risk group in NCCN guidelines. Both guidelines are clinically accepted.

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Component	Description
Prior tests (for investigative medical services only)	For initial staging, patients will likely have undergone a digital rectal exam (DRE) and/or prostate specific antigen (PSA) testing, prostate biopsy, and multiparametric magnetic resonance imaging (MRI) prior to referral for PSMA PET/CT (or comparator) imaging. For restaging in patients with BCR after locoregional ablative therapies, patients will have undergone routine PSA testing (i.e. serial PSA tests) prior to referral for PSMA PET/CT (or comparator) imaging.
Intervention	PSMA PET/ CT imaging. PSMA PET/CT is to be treated as a single intervention, irrespective of which radiopharmaceutical tracer is used. Choice of tracer is not expected to impact the safety or effectiveness outcomes of PSMA PET/CT. Nonetheless, data permitting, secondary analysis comparing outcomes between various tracers should be considered to confirm this assumption.
Comparators	- CT, and/or - whole-body bone scan (WBBS) with single photon emission computed tomography (SPECT)/CT.
Outcomes	***Safety outcomes*** - Radiation exposure (patients, nuclear medicine technologists, nurses) - Adverse reaction to the contrast agents, including renal toxicity ***Effectiveness outcomes*** *Diagnostic accuracy* - Sensitivity and specificity - Positive predictive value (PPV), negative predictive value (NPV) - Area under the curve (AUC) of the receiver operating characteristic (ROC) curve - Number of equivocal findings *Change in management* - Need for subsequent diagnostic tests, including biopsy i.e. investigations avoided - Change in planned management (intent), including change in planned treatment modality, extension of radiation field - Change in management i.e. overall change, types of changes, futile locoregional curative intent treatments avoided, therapies instigated

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Component	Description
	Oncologic and patient outcomes • Morbidity • Mortality, including cancer specific mortality • Survival, including overall survival, progression-free survival, metastases-free survival, androgen deprivation therapy (ADT)-free survival • Quality of life ***Healthcare system outcomes*** • Cost of PSMA PET/CT (or comparator) imaging used for initial staging, or for restaging in patients with PSA persistence/recurrence • Cost of additional imaging tests or biopsies required • Cost of treatments received and/or costs offset due to avoidance of futile locoregional ablative procedure • Total cost to Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and other government health budgets ***Economic outcomes*** • Cost effectiveness or cost utility

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Application 1632: PSMA PET/CT imaging for informing
treatment in patients with prostate cancer

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

This application covers two patient populations that benefit from PSMA PET/CT imaging:

1. PSMA PET/CT performed 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.
2. PSMA PET/CT performed for restaging of recurrent prostate adenocarcinoma, for patients considered suitable for locoregional therapy to delay systemic therapy.

PASC considered for Population 1, that 'initial (N- and M-) staging' was the correct term for the use of the intervention rather than 'primary (T-) staging', which is done with digital rectal examination and multiparametric-magnetic resonance imaging (mpMRI).

PASC advised that, for Population 2, the words "with curative intent" should be replaced with "to delay systemic therapy". PASC noted that the treatment goal for recurrent disease is not curative, but that the intent of treatment should be specified to prevent leakage to therapy monitoring.

Context

The MBS Review Taskforce recommended that the Medical Services Advisory Committee (MSAC) consider the inclusion of gallium-68 (^{68}Ga)-PSMA PET/CT on the MBS, referring to the modality's superiority over conventional imaging for staging and restaging of prostate cancer and its ability to change management intent for newly diagnosed and recurrent prostate cancer patients (Medicare Benefits Schedule Review Taskforce, 2018).

PSMA PET/CT was developed to improve detection of metastatic disease in prostate cancer, particularly in the setting of disease recurrence (Perera et al., 2020). Research shows that PSMA PET/CT improves detection of metastases in patients with biochemical recurrence [BCR] (particularly at low PSA levels) (Perera et al., 2020), and improves staging of patients with high-risk prostate cancer (Hofman et al., 2020).

A multicentre Australian prospective study has shown that use of ^{68}Ga-PSMA PET/CT for initial staging or restaging on BCR has a considerable impact on management intent, changing the planned management for approximately half of patients overall (Roach et al., 2018).

Full health technology assessment (HTA) evaluations for Populations 1 and 2 (as defined above) are recommended.

PASC advised that the assessment group should first consider the safety, effectiveness and cost-effectiveness of Population 1. Population 2 should be considered as an incremental add-on to Population 1 (i.e. stepped evaluation).

Background

The prostate is a small, walnut-size gland of the male reproductive system, which produces the fluid that combines with sperm to form semen (Cancer Council, 2020; Prostate Cancer Foundation of Australia, 2020b). It is normal for the prostate to enlarge with age, which can cause problems for

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older males, particularly difficulty urinating. These problems are not always symptoms or signs of cancer.

Prostate cancer is caused by the development and uncontrolled multiplication of abnormal cells in the prostate gland (Cancer Council, 2020; Prostate Cancer Foundation of Australia, 2020b). It is often slow growing and remains within the prostate (localised or early stage disease). Some prostate cancers grow quickly, spreading to nearby body parts such as the bladder or rectum, nearby lymph nodes, or distant sites such as the bones, liver or lungs (National Comprehensive Cancer Network, 2019; Prostate Cancer Foundation of Australia, 2020a).

In the early stages, prostate cancer rarely causes symptoms. Patients with advanced disease may experience symptoms such as unexplained weight loss; frequent or urgent need to urinate; difficulty or discomfort while urinating; blood in the urine or semen; or pain in the lower back, upper thighs or hips (Cancer Council, 2020; Prostate Cancer Foundation of Australia, 2020b).

Stage and grade terminology

(a) Stage

Stage refers to how far the prostate cancer has spread. The most common staging system for prostate cancer is the tumour, node, metastasis (TNM) system, which describes the size of the primary tumour (T) and whether the cancer has spread to nearby lymph nodes (N) or to bones and other organs (M) (Cancer Council, 2020).

A simple overview of the TNM staging system is provided in Table 1 (National Comprehensive Cancer Network, 2019). Details of further sub-divisions (e.g. T2a) are not shown.

Table 1   Tumour, node, metastases staging system (simplified) for prostate cancer

Stage	Primary tumour (T)	Regional lymph nodes (N)	Distant metastases (M)
Localised	T1 Tumour cannot be felt during DRE and is not found on imaging tests, but cancer is present	N0 No cancer in nearby lymph nodes	M0 Cancer has not spread to other parts of body
	T2 Tumour is felt during DRE and is found only in prostate	N0	M0
	T3 Tumour has broken through outside layer of prostate and may have grown into seminal vesicle(s)	N0	M0
	T4 Tumour has spread to nearby structures such as bladder, rectum, pelvic muscles and/or pelvic wall	N0	M0
Regional	Any T	N1 Cancer present (metastasis) in nearby lymph nodes	M0
Metastatic	Any T	Any N	M1 Cancer has spread to other parts of body (metastasized)

Abbreviations: DRE = digital rectal exam
Source: NCCN Guidelines for Patients: Prostate Cancer, 2019

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TNM scores may be combined to describe an overall cancer stage (I to IV). These are outlined in Table 2 (Cancer Council, 2020). Higher numbers indicate larger size or spread.

Table 2   Overall prostate cancer stages, I to IV

Stage I and II	Localised	Cancer is contained inside prostate.
Stage III	Locally advanced	Cancer is larger and has spread outside prostate to nearby tissues or organs such as bladder, rectum or pelvic wall.
Stage IV	Advanced	Cancer has spread to distant parts of the body such as lymph glands or bone.

Source: Cancer Council (2020)

(b) Grade

Grade describes the appearance of prostate cancer cells under a microscope. Either the Gleason scoring system or the International Society of Uropathology (ISUP) grade group system is used to grade tissue taken during biopsy. Higher scores indicate a more aggressive appearance.

The Gleason scoring system was superseded by the ISUP grade group system in 2014 (Cancer Council, 2020; Srigley et al., 2019). Grade groups are derived from Gleason scores, however they are more equipped to reflect modern diagnostic and therapeutic practices (Mohler et al., 2019; Srigley et al., 2019). A simplified overview of the link between the two systems is provided in Table 3 (Cancer Council, 2020).

Table 3   Link between Gleason scores and ISUP grade groups

ISUP Grade Group	Gleason Score
1	≤6
2–3	7
4–5	≥8

Abbreviations: ISUP = International Society of Uropathology
Source: Cancer Council (2020)

Disease burden

Prostate cancer is the most frequently diagnosed cancer among Australian males. The Australian Institute of Health and Welfare (AIHW) estimated that 19,508 men would be diagnosed with the disease in 2019 (Australian Institute of Health and Welfare, 2019). The age-standardised incidence rate was estimated at 130.2 per 100,000 men (62.6 per 100,000 people).

