



**Australian Government**

**Department of Health**

# **Application Form**

## **PSMA PET/CT imaging for guiding treatment of men with Prostate Cancer**

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

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

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

Email: [hta@health.gov.au](mailto:hta@health.gov.au)

Website: [www.msac.gov.au](http://www.msac.gov.au)

# PART 1 – APPLICANTS DETAILS

## 1. Applicants details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: CYCLOTEK (AUST) PTY LTD

ABN: 30 096 066 796

Business trading name: CYCLOTEK

Corporation name: Australasian Association of Nuclear Medicine Specialists (AANMS)

ABN: 71 158 642 267

Business trading name: Australasian Association of Nuclear Medicine Specialists

Primary contact name 1: [REDACTED]

Primary contact numbers

Business: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

Primary contact name 2: [REDACTED]

Primary contact numbers

Business: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

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

Yes

No

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

Yes

No

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 3. Application title

PSMA PET/CT for guiding treatment of men with prostate cancer

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

Prostate cancer is the most commonly diagnosed cancer (>19000 cases pa) and second most common cause of cancer death (> 3000 pa) in Australian men.

Between 1986–1990 and 2011–2015, five-year relative survival from prostate cancer improved from 59% to 95%. More than 90000 Australian men are estimated to be living with prostate cancer.

Men with prostate cancer are living longer, but not necessarily living well. Depression, anxiety, urinary incontinence, and impairments in sexual and bowel function are common. Quality of life declines over time with 35–40% of men experiencing poorer physical and mental quality of life outcomes and life satisfaction 10 years after the diagnosis due to effects of the disease and treatment.

The cost of treating prostate cancer is high, estimated to be \$500 million in 2013 for persons diagnosed between 2009 and 2013 and these figures don't include costs paid by patients.

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

In Australia PET/CT imaging is recognised as a safe, simple, and cost-effective diagnostic imaging test facilitating healthcare outcomes for patients with several lethal cancers.

PSMA PET/CT imaging involves the administration of one of several radiopharmaceuticals that share the characteristic of highly specific binding to Prostate Specific Membrane Antigen (PSMA). PSMA is present in much higher concentrations in prostate cancer cells than in normal prostate and other tissues. This overexpression of PSMA by prostate cancers allows for highly specific detection of tumour sites throughout the body with far greater sensitivity than other imaging modalities currently funded through the MBS. It is already used around the world to make critical treatment decisions. The advantages of PSMA PET/CT are particularly apparent for men in whom spread has occurred outside the prostate gland both at staging and later in the course of the disease and for whom prognosis is significantly impaired.

### 6. (a) Is this a request for MBS funding?

- Yes  
 No

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

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

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

Not applicable

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

- i.  An amendment to the way the service is clinically delivered under the existing item(s)
- ii.  An amendment to the patient population under the existing item(s)
- iii.  An amendment to the schedule fee of the existing item(s)

- iv.  An amendment to the time and complexity of an existing item(s)
- v.  Access to an existing item(s) by a different health practitioner group
- vi.  Minor amendments to the item descriptor that does not affect how the service is delivered
- vii.  An amendment to an existing specific single consultation item
- viii.  An amendment to an existing global consultation item(s)
- ix.  Other (please describe below):

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

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

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

- Yes
- No

**(g) If yes, please advise:**

Not applicable

**7. What is the type of service:**

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

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

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

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

- Pharmaceutical / Biological
- Prosthesis or device
- No

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

- Yes
- No

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

**(c) Not applicable If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?**

- Yes (please provide PBAC submission item number below)
- No

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

Not applicable

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

- Yes  
 No

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

Not applicable

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

- Yes  
 No

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

- Yes  
 No

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

Not applicable

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

Single use consumables: Insert description of single use consumables here

Multi-use consumables: Insert description of multi use consumables here

## PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: Sterile radioactive tracer for intravenous injection

Manufacturer's name: CYCLOTEK (AUST) PTY LTD and it's subsidiary manufacturing companies  
Public Hospitals, Private Hospitals, Private Imaging Practices, other companies operating GMP  
manufacturing facilities