Prostate cancer is the second most common cause of death in Australian men, behind lung cancer. The AIHW reported that prostate cancer would be responsible for an estimated 3,306 deaths in 2019, or 23.0 deaths per 100,000 men (10.0 per 100,000 people) (Australian Institute of Health and Welfare, 2019).

The overall five-year relative survival rate (i.e. the probability of being alive 5 years after diagnosis compared to the general population) for men with prostate cancer was 95.2% between 2011 and 2015 (Australian Institute of Health and Welfare, 2019). For patients with stage I–III disease, the five-year relative survival rate was close to 100%, whilst for patients with stage IV disease it was significantly lower, at 36%.

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The five-year relative survival for prostate cancer has significantly improved over the last 25 years. According to data collected by Cancer Australia in collaboration with the AIHW, most prostate cancer cases are now diagnosed as stage I or II (82.0% in 2011) (Australian Institute of Health and Welfare, 2019). It is possible the advent of PSA testing is linked to the early diagnosis of most cases (Australian Institute of Health and Welfare, 2019).

Population 1

Population 1 comprises patients with biopsy-proven prostate adenocarcinoma with intermediate- or high-risk features, for whom locoregional therapy with curative intent is considered suitable. PSMA PET/CT imaging in this population is used for initial staging.

Patients with intermediate-risk features include those with at least one of the following risk factors, in the absence of any high-risk features:

- PSA of 10-20ng/ml, or
- Gleason score of 7 or ISUP grade group 2 or 3, or
- Stage T2b or T2c (depending on guideline)[2].

Patients with high-risk features include those with at least one of the following risk factors:

- PSA of >20ng/ml, or
- Gleason score >7 or ISUP grade group 4 or 5, or
- Stage T2c (depending on guideline), or ≥T3.

Initial risk stratification

Risk stratification of patients with localised or locally advanced disease assists in treatment decision-making and moreover, predicts the patient's risk of BCR after definitive treatment (Mohler et al., 2019). At a minimum, a patient's PSA level, and stage and grade of cancer are taken into consideration.

The intermediate- and high-risk features of clinically localised (or locally advanced) disease specified in European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines are summarised in Table 4 (Mohler et al., 2019; Mottet et al., 2020). Both NCCN and EAU guidelines are accepted in clinical practice (personal communication, expert radiation oncologist, 25 June 2020).

Table 4   EAU and NCCN guideline definitions of intermediate risk and high risk

	EAU guidelines	NCCN guidelines
Intermediate risk	- PSA 10-20 ng/ml, or - Gleason score of 7 or ISUP grade group 2 or 3, or - Stage T2b	- PSA 10-20 ng/ml, or - ISUP grade group 2 or 3, or - Stage T2b–T2c *Favourable intermediate:* 1 IRF, and grade group 1 or 2, and <50% biopsy cores positive *Unfavourable intermediate:* 2 or 3 IRFs, and/or grade group 3, and/or ≥50% biopsy cores positive

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[2] Stage T2c appears in the high-risk group in EAU guidelines, however it appears in the intermediate-risk group in NCCN guidelines. Both guidelines are clinically accepted.

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	EAU guidelines	NCCN guidelines
High risk	• PSA >20ng/mL, or • Gleason score >7 or ISUP grade group 4 or 5, or • Stage T2c *Or, for locally advanced disease:* • Any PSA • Any Gleason score or ISUP grade group, and • Stage T3–T4, or N+	• PSA >20ng/ml, or • ISUP grade group 4 or 5, or • Stage T3a *Very-high-risk features:* • Primary Gleason pattern 5, or • >4 cores of ISUP grade group 4 or 5, or • Stage T3b–T4

Abbreviations: EAU = European Association of Urology, ISUP = International Society of Uropathology, IRF = intermediate risk factor, NCCN = National Comprehensive Cancer Network, N+ = cancer present in regional lymph nodes, PSA = prostate specific antigen

Source: EAU guidelines (Mottet et al., 2020) and NCCN guidelines (Mohler et al., 2019)

The guidelines are in alignment with respect to PSA levels (10-20ng/ml for intermediate risk, >20ng/ml for high risk) and ISUP grade group (grade 2 or 3 for intermediate risk, grade 4 or 5 for high risk). Clinical stage T2c is defined as an intermediate-risk feature in NCCN guidelines, but a high-risk feature in EAU guidelines.

Intermediate- and high-risk features defined in the inclusion criteria of two recent Australian clinical studies on PSMA PET/CT (Hofman et al., 2020; Roach et al., 2018), and in baseline risk stratification of a UK clinical trial cohort (Bryant et al., 2020) are listed in Table 5.

Table 5   Representative clinical study definitions of intermediate- and high-risk features

	Roach et al. (2018)	Hofman et al. (2020)	Bryant et al. 2020
Intermediate	• PSA 10-20 ng/ml • Gleason score of 7, **and** • Clinical or MRI evidence of stage T2 disease	Not included in study population	• PSA >10 and ≤20ng/ml • Gleason score 7 (grade group 2 or 3), or • T2b disease
High	• PSA >20ng/ml, or • Gleason score ≥8, **and** • Clinical or MRI evidence of disease stage T3 or greater	• PSA concentration ≥20ng/ml (measured within last 12 weeks) • ISUP grade group 3 or 5, **or** • Clinical stage T3 or greater	• PSA >20ng/ml • Gleason score ≥8 (grade group ≥4) • T2c disease

Abbreviations: ISUP = International Society of Uropathology, MRI = magnetic resonance imaging, PSA = prostate specific antigen

Source: (Bryant et al., 2020; Hofman et al., 2020; Roach et al., 2018)

There is slight variation between the inclusion criteria used by Hofman et al. (2020) and guideline definitions regarding ISUP grade groupings, with Hofman et al. (2020) defining ISUP grade group 3 as a high-risk feature.

Clinical stage T2c is defined by Hofman et al. (2020) and Roach et al. (2018) as an intermediate-risk feature for patients with a histologic diagnosis of prostate cancer undergoing initial staging, in line with NCCN guidelines. Bryant et al. (2020) define clinical stage T2c as a high-risk feature in post hoc risk stratification of patients diagnosed with clinically localised disease randomised to active monitoring, surgery or radiotherapy, conforming to EAU risk groups. Higher clinical stages consistent with locally advanced disease (T3 and T4) were not included (Bryant et al., 2020; Hamdy et al., 2016).

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Estimated patient numbers for Population 1

The Applicant estimated that of the approximate 20,000 new cases of prostate cancer diagnosed per annum, around half (10,000 cases) would show intermediate- to high-risk features and thus be considered for PSMA PET/CT imaging.

Post hoc risk stratification undertaken by Bryant et al. (2020) on a cohort of patients with an initial diagnosis of clinically localised disease (T1c or T2a–c) found 34% of patients to have intermediate- or high-risk features (Bryant et al., 2020). This estimate does not take into those with locally advanced disease (T3 or T4).

AIHW data suggests that of all localised or locally advanced prostate cancers diagnosed in 2011, approximately 12.0% were diagnosed with locally advanced (stage III) disease (see Table 6). According to clinical guidelines, patients with locally advanced disease are high risk (see Table 4).

Table 6   Number of patients diagnosed with stage I, II or III disease in Australia, 2011

Clinical stage at diagnosis	Stage I	Stage II	Stage III	Total	Cross reference and/or source
Extent of disease	Localised	Localised	Locally advanced		Table 2, (Cancer Council, 2020)
Number of cases	7,186	9,245	2,246	18,677	(Australian Institute of Health and Welfare, 2019)
Proportion †	38.5%	49.5%	12.0%	100%	Calculated

Notes: † = excluding stage IV and disease of unknown stage

With a combined estimate of 46%, these figures support the Applicant's estimate that approximately half of the patients diagnosed with prostate cancer have intermediate- or high-risk features at diagnosis.

Population 2

Population 2 includes patients with recurrent prostate adenocarcinoma, for whom locoregional therapy to delay systemic therapy is considered suitable. For these patients, PSMA PET/CT is used for restaging; primarily, for ruling out metastatic disease to help guide treatment decisions. Moreover, for patients for whom radiotherapy is the best option, PSMA PET/CT may help guide the radiation field and dose.

Specifically, Population 2 includes patients with PSA persistence/recurrence after prior locoregional therapy. This includes patients with:

- a PSA increase of 2ng/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.

PSA persistence

A detectable or persistent PSA level after radical prostatectomy is considered PSA persistence (Van den Broeck et al., 2020). The presence of persistent local disease, pre-existing metastases or residual benign prostate tissue may be responsible (Mottet et al., 2020).

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Biochemical recurrence

BCR occurs when there is a significant rise in PSA levels following definitive treatment. Relapse following curative intent treatment is thought to be due, in part, to poor sensitivity and specificity of conventional imaging in detecting non-localised disease (Hofman et al., 2020).

Van den Broeck et al. (2020) note heterogeneity in the definition of BCR between and within the main curative intent treatments (Van den Broeck et al., 2020).

The Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology Phoenix Consensus Conference proposed a PSA increase of 2ng/ml or more above the PSA nadir— regardless of the nadir value—as a standard definition for BCR after EBRT (Roach et al., 2006; Van den Broeck et al., 2020). Expert clinical advice confirmed that this 'Phoenix definition' is accepted clinically, although this is not definitive (personal communication, expert radiation oncologist, 25 June 2020).

American Society for Radiation Oncology/American Urological Association guidelines recommend clinicians define BCR after prostatectomy as a rise in PSA levels of ≥0.2ng/ml with a secondary confirmatory level ≥0.2ng/ml (Thompson et al., 2019). The guidelines note that most published studies use a PSA threshold of 0.2ng/ml to define recurrence after surgery. However, a lower threshold (PSA level ≥0.05ng/ml) has been used in some studies (Huits et al., 2020; van Leeuwen et al., 2016). Expert clinical advice confirmed that, generally, a PSA level of 0.2ng/ml and rising is accepted clinically to signify BCR after radical prostatectomy, although again, is not definitive (personal communication, expert radiation oncologist, 25 June 2020).

According to EAU guidelines, the following can be considered evidence of BCR (Mottet et al., 2020):

- increase in PSA of >2ng/ml above the nadir (lowest PSA value) after radiotherapy
- rising serum PSA level after radical prostatectomy.

Estimated patient numbers for Population 2

BCR is a common occurrence, it being reported that 27-53% of patients who undergo curative intent ablative procedures will experience BCR (Van den Broeck et al., 2020). A detectable or persistent PSA after radical prostatectomy may occur in 5-20% of patients (Mottet et al., 2020).

The Applicant advised that of all patients who undergo curative intent ablative procedures, around half (5,000 men) experience BCR. Thus, the Applicant's estimate of 50% BCR frequency falls within the range of reported figures.

The Applicant further advised that of those with BCR, approximately 80% (4,000 patients) would benefit from PSMA PET/CT imaging.

Not all patients with BCR develop disease progression and metastatic disease. A patient's risk of progression may influence whether early salvage treatment is initiated, or if treatment can be deferred (Van den Broeck et al., 2020). For patients with BCR and low-risk features who may not benefit from intervention, the guidelines recommend offering PSA monitoring.

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Rationale

For patients with low-risk features and a life expectancy of 10 years or greater, active surveillance as an alternative to immediate radical treatment is recommended (Carroll and Mohler, 2018; Mottet et al., 2020; National Institute of Health and Care Excellence, 2019).

PSMA PET/CT is a helpful test in early high-risk prostate cancer because most of these cancers have high (>95%) PSMA expression (Hofman, 2019). Early-stage prostate adenocarcinoma with neuroendocrine differentiation, and small- or large-cell neuroendocrine tumours of the prostate have low PSMA expression, therefore PSMA PET/CT is inadequate as a lone staging modality in these circumstances (Alipour et al., 2019).

Thus, this application is restricted to adenocarcinoma type prostate cancers (personal email communication, Applicant, 10 July 2020).

Monitoring systemic treatment in metastatic disease

PSMA PET/CT imaging for the monitoring of systemic therapy in metastatic disease is not included in the current submission (personal email communication, Applicant, 26 June 2020) given the present lack of evidence. However, the Applicant has advised that there is clinical utility for PSMA PET/CT in guiding therapy for patients with metastatic prostate cancer. Given a growing evidence base, the Applicant believes that this population should receive future consideration from MSAC.

Expert clinical advice confirmed that, at present, PSMA PET/CT has very little clinical role in therapeutic monitoring except perhaps when prostate cancer patients are transitioning or progressing to a castrate resistant state as new treatment regimens are decided upon (personal communication, expert radiation oncologist, 25 June 2020). In hormone-sensitive patients where ADT is still working, PSMA PET/CT imaging is thought to be of no or minimal clinical value (personal teleconference communication, Applicant, 25 June 2020).

PSMA-directed radionuclide therapy

PSMA-directed radionuclide therapy is a potential second-line systemic treatment for metastatic prostate cancer with high PSMA expression.

Radionuclide treatment with 177 Lutetium [^{177}Lu]-PSMA-617 has been shown to have high response rates and low toxic effects, while reducing pain in patients with metastatic castrate-resistant prostate cancer (CRPC) who have progressed after conventional treatments (Hofman et al., 2018). Two randomised clinical trials of [^{177}Lu]-PSMA-617 radionuclide therapy in progressive CPRC are currently underway.

The Applicant advises that patients having PSMA-targeting radionuclide therapy, or those being assessed for its suitability, require PSMA PET/CT imaging because comparator imaging modalities are not helpful.

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The Applicant notes that evidence supporting PSMA-targeting radionuclide therapy is currently available only in the setting of very-late-stage CRPC. This indication for PSMA PET/CT is beyond the scope of the current application. The applicant advised that a separate submission will be completed when further evidence on PSMA-based radionuclide therapy becomes available. PSMA PET/CT used in combination with radionuclide PSMA therapy is to be assessed as a co-dependent therapy in a subsequent submission (personal email communication, Applicant, 25 June 2020).

PASC noted that the applicant had decided to remove two populations from its initial application: PSMA PET/CT imaging for the monitoring of patients treated with systemic therapy in metastatic disease (i.e. therapy monitoring); and for patients with metastatic prostate cancer being considered for targeted radionuclide treatment with Lutetium-177 [^{177}Lu]-PSMA-617 (i.e. therapy guidance).

Prior tests

Population 1

Prior to being referred for PSMA PET/CT (or comparator) imaging, patients will likely have undergone a DRE and/or PSA testing, multiparametric MRI and prostate biopsy to diagnose prostate cancer.

DRE and/or PSA testing are used initially, to find prostate cancer early (Prostate Cancer Foundation of Australia and Cancer Council Australia, 2016).

If cancer is suspected based on DRE and/or PSA results, for a diagnosis to be made a prostate biopsy is required to provide histopathological evidence of adenocarcinoma (Mottet et al., 2020). Current standard of care is an ultrasound-guided biopsy by either the transrectal or transperineal approach.

Clinical practice guidelines increasingly recommend the use of multiparametric MRI prior to biopsy for initial prostate cancer diagnosis. For example, NCCN 2015 guidelines recommended multiparametric MRI in select cases *after* a previous negative biopsy, whilst 2018 guideline updates recommend consideration of multiparametric MRI or biomarker testing *before* biopsy (Carroll and Mohler, 2018; Carroll et al., 2015). Both EAU guidelines and National Institute of Health and Care Excellence (NICE) guidelines recommend multiparametric MRI prior to biopsy (Mottet et al., 2020; National Institute of Health and Care Excellence, 2019).

In Australia, multiparametric MRI is listed on the MBS for the diagnosis of prostate cancer (item 63541) and the surveillance of prostate cancer in patients not currently undergoing treatment (item 63543) (Australian Government Department of Health, 2020a).

Population 2

For restaging after locoregional ablative therapies, patients will have undergone routine PSA monitoring prior to being referred for PSMA PET/CT (or comparator) imaging.

13 | P a g e   R A T I F I E D   P I C O — O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

NICE recommends PSA levels be checked no earlier than six weeks after radical treatment, at least every six months for the first two years, and then at least once per year after that (National Institute of Health and Care Excellence, 2019). EAU guidelines recommend that after local treatment, asymptomatic patients be routinely followed up for disease-specific history and serum PSA levels at 3, 6 and 12 months; then every 6 months up to 3 years; then annually (Mottet et al., 2020).

Intervention

The intervention is PSMA PET/CT.

Background on PET/CT

PET imaging measures the biodistribution of an intravenously injected biological tracer labelled with a positron-emitting radionuclide (Scott, 2001). In this way, PET imaging can detect and quantify a biological process occurring within the body.

PET imaging is now almost always combined with CT, with scans collected using a single, hybrid PET/CT scanner. If used alone, PET imaging provides limited anatomical information and attenuation correction is a time-consuming process (Lau et al., 2005). Sequential CT imaging allows for accurate localisation of the tracer, helps distinguish pathologic uptake from normal physiological uptake, and allows an attenuation map to be constructed that provides improved attenuation correction in a shorter time frame (Lau et al., 2005).

Various radiolabelled compounds targeting different physiological or biochemical processes can be used for PET/CT imaging.

PSMA PET/CT

PSMA is a glycoprotein found on the surface of prostate cells. It is highly overexpressed in prostate cancer cells (particularly in metastatic and castrate-resistant disease) and is thus a good target for staging and treatment (Hofman, 2019). Its exact function in prostate cancer is unclear.

During a PSMA PET/CT scan, small radiolabelled molecules that bind to PSMA receptors are intravenously injected into the patient and given time to disperse throughout the body. PET/CT imaging detects these molecules, with a concentration at any location suggesting prostate cancer cells may be present.

The Applicant specified that after intravenous administration of the tracer, 45 to 120 minutes may pass prior to PET/CT imaging. Imaging time is approximately 30 minutes, after which the image is interpreted by a qualified specialist and a report provided to the referring specialist.