Sponsor's name: CYCLOTEK (AUST) PTY LTD; AANMS

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

- Class III  
 AIMD  
 N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

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

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

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

ARTG listing, registration or inclusion number: Insert ARTG number here

TGA approved indication(s), if applicable: Insert approved indication(s) here

TGA approved purpose(s), if applicable: Insert approved purpose(s) here

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

- Yes (please provide details below)  
 No

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

- Yes (please provide details below)  
 No

Estimated date of submission to TGA: Insert date of submission here

Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)

Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

## PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Scope of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
<p>Please note that only a small sample of the available evidence has been summarised here. Please see the attached spreadsheet where the published evidence has been categorised according to the Fryback and Thornbury hierarchical model of Diagnostic Imaging Efficacy, PSMA PET tracer used and clinical indication. Original papers have also been supplied where available</p>					
1.	Meta-analysis of Management Impact	Impact of 68Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis	Fifteen studies (1163 patients) were included. The pooled proportion of management changes was 54% (95% confidence interval 47–60%). 68Ga-PSMA PET had a large impact on the management of patients with prostate cancer. Greater PET positivity was associated with higher proportion of management changes.	<a href="https://doi.org/10.1016/j.eururo.2018.03.030">https://doi.org/10.1016/j.eururo.2018.03.030</a>	2018
2.	Non Randomised Trial	The impact of 68Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study.	Australian prospective multicentre trial of 431 patients examining management impact of 68GaPSMA11 PET/CT scanning using pre/post scanning questionnaire. Overall management change occurred in 51% of patients	<a href="https://doi.org/10.2967/jnumed.117.197160">doi:10.2967/jnumed.117.197160</a>	2018

	<b>Scope of study design*</b>	<b>Title of journal article or research project (including any trial identifier or study lead if relevant)</b>	<b>Short description of research (max 50 words)**</b>	<b>Website link to journal article or research (if available)</b>	<b>Date of publication***</b>
3.	Non Randomised Trial	A Prospective Study on 18F-DCFPyL PSMA PET/CT Imaging in Biochemical Recurrence of Prostate Cancer	130 patients with biochemical recurrence after radical prostatectomy or curative intent radiotherapy investigated with 18F-DCFPyL PET/CT. Found detection rates increasing from 60% to 92% for PSA levels <.5 and >2ng/ml respectively. Management plans changed in 87% of patients	DOI: 10.2967/jnumed.119.226381	2019
4.	Retrospective observational study	18F-DCFPyL PET/CT in primary staging of prostate cancer	131 consecutive patients undergoing 18F-DCFPyL PET/CT for primary staging found 98% positivity in primary tumour. 69 patients had positive nodal uptake with less than half positive on CT. Nodes were found outside the field of extended lymph node dissection in 43% of patients	<a href="https://doi.org/10.1186/s41824-018-0044-0">https://doi.org/10.1186/s41824-018-0044-0</a>	2018
5.	Prospective observational study	A Prospective Study of 18F-DCFPyL PSMA PET/CT Restaging in Recurrent Prostate Cancer following Primary External Beam Radiotherapy or Brachytherapy	Multi-institutional study of 79 men with biochemical recurrence following primary radiotherapy showing increased detection with 18F-DCFPyL PET/CT of recurrence sites in prostate, nodes and distant metastases and management change in 43%	<a href="https://doi.org/10.1016/j.ijrobp.2019.11.00">doi.org/10.1016/j.ijrobp.2019.11.00</a>	2019



	<b>Scope of study design*</b>	<b>Title of journal article or research project (including any trial identifier or study lead if relevant)</b>	<b>Short description of research (max 50 words)**</b>	<b>Website link to journal article or research (if available)</b>	<b>Date of publication***</b>
6.	Retrospective observational study	Early lesion detection with 18F-DCFPyL PET/CT in 248 patients with biochemically recurrent prostate cancer	Analysis 248 patients with biochemical recurrence looking at positivity related to disease site/Gleason score /PSA level. Overall postivity 86%, 59% PSA<.5ng/ml. Extraprostatic lesions in >39% of PSA < 1ngm/ml in patients thought suitable for prostate bed radiotherapy prior to 18F-DCFPyL PET/CT findings	10.1007/s00259-019-04385-6	2019
7.	Retrospective Observational Study	Evaluation of Hybrid 68Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy	Study of comparative accuracy of 68GaPSMA11 PET/CT compared to CT in 248 patients with BCR showing only 3 patients with exclusively positive findings on CT	DOI: 10.2967/jnumed.115.154153	2015