Health professionals involved in the delivery of PSMA PET/CT include nuclear medicine technologists, medical physicists, radiochemists, radiopharmacists, nuclear medicine physicians and radiologists. The proposed medical service cannot be delegated or referred to another professional for delivery.

14 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

The Applicant advises that no additional healthcare resources or medical services need to be delivered at the same time as PSMA PET/CT.

Access to PSMA PET/CT imaging is limited by the number of PET/CT equipped sites. As of 31 March 2019, 77 sites were listed on the Australian Department of Health's website (Australian Government Department of Health, 2020b). According to the Applicant, approximately 91 scanners are currently available, with 9 more under consideration. Notably, most PET scanners are in major cities, therefore uptake of PSMA PET/CT among patients in rural or remote areas may be restricted.

The radioactive tracer

The most widely used radiopharmaceutical tracer is ^{68}Ga-PSMA-11, which combines a small molecule that binds to PSMA receptors (PSMA-11) with a radioactive carrier (^{68}Ga). Two other radiopharmaceutical tracers gaining in popularity are the Fluorine-18 (^{18}F)-labelled tracers ^{18}F-DCFPyL and ^{18}F-PSMA1007 (Hofman, 2019). Many others have been used in preclinical and clinical research (Alipour et al., 2019). Results of PSMA PET/CT are believed to be comparable across the various tracers currently in use (Alipour et al., 2019).

PASC noted that the most widely used radiopharmaceutical tracer in clinical practice in Australia and internationally is ^{68}Ga-PSMA-11. The Fluorine-18 (^{18}F)-labelled tracer: ^{18}F-DCFPyL is currently used in clinical trials in Australia ([ACTRN12620000261910](); [ACTRN12618001530213]()).

The applicant noted that ^{18}F-DCFPyL is not only used in the clinical trial setting, and approximately 8000 patient doses had been dispensed under the SAS provisions to support clinical management decisions. The applicant further noted that clinical expert Professor Declan Murphy, confirmed that in practice at Peter MacCallum Cancer Centre, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL were considered to be clinically equivalent and were used interchangeably depending upon daily availability.

Supply of radioactive tracers is regulated by the Therapeutic Goods Act 1989, administered by the Therapeutic Goods Administration. Radiopharmaceuticals prepared extemporaneously are specifically exempt from the requirement for an Australian Register of Therapeutic Goods (ARTG) listing.[3]

The Applicant advised that these radioactive tracers are supplied either by in-house production of ^{68}Ga-based pharmaceuticals or by commercial provision of longer lasting fluorine-based tracers, and supply is expected to be able to keep pace with increasing demand. Expert clinical advice confirmed that there is now a well-established distribution network across major centres, noting the greatest logistical issues are around the supply of ^{68}Ga tracers, which must be made in-house due to their shorter half-life (personal communication, expert radiation oncologist, 25 June 2020).

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[3] Supporting documentation was provided as an attachment to the application form.

15 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

The Applicant provided the following advice for the two populations included in this application:

- Approximately half of all patients will be cured by primary therapy. For these patients only a single PSMA PET/CT scan for initial staging is required.
- For patients who experience BCR, a second PSMA PET/CT scan would be required to inform treatment decisions when planning active therapy. This may occur months to many years after initial curative intent therapies.

Current use in Australian clinical practice

The MBS Review Taskforce recommended that MSAC consider listing ^{68}Ga-PSMA PET/CT for patients with prostate cancer (Medicare Benefits Schedule Review Taskforce, 2018). The Taskforce noted that ^{68}Ga-PSMA PET/CT is now being offered in private practice settings around Australia despite a lack of MBS funding.

The Applicant advises that Australian clinicians have accepted the superiority of PSMA PET/CT over MBS-funded conventional imaging modalities for defining the location and extent of active prostate cancer, and that PSMA PET/CT is now routinely used in patients who can arrange funding for the scan. The MBS Review Taskforce noted that the lack of federal funding—despite adoption of the modality in routine practice—has resulted in an equity gap (Medicare Benefits Schedule Review Taskforce, 2018).

There are no current listings of PSMA PET/CT on the MBS, however, PET imaging combined with a different tracer (fluorodeoxyglucose, a radio-analogue of glucose), is listed for a restricted number of indications, not including prostate cancer (Items 61523–61646). A single MBS item for ^{68}Ga DOTA-peptide PET is also listed (Item 61647) (Australian Government Department of Health, 2020a).

Rationale

As discussed above, one of several radiopharmaceutical tracers may be used during a PSMA PET/CT scan. It has been advised that PSMA PET/CT can be treated as one intervention, irrespective of which tracer is used to target the PSMA receptor. Secondary analysis comparing across tracer options available in Australia should be considered, data permitting.

PASC noted the applicant's preference to not specify the radioactive tracer for the intervention, which would allow any available tracer to be used, including new tracers that may become available in the future. However, PASC advised that the application would need to demonstrate equivalence among tracers before a generic item descriptor could be considered appropriate, or else the evidence-supported tracer(s) would need to be specified.

According to expert clinical advice, there is no standard or preferred tracer in Australia. Choice is largely dictated by availability and logistics, namely, whether the tracer is made in-house or sourced through an external distribution network (personal communication, expert radiation oncologist, 25 June 2020).

16 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

The Applicant notes that where multiple similar radiotracers are available, MBS item descriptors for nuclear medicine do not specify which individual radiotracer should be used (personal email communication, 25 June 2020). However, this is not true for PET items, which specify the radiopharmaceutical (FDG, Ga-68 DOTA-peptide).

The PSMA ligand can be also be imaged with PET/MRI combinations, noting there is a prospective single centre, single arm Australian study comparing PSMA PET/MRI with conventional imaging in the clinical setting of BCR following definitive therapy (ACTRN12616000186459).

Comparator

The comparators for this application are conventional imaging modalities with:

- CT, and/or
- WBBS with SPECT/CT.

PASC agreed with the proposed comparators, noting that these are listed in European and US guidelines.

Background

A CT scan of the abdomen and/or pelvis is one of the tests that may be used to look for cancer that has metastasized, particularly in the lymph nodes and the area around the prostate (National Comprehensive Cancer Network, 2019).

A bone scan is a nuclear medicine imaging technology used to look for cancer that has metastasized to the bones. A bone scan may be used for patients with bone pain, for those at high risk of bone metastases, if there are changes in certain tests results, or to monitor treatment (National Comprehensive Cancer Network, 2019).

During a bone scan, a bisphosphonate labelled with technetium 99m (radioactive tracer) is injected intravenously to identify sites of active bone formation (osteogenesis) (Lee et al., 2012; National Comprehensive Cancer Network, 2019). Whole-body planar bone scans (i.e. WBBS) are widely used to detect bone metastases, but are limited by poor specificity (high false positive rate) (Palmedo et al., 2014). Combining WBBS with SPECT/CT permits precise co-registration of abnormal bone scan activity with skeletal anatomy (Lee et al., 2012). Importantly, specificity can be improved for histopathological-confirmed prostate cancer patients referred for a bone scan for staging or restaging (Palmedo et al., 2014).

The comparator diagnostic tests are currently MBS funded, with relevant item numbers listed below (Table 7). The Applicant advises that for most patients with prostate cancer, no additional healthcare resources are required when providing these comparator tests.

17 | P a g e   R A T I F I E D   P I C O   −   O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Table 7   Relevant MBS items for comparator CT and bone scan with SPECT/CT imaging modalities

MBS item number	Item descriptor and fee
56507	Computed tomography—scan of upper abdomen and pelvis with intravenous contrast medium and with any scans of upper abdomen and pelvis before intravenous contrast injection, when performed, not for the purposes of virtual colonoscopy and not being a service to which item 56807 or 57007 applies (R) (Anaes.) Fee: $480.05 Benefit: 75% = $360.05 85% = $408.05
56807 †	Computed tomography—scan of chest, abdomen and pelvis with or without scans of soft tissues of neck with intravenous contrast medium and with any scans of chest, abdomen and pelvis with or without scans of soft tissue of neck before intravenous contrast injection, when performed, not including a study performed to exclude coronary artery calcification or image the coronary arteries (R) (Anaes.) Fee: $560.00 Benefit: 75% = $420.00 85% = $476.00
61425	Bone study—whole body and single photon emission tomography, with, when undertaken, blood flow, blood pool and delayed imaging on a separate occasion (R) Fee: $600.70 Benefit: 75% = $450.55 85% = $516.00
61505	CT scan performed at the same time and covering the same body area as single photon emission tomography or positron emission tomography for the purpose of anatomic localisation or attenuation correction if no separate diagnostic CT report is issued and only in association with items 61302 to 61647 (R) Fee: $100.00 Benefit: 75% = $75.00 85% = $85.00

Notes: † = the Applicant advises that item 56807, which includes the chest, is used less frequently than item 56507 (upper abdomen & pelvis only).

Source: Item numbers listed on p.29 of application form, excluding item 61719 which has been removed (personal email communication, Applicant, 10 July 2020); item descriptor and fee information sourced from the MBS (Australian Government Department of Health, 2020a)

Population 1

The Applicant advises that prostate cancer patients with intermediate- to high-risk features would, in the absence of PSMA PET/CT, be referred for an abdominopelvic CT and a bone scan to determine nodal and metastatic spread. A regional MRI may be required to clarify findings of the CT/bone scan.

NCCN guidelines recommend the following imaging modalities for initial staging workup of patients with intermediate- or high-risk features (Mohler et al., 2019):

- Pelvic ± abdominal imaging for patients with intermediate- or high-risk features and predicted >10% probability of pelvic lymph node involvement.
- Bone imaging for patients with unfavourable intermediate-risk features who have T2 stage cancer and PSA level >10ng/ml.
- Bone imaging for all patients with high-risk features.

EAU guidelines recommend metastatic screening with at least cross-sectional abdominopelvic imaging plus a bone scan for patients with intermediate-risk features if their cancer is graded ISUP grade group 3 or above, and for all patients with high-risk features (Mottet et al., 2020).The Applicant predicts a near perfect substitution of conventional imaging modalities (CT and bone scan) with PSMA PET/CT for detecting pelvic nodal and distant metastatic disease in initial staging when ablative locoregional therapies are planned.

18 | P a g e   R A T I F I E D   P I C O   –   O C T O B E R   2 0 2 0

A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

PASC noted that the applicant expects near-complete substitution of conventional imaging with PSMA PET/CT.

Population 2

The Applicant advises that some patients with recurrent prostate cancer may be offered salvage radiotherapy to the pelvic lymph node pathways and/or prostate bed with the field of treatment determined empirically.

EAU guidelines specify that histological proof of local recurrence is not required prior to salvage radiotherapy, and that most patients undergo treatment without local imaging (Mottet et al., 2020). Precise localisation of local recurrences is required for focal dose escalation however, this treatment remains investigational at present (Mottet et al., 2020).

Alternatively, and despite the low sensitivity of conventional imaging, the Applicant advises that patients with recurrent prostate cancer may be referred for a bone scan and/or CT prior to salvage therapy to look for previously undetected metastatic disease, or in the hope that identifying the sites of disease will enable localised increases in radiotherapy doses.

NICE guidelines (NG131) recommend that patients with evidence of BCR after radical treatment, who are considering radical salvage therapy, be offered an isotope bone scan if their symptoms or PSA trends suggest metastasis (National Institute of Health and Care Excellence, 2019).

EAU guidelines recommend PSMA PET/CT rather than conventional imaging modalities in circumstances of BCR, noting that in asymptomatic patients, conventional imaging techniques such as abdominopelvic CT and bone scan imaging have a low diagnostic yield because BCR precedes clinical metastases by many years (Mottet et al., 2020). EAU guidelines also recommend PSMA PET/CT for excluding metastases for patients with persistent PSA >0.2ng/ml, given standard imaging with bone scan and MRI has a low diagnostic yield at PSA levels below 2ng/ml (Mottet et al., 2020).

In a review of the management of BCR, Artibani et al. (2018) document that the standard workup for detecting metastases involves a bone scan and abdominopelvic CT but highlight the poor ability of these imaging modalities to detect metastases in asymptomatic patients (Artibani et al., 2018).The Applicant predicts a near perfect substitution of conventional imaging modalities (CT and WBBS with SPECT/CT) with PSMA PET/CT for detecting pelvic nodal and distant metastatic disease in the setting of BCR when ablative locoregional therapies offer the best opportunity for improved oncological outcomes.

PASC noted that the applicant expects near-complete substitution of conventional imaging with PSMA PET/CT.

Rationale

For the purpose of ruling out pelvic nodal and distant metastatic disease, CT and bone scan are the relevant comparators.

19 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Other modalities may be used to confirm the presence of local recurrence. After radiation therapy, biopsy is a major predictor of outcomes when performed 18-24 months after treatment, and histological proof of local recurrence is needed prior to treatment (Artibani et al., 2018; Mottet et al., 2020).

Multiparametric MRI can be used for biopsy-targeting and guiding local treatment (Mottet et al., 2020) although in Australia, is not reimbursed for use in recurrent prostate cancer.

Outcomes

PASC considered that morbidity and mortality as a result of subsequent treatment was not an appropriate safety outcome for a diagnostic/staging intervention, and advised that this be removed. The Outcomes below were updated accordingly.

Patient relevant

The clinical claim is that PSMA PET/CT is superior to CT and WBBS with SPECT/CT in terms of analytical validity, clinical validity and clinical utility, in patients with biopsy-proven prostate adenocarcinoma with intermediate- and high-risk features, and in patients with recurrent prostate adenocarcinoma.

Safety outcomes

- Radiation exposure (patients, nuclear medicine technologists, nurses)
- Adverse reaction to the contrast agents, including renal toxicity

PASC noted that there are no adverse reactions to the radiopharmaceutical tracers, but adverse reactions can occur from the administration of radiological contrast agents

Effectiveness outcomes

Diagnostic accuracy

- Sensitivity and specificity
- Positive predictive value (PPV), negative predictive value (NPV)
- Area under the curve (AUC) of the receiver operating characteristic (ROC) curve
- Number of equivocal findings

Change in management

- Need for subsequent diagnostic tests, including biopsy i.e. investigations avoided
- Change in planned management (intent), including change in planned treatment modality, extension of radiation field
- Change in management i.e. overall change, types of changes, futile locoregional curative intent treatments avoided, therapies instigated

20 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Oncologic and patient outcomes

- Morbidity
- Mortality, including cancer specific mortality
- Survival, including overall survival, progression-free survival, metastases-free survival, ADT-free survival
- Quality of life

Healthcare system outcomes

- Cost of PSMA PET/CT (or comparator) imaging used for initial staging or restaging in patients with PSA persistence/recurrence
- Cost of additional imaging tests or biopsies required
- Cost of treatments received and/or costs offset due to avoidance of futile locoregional ablative procedure
- Total cost to MBS, PBS and other government health budgets.

Reference standard

The reference standard is an investigative medical test or series of tests used to determine the presence or absence of the target condition, assumed to be, theoretically, 100% sensitive and specific (Medical Services Advisory Committee, 2017).

The reference standard for detecting prostate cancer is usually histopathologic assessment combined with other imaging, clinical and biochemical findings.

A recently published systematic review and meta-analysis of ^{68}Ga-PSMA PET/CT for initial staging or restaging in BCR reported that half of the included studies (18 of 37) included histopathological correlation of ^{68}Ga-PSMA PET-positive lesions as a reference test (Perera et al., 2020). However, many studies performed targeted biopsies of suspicious lesions only. Five studies performed ^{68}Ga-PSMA PET prior to planned lymph node sampling (Perera et al., 2020).

In a key randomised controlled trial of PSMA PET/CT versus conventional imaging in initial staging of high-risk prostate cancer (Hofman et al., 2020), the reference standard for presence of nodal or distant metastases used a predefined composite panel that included histopathologic, imaging, clinical and biochemical findings. Cases were considered positive if one hard criterion (histopathological confirmation of adenocarcinoma or change of bone lesion to sclerotic or blastic on follow-up imaging), or three of the nine soft criteria (not listed here) were met.

PASC noted that histopathology is rarely used alone as a reference standard, and advised that a composite reference standard after 6 months' follow-up is more frequently used in the diagnostic accuracy studies, combining histopathology, imaging, clinical and biochemical findings.

21 | P a g e   R A T I F I E D   P I C O — O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Linked-evidence approach

A linked-evidence approach is the synthesis of systematically acquired evidence on the accuracy of a medical test, its impact on clinical decision-making, and the effectiveness of consequent treatment options (Merlin et al., 2013). By linking evidence from different sources, a linked-evidence approach forms a chain of argument to estimate the impact of a diagnostic test (Medical Services Advisory Committee, 2017).

MSAC guidelines specify that for a linked-evidence approach, the following pieces of information are generally required (Medical Services Advisory Committee, 2017):

- diagnostic performance and clinical validity (where relevant) of the investigative medical service
- clinical utility of the investigative medical service in terms of impact of positive vs. negative test results on patient management, contribution and clinical importance of false negatives vs. false positives, and direct impact of each therapeutic medical service option on health outcomes
- impact of repeat testing (if relevant)
- relative safety of performing the investigative service, encompassing immediate safety issues of directly performing the test and 'flow on' safety issues arising as a result of conducting the investigative service.

Rationale

Whilst direct evidence suggests PSMA PET/CT has superior sensitivity and specificity over conventional imaging (Hofman et al., 2020; Perera et al., 2020) and leads to changes in management in approximately half of patients (Han et al., 2018; Roach et al., 2018), determining the consequences of treatment instigated or avoided following PSMA PET/CT is challenging. A linked-evidence approach will likely be required to determine the patient relevant outcomes resulting from such changes in management.