	<b>Scope of study design*</b>	<b>Title of journal article or research project (including any trial identifier or study lead if relevant)</b>	<b>Short description of research (max 50 words)**</b>	<b>Website link to journal article or research (if available)</b>	<b>Date of publication***</b>
8.	Systemic Review and Meta-analysis	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	37 articles including 4790 patients analysed. Ga-68-PSMA PET improves detection of metastases with biochemical recurrence, particularly at low pre-PET PSA levels of >0.2 ng/ml (33%) and 0.2–0.5 ng/ml (45%). Significant differences in positivity after biochemical recurrence in the prostate bed were noted between radical prostatectomy (22%) and radiotherapy (52%) patients. On per-node analysis, high sensitivity (75%) and specificity (99%) were observed.	<a href="https://doi.org/10.1016/j.eururo.2019.01.049">doi.org/10.1016/j.eururo.2019.01.049</a>	2019
9.	Systemic Review and Meta-analysis	68Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis	Fifteen 68Ga-PSMA PET/CT studies with 1256 patients met the inclusion criteria. Overall detection rate of 81% and 53% for PSA < .5ng/ml in biochemical recurrence group. In histologically validated studies FP rate for lymph node metastases 3%	<a href="https://dx.doi.org/10.1016/j.euf.2016.11.002">dx.doi.org/10.1016/j.euf.2016.11.002</a>	2016

	<b>Scope of study design*</b>	<b>Title of journal article or research project (including any trial identifier or study lead if relevant)</b>	<b>Short description of research (max 50 words)**</b>	<b>Website link to journal article or research (if available)</b>	<b>Date of publication***</b>
10.	Prospective diagnostic accuracy study	Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer  A Prospective Single-Arm Clinical Trial	single arm study of 635 BCR patients. detection rates significantly increased with prostate-specific antigen (PSA): 38%for <0.5 ng/mL (n = 136), 57%for 0.5 to <1.0 ng/mL (n = 79), 84%for 1.0 to <2.0 ng/mL (n = 89), 86%for 2.0 to <5.0 ng/mL (n = 158), and 97%for5.0 ng/mL (n = 173, P < .001). Interreader reproducibility was substantial (Fleiss $\kappa$ , 0.65-0.78). 73 of 79 (92%)	doi:10.1001/jamaoncol.2019.0096	2019
11.	Comparative Diagnostic Accuracy Study	PSA-stratified performance of 18F- and 68Ga-labeled tracers in PSMA-PET imaging  of patients with biochemical recurrence of prostate cancer	Study of 191 patients with PSMA 11 and DCFPyL PET/CT imaging for BCR. 25 patients examined sequentially with both tracers. Found PSA-stratified sensitivity was 88% (15/17) for 18F-DCFpyL and 66% (23/35) for 68Ga-PSMA-HBED-CC.	doi:10.2967/jnumed.116.185538	2017
12.	Non randomised trial	68Ga-PSMA-11 PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: Impact on Salvage Radiotherapy Planning	Prospective study of 270 patients with BCR. Post-hoc analysis of 68Ga-PSMA-11 PET/CT implies a major impact on prospective SRT planning in 52/270 patients (19%) with PCa early BCR (PSA<1.0 ng/ml).	doi:10.2967/jnumed.117.201749	2018

	<b>Scope of study design*</b>	<b>Title of journal article or research project (including any trial identifier or study lead if relevant)</b>	<b>Short description of research (max 50 words)**</b>	<b>Website link to journal article or research (if available)</b>	<b>Date of publication***</b>
13.	Retrospective observational study	68Ga-PSMA-11 PET/CT in Primary and Recurrent Prostate Carcinoma: Implications for Radiotherapeutic Management in 121 Patients	Mixed population with change in disease extent planned radiotherapy field compared to conventional imaging in 41% and 51% of patients respectively	doi:10.2967/jnumed.118.211086	2018
14.	Retrospective Diagnostic Accuracy Study	Diagnostic Accuracy of Ga-68-HBED-CC-PSMA-Ligand- PET/CT before Salvage Lymph Node Dissection for Recurrent Prostate Cancer	Pathologically controlled study of 30 patients treated with salvage pelvic lymph node dissection after 68GaPSMA11 PET/CT assessment. Necessary short diameter of tumor deposits in LNM required to reach a detection rate of 50% and 90% was estimated to be $\geq 2.3$ mm and $\geq 4.5$ mm, respectively.	doi: 10.7150/thno.18421	2017
15	RCT	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	A randomised controlled trial of 300 patients examining the diagnostic accuracy of 68GaPSMA11PET/CT compared to conventional imaging in primary prostate cancer staging prior to curative intent therapy with respect to diagnostic accuracy and independent and incremental management impact	<a href="https://doi.org/10.1016/S0140-6736(20)30314-7">https://doi.org/10.1016/S0140-6736(20)30314-7</a>	2020