Safety

The Applicant advises that adverse events relating to the administration of diagnostic PSMA-targeting PET radiotracers are extremely rare. Expert clinical advice confirmed the low risks associated with PSMA PET/CT (personal communication, expert radiation oncologist, 25 June 2020).

Notably, the patient is exposed to a low radiation dose during delivery of the intervention. A recent Australian clinical study found radiation exposure to be 10.9 mSv (95% confidence interval [CI] 9.9, 12.0) higher during conventional imaging than during PSMA PET/CT (Hofman et al., 2020). The radiation dose delivered with PSMA PET/CT was 8.4 mSv (95% CI 8.1, 8.7).

22 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Current and proposed clinical management algorithms

PASC accepted the current and proposed clinical management algorithms, noting that 'initial (N- and M-) staging' was the correct term for Population 1. However, PASC considered that "extrapelvic" should be clarified in the algorithms, since it is claimed that conventional imaging may underestimate the extent of pelvic lymph node involvement. PASC also queried for Population 2 whether it was limited to BCR or included 'PSA persistence'. The clinical management algorithms below have been updated according to PASC's advice.

Current clinical management algorithm for identified population

Clinical management algorithms depicting the management of patients in Populations 1 and 2 in the absence of PSMA PET/CT imaging are shown in Figure 1 and Figure 2, below.
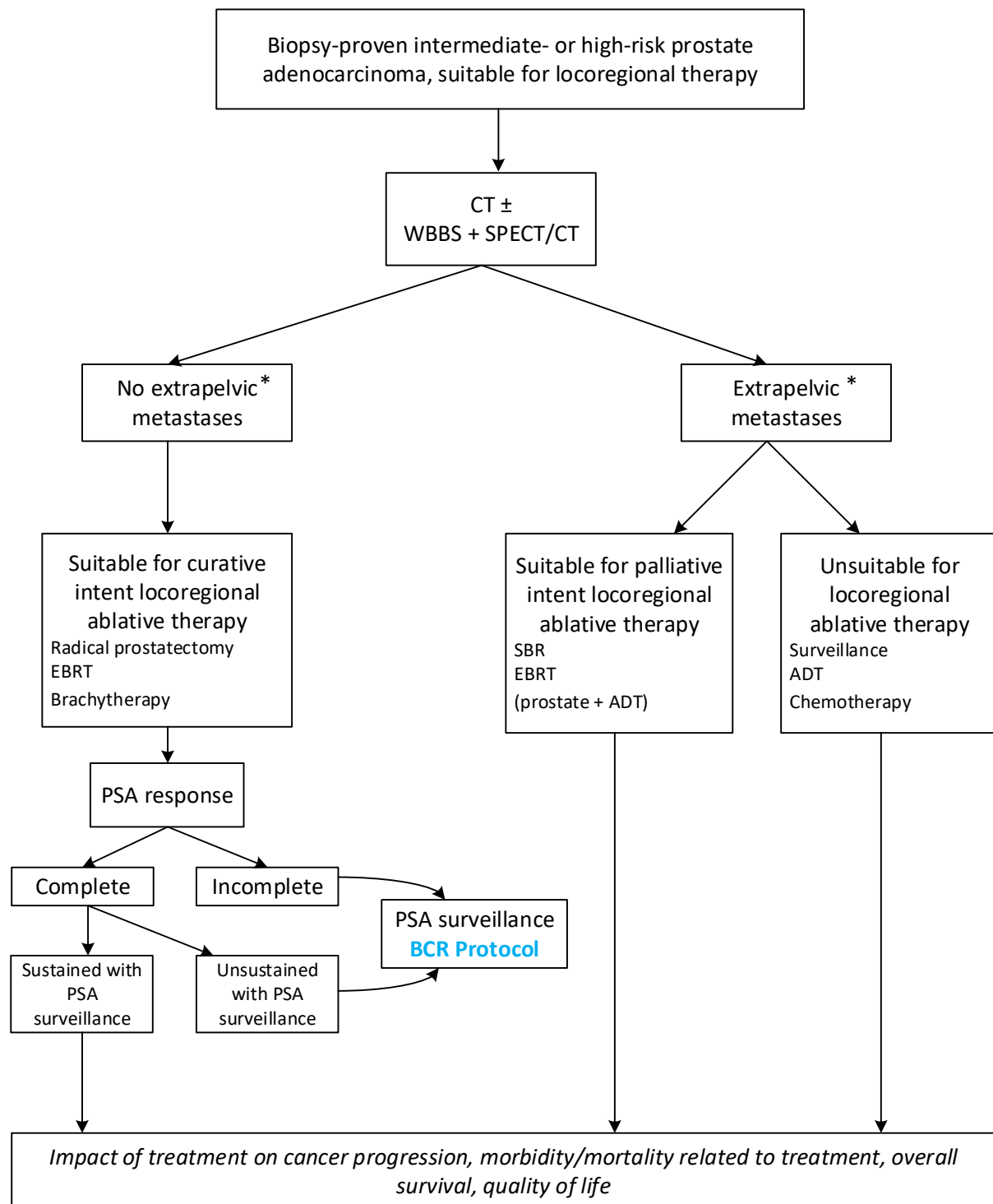
Proposed clinical management algorithm for identified population

Clinical management algorithms depicting the management of patients in Populations 1 and 2 if PSMA PET/CT imaging was available are shown in Figure 3and Figure 4, below.

Figure 1 Current clinical management algorithm for the initial N- and M-staging of intermediate- and high-risk patients (Population 1)

```
┌──────────────────────────────────────────────────┐
│  Biopsy-proven intermediate- or high-risk prostate│
│   adenocarcinoma, suitable for locoregional therapy│
└──────────────────────────────────────────────────┘
                        │
                        ▼
              ┌──────────────────┐
              │      CT ±         │
              │  WBBS + SPECT/CT  │
              └──────────────────┘
               /                  \
              ▼                    ▼
  ┌──────────────────┐      ┌──────────────────┐
  │ No extrapelvic *  │      │ Extrapelvic *     │
  │   metastases      │      │   metastases      │
  └──────────────────┘      └──────────────────┘
          │                   /              \
          ▼                  ▼                ▼
```

Suitable for curative intent locoregional ablative therapy	Suitable for palliative intent locoregional ablative therapy	Unsuitable for locoregional ablative therapy
Radical prostatectomy EBRT Brachytherapy	SBR EBRT (prostate + ADT)	Surveillance ADT Chemotherapy

```
          │
          ▼
   ┌──────────────┐
   │ PSA response │
   └──────────────┘
      /        \
     ▼          ▼
┌─────────┐ ┌───────────┐      ┌──────────────────┐
│Complete │ │Incomplete │─────▶│ PSA surveillance │
└─────────┘ └───────────┘      │   BCR Protocol   │
    │  \       /                └──────────────────┘
    ▼   ▼     ▼
┌──────────┐ ┌──────────┐
│Sustained │ │Unsustained│
│  with    │ │  with PSA │
│  PSA     │ │surveillance│
│surveillance│└──────────┘
└──────────┘
```