	<b>Scope of study design*</b>	<b>Title of journal article or research project (including any trial identifier or study lead if relevant)</b>	<b>Short description of research (max 50 words)**</b>	<b>Website link to journal article or research (if available)</b>	<b>Date of publication***</b>
16	Observational Study	Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer	Retrospective study of 10 patients with metastatic prostate cancer before and after ADT demonstrating 6 with residual 68GsPSMA11 PET/CT uptake with PSA complete response (<.1ng/ml)	<a href="https://doi.org/10.1007/s00259-018-4079-z">doi.org/10.1007/s00259-018-4079-z</a>	2018
18	Prospective Observational Study	Rapid modulation of PSMA expression by Androgen deprivation: Serial 68Ga PSMA-11 PET in men with hormone sensitive and castrate resistant prostate cancer commencing androgen blockade.	ADT commenced in 8 men with castrate naive (CS) and 7 patients castrate resistant (CR) metastatic prostate cancer following baseline 68GaPSMA11 PET/CT imaging with sequential follow up imaging at 9,18 and 28 days post ADT (second generation). All CS showed decreased PSMA PET uptake at day 9 and fall in PSA by day 28. Following early response 3/8 demonstrated increased or stable PSMA uptake despite ongoing PSA response. In CR patients PSMA uptake increased in all with more delayed PSA response occurring in 5/7 with 2/7 showing no PSA decline	<a href="https://doi.org/10.2967/jnumed.118.223099">doi:10.2967/jnumed.118.223099</a>	2019

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

\*\*\* If the publication is a follow-up to an initial publication, please advise.

**18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.**

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Non-randomised Trial	IMPPORT Trial	Impact of 18F-DCFPyL PET scanning in 100 patients undergoing post-prostatectomy Radiotherapy for BCR compared to CT	ACTRN12618001530213	Interim data on first 76 patients to be presented at EAU 19 March.
2.	Non-randomised Trial	COMPyL Trial	Evaluating concordance between sites of prostate cancer reported on 18F-DCFPyL PET, 68GaPSMA11PET/CT and histopathology in patients undergoing radical prostatectomy and	ACTRN pending	January 2021
3.	Intervention Model: Single Group Assignment Primary Purpose: Diagnostic Masking: None (Open Label)	Differences in Optimal Prostate Cancer Patient Management as Proposed by a Panel of Experts Before and After 18F-DCFPyL PET/CT	Multi-centre, single-arm, open-label, phase III trial 1500 patients with biopsy-proven prostate cancer. Administration of 18F-DCFPyL followed by a PET/CT scan. Differences in theoretical optimal clinical management based on a review of clinical, biochemical and radiographic subject data before and after 18F-DCFPyL PET/CT imaging by a central panel of experts.	NCT03459820, 18-002	unknown

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
4.	Diagnostic Accuracy	A PrOspective Phase 2/3 Multi-Center Study of 18F-DCFPyL PET/CT Imaging in Patients With PRostate Cancer: Examination of Diagnostic AccuracY (OSPREY)	385 patients enrolled in study. Sensitivity and Specificity of 18F-DCFPyL PET/CT imaging to detect metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in patients with high risk prostate cancer undergoing radical prostatectomy with lymph node dissection. Sensitivity of 18F-DCFPyL PET/CT imaging to detect prostate cancer within sites of metastasis or local recurrence relative to histopathology in Cohort B	<a href="#">NCT02981368</a>	Results reported in abstract form only.  J Nucl Med May 1, 2019 vol. 60

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
5.	Diagnostic Accuracy	CONDOR A Phase 3, Multi-Center, Open-Label Study to Assess the Diagnostic Performance and Clinical Impact of 18F-DCFPyL PET/CT Imaging Results in Men With Suspected Recurrence of Prostate Cancer	200 patients evaluated with uninformative other imaging results for correct Localization Rate (CLR), defined as percentage of subjects with a one-to-one correspondence between localization of at least one lesion identified on 18F-DCFPyL PET/CT imaging and the composite truth standard. Percentage of subjects with a change in intended prostate cancer treatment plans due to 18F-DCFPyL PET/CT imaging results.	NCT03739684	Initial results reported December 23 2019 in press release.
6.	Randomised Phase 2 Trial	TherapP Trial	200 men with recurrent prostate cancer randomised to either 177LuPSMA 617 therapy or carbazitaxol. Suitability for treatment determined with 68GaPSMA11, primary end point PSA response.	doi: 10.1111/bju.14876.	Primary analysis completed with abstract submitted for ASCO 2020

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

\*\*\*Date of when results will be made available (to the best of your knowledge).



## PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

**19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

Australian Association of Nuclear Medicine Specialists

The Royal Australian and New Zealand College of Radiologists

Australian and New Zealand Society of Nuclear Medicine

These are the peak bodies who represent the only health care professionals who are licensed to provide PET/CT scan services in Australia

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

Australian Association of Nuclear Medicine Specialists

Royal Australian and New Zealand College of Radiologists

Australian and New Zealand Society of Nuclear Medicine

**21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

Movember -letter of support for this MSAC application to be progressed is attached.

Cancer Council of Australia (The Executive Assistant to the CEO advised that Cancer Council would only engage as part of a public consultation process)

Prostate Cancer Foundation Australia (The Head of Advocacy and Strategy was contacted and she indicated that organisational policy does not allow providing support letters as MSAC has requested)

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

Other manufactures are:

Royal Brisbane Hospital

Royal Prince Alfred Hospital (Sydney)

Royal North Shore Hospital (Sydney)

Westmead Hospital (Sydney)

St Vincent's Hospital (Sydney)

Peter MacCallum Cancer Centre (Melbourne)

Brett and Peter Proprietary Limited

SAMRI (Adelaide)

Sir Charles Gardner Hospital (Perth)

Royal Hobart Hospital

MIA Frankston

RIL Albury Base Hospital

Numerous Nuclear Medicine Private Practices throughout Australia

**23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

Name of expert 1: [REDACTED]

Telephone number(s): [REDACTED]

Email address: [REDACTED]

Justification of expertise: Urological Surgeon and Prostate Cancer Researcher

Name of expert 2: [REDACTED]

Telephone number(s): [REDACTED]

Email address: [REDACTED]

Justification of expertise: Radiation Oncologist and Prostate Cancer Researcher

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

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

## **PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION**

### **24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:**

Currently prostate cancer is the most commonly diagnosed cancer (>19000 cases per annum) and the second most common cause of death (> 3000 per annum) in Australian men. The risk of developing prostate cancer before their 85<sup>th</sup> birthday is 1 in 6 for Australian men.

More than 90000 Australian men are estimated to be living with prostate cancer.

Between 1986–1990 and 2011–2015, five-year relative survival from prostate cancer improved from 59% to 95%. This improvement in survival is most likely due to the impact of better diagnosis and treatment on the natural history of the disease.

Prostate Cancer originates in the prostate gland and is most commonly adenocarcinoma in type. Many prostate cancers are indolent by nature and do not affect longevity, particularly in older men with significant co-morbidities. However, untreated prostate cancers grow locally and can reach a size where men experience difficulty and/or discomfort urinating and blood in the urine or sperm. Over time, if untreated, prostate cancer spreads to other tissues such as lymph nodes, bones, lungs and liver and can lead to bone pain, spinal cord compression, weight loss, fatigue, shortness of breath and is ultimately fatal.

By the time symptoms have developed prostate cancer is most commonly incurable. Screening by digital rectal examination is very insensitive for detecting early stage curable disease.

With the advent of Prostate Specific Antigen Testing (PSA) earlier diagnosis has been facilitated and currently nearly 80% of patients