┌──┐
│ *Impact of treatment on cancer progression, morbidity/mortality related│
│   to treatment, overall survival, quality of life*   │
└──┘
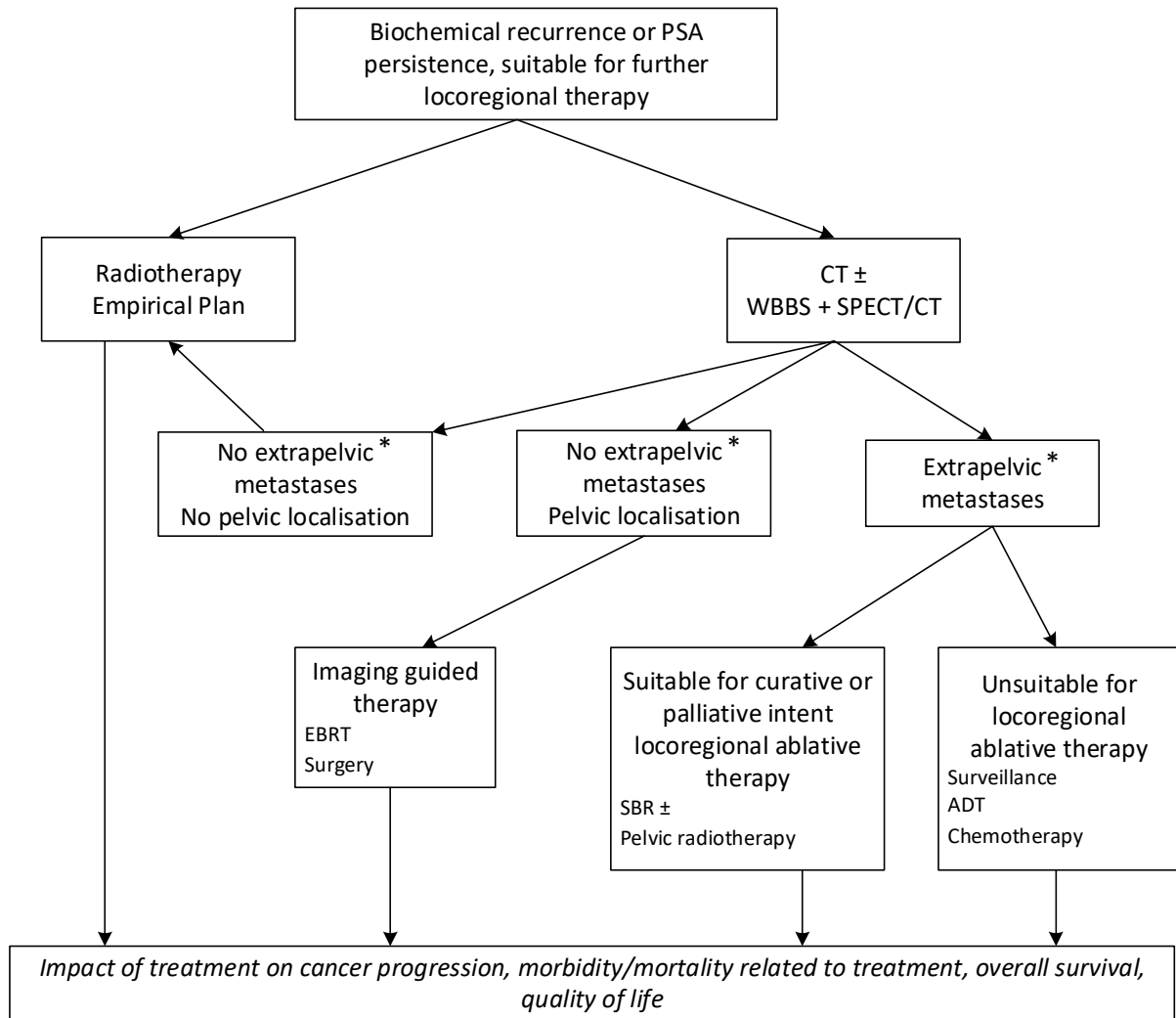
Abbreviations: ADT = androgen deprivation therapy; BCR = biochemical recurrence; CT = computed tomography; EBRT = external beam radiotherapy; PSA = prostate specific antigen; SBR = stereotactic body radiotherapy; SPECT = single photon emission tomography; WBBS = whole-body bone scan
*Extrapelvic refers to distant metastases

Source: adopted from management pathways provided by the Applicant

24 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Figure 2 Current clinical management algorithm for the restaging of patients with biochemical recurrence or PSA persistence (Population 2)

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

Source: adopted from management pathways provided by the Applicant

25 | P a g e   R A T I F I E D   P I C O   −   O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

Figure 3 Proposed clinical management algorithm for the initial N- and M-staging of intermediate- and high-risk patients (Population 1)
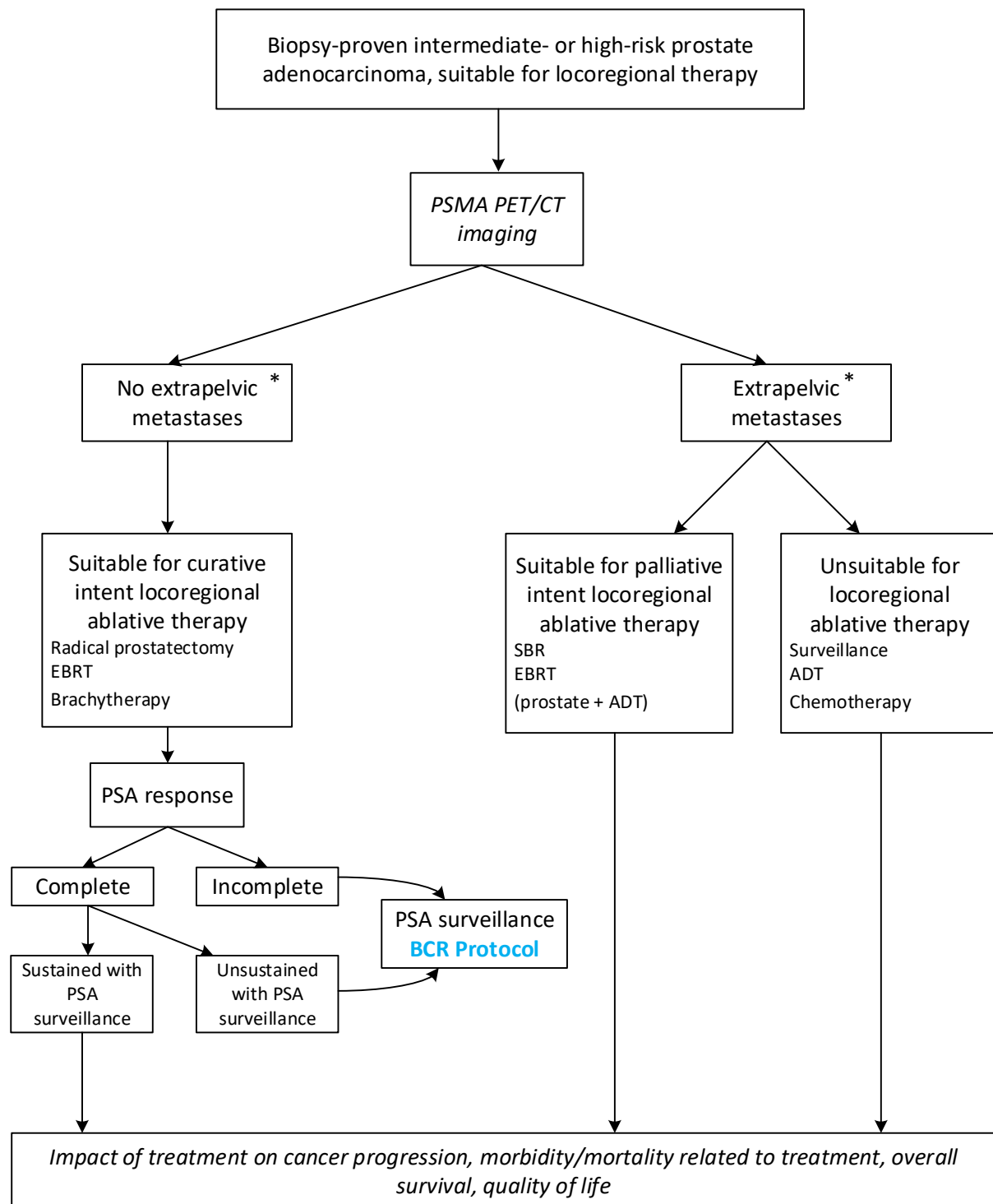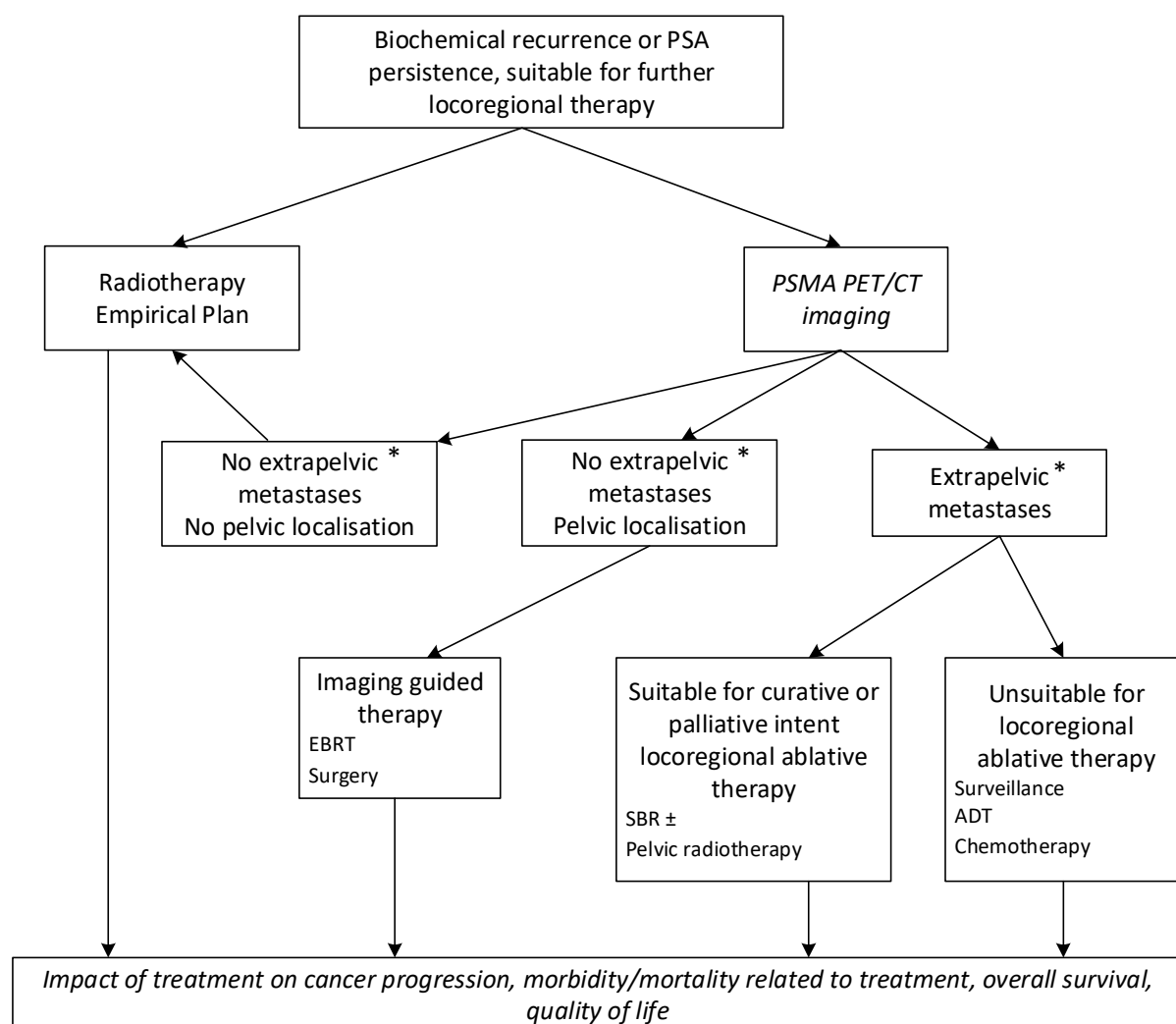

Abbreviations: ADT = androgen deprivation therapy; BCR = biochemical recurrence; EBRT = external beam radiotherapy; PSA = prostate specific antigen; PSMA PET/CT = prostrate specific membrane antigen positron emission tomography/computed tomography; SBR = stereotactic body radiotherapy
*Extrapelvic refers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

Source: adopted from management pathways provided by the Applicant

26 | P a g e   R A T I F I E D   P I C O   −   O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

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

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

Source: adopted from management pathways provided by the Applicant

Proposed economic evaluation

The Applicant claims that PSMA PET/CT has superior diagnostic accuracy compared to conventional imaging (CT ± WBBS with SPECT/CT) for detecting pelvic nodal and distant metastases. The Applicant claims that PSMA PET/CT, by virtue of its superior diagnostic accuracy, improves a range of health care outcomes for individual patients.

27 | P a g e   R A T I F I E D   P I C O — O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

By detecting previously unknown sites of prostate cancer, PSMA PET/CT may reduce the number of patients subjected to futile locoregional interventions, facilitate the delivery of metastasis-directed therapy such as surgery or SBRT for patients with oligometastatic disease, and improve treatment delivery for patients receiving locoregional ablative procedures with curative intent.

The most appropriate economic evaluation is a cost-effectiveness or cost-utility analysis to determine overall costs relative to the effectiveness of the intervention in improving the detection of pelvic nodal and distant metastasis, the choice and delivery of treatment, and subsequent oncologic and patient outcomes (relative to the comparator).

PASC confirmed that a cost-effectiveness or cost-utility analysis was appropriate.

Proposed item descriptor and fee

PASC advised that, for Population 2, the words "with curative intent" should be replaced with "to delay systemic therapy". PASC noted that the treatment goal for recurrent disease is not curative, but that the intent of treatment should be specified to prevent leakage to therapy monitoring. The wording in the MBS item descriptor for population 2 was updated to reflect PASC's advice.

The MBS item descriptors and associated fees proposed by the Applicant are listed below. The application provided a breakdown of the proposed fee comprising of the radiotracer and transport ($500) and the PET/CT imaging and report ($900).

Category 5 – DIAGNOSTIC IMAGING SERVICES
Prostate specific membrane antigen (PSMA) PET study, performed for the initial N- and M- 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: $1,400

Category 5 – DIAGNOSTIC IMAGING SERVICES
Prostate specific membrane antigen (PSMA) PET 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 Fee: $1,400

PASC noted that the proposed item descriptors do not align with other MBS items for PET. For example, the proposed descriptors specify "PET/CT", while other descriptors specify "PET" only. PASC advised that alignment with other PET items should be considered in the application.

PASC advised that the application would need to justify the proposed fee, which is higher than the fee for other PET items (including Item 61647 for Ga-68 DOTA-peptide PET).

PASC noted that there is a separate fee of $100 for CT when performed at the same time as PET (MBS item 61505).

28 | P a g e   R A T I F I E D   P I C O – O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

The applicant noted PASC's advice, however it noted all the current MBS descriptors follow from the 2000 PET review process before PET/CT was available. The applicant noted that the accuracy figures for PET alone have not been defined and claim that the false positive rate would be higher with PET alone. Further, the applicant considered the economics and patient inconvenience of longer scan times using PET alone indicate that the indication should reflect current practice and not historical largely irrelevant precedent. Therefore, the applicant concluded that in that case the current fee for CT in conjunction with PET should be rolled up into the proposed PET/CT fee. The applicant agreed that adequate justification for higher fee for PSMA PET/CT than existing PET +CT item numbers requires justification in the application.

Consultation Feedback

Targeted consultation feedback

Eight organisations responded to the request for targeted consultation feedback, universally in support of MBS funding for PSMA PET/CT imaging in prostate cancer.

Population

The value of PSMA PET/CT in the settings of high-risk localised disease prior to definitive therapy, and in biochemical recurrence prior to salvage radiation therapy is apparent.

Two organisations commented that PSMA PET/CT has a limited role in advanced disease, unless linked to PSMA-directed therapy, and that the argument supporting PSMA PET/CT in the therapeutic monitoring setting is speculative at present. Therapeutic monitoring has since been removed as a population from the current application.

Two organisations recommended MBS items also be made available for PSMA PET/CT for the following indications:

- Investigation of raised PSA where MRI is contraindicated,
- Initial staging in low-grade disease, and
- Re-staging in patients with metastatic prostate cancer where such information would influence treatment options.

Intervention

Multiple organisations supported an MBS item descriptor that is open to any PSMA radiotracer (as proposed).

One responder noted that ^{68}Ga- and ^{18}F-labelled radiotracers are not interchangeable. Another noted a distinction should be made between ^{68}Ga- and ^{18}F-labelled radiotracers, given the potential differences in performance, and associated logistics.

29 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
Application 1632: PSMA PET/CT imaging for informing
treatment in patients with prostate cancer

Comparator

Where discussed, responders agreed with the comparators identified in the application form.

Other

Where discussed, responders agreed with the proposed MBS fee. Two organisations acknowledged the proposed fee is higher than the existing fee for FDG PET; one justified this as appropriate given the higher radiopharmaceutical cost of PSMA (*vs.* FDG), the other felt the scheduled fee for FDG PET is inadequate.

Many responders expressed a preference for a single MBS item (rather than multiple) to avoid unnecessary confusion.

Two organisations discussed the possibility of restricting patients approved for PSMA PET/CT from accessing an MBS-funded CT and/or bone scan for the same indication, one responder emphasising the need to ensure patients' radiation doses are kept as low as reasonably possible (radiation dose is cumulative over a lifetime). The same responder emphasised the importance of ensuring WBBS and CT with contrast are still available in circumstances were PSMA PET/CT is not (e.g. rural settings).

PASC noted the extensive consultation feedback, which was supportive of the application. PASC noted two organisations raised the issue of ownership of intellectual property for the radiopharmaceuticals. PASC considered this may need to be considered in the application. The Assessment Report should note intellectual property details for each radiopharmaceutical, and any impact this may have on patient access or cost.

The applicant clarified that one of the applicants, Cyclotek Australia Pty Ltd, had obtained an exclusive license to distribute ^{18}F-DCFPyL in Australia from John Hopkins University (USA) who hold the IP for this molecular entity. They noted that the IP rights to ^{68}Ga-PSMA-11 and several other PSMA radiotracers was unclear at the time of the PSAC meeting, however the issue will be addressed within the Assessment Report and any related access and cost issues will also be addressed.

PASC noted two organisations discussed the possibility of restricting patients approved for PSMA PET/CT from accessing an MBS-funded CT and/or bone scan for the same indication. However, PASC advised that restricting access to subsequent MBS-funded CT and/or whole-body bone scan was not appropriate, as patients may receive these scans for various reasons that are unrelated to prostate cancer.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR (applicant-developed assessment report).

30 | P a g e   R A T I F I E D   P I C O − O C T O B E R   2 0 2 0
A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
t r e a t m e n t   i n   p a t i e n t s   w i t h   p r o s t a t e   c a n c e r

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31 | P a g e   R A T I F I E D   P I C O   −   O C T O B E R   2 0 2 0

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A p p l i c a t i o n   1 6 3 2 :   P S M A   P E T / C T   i m a g i n g   f o r   i n f o r m i n g
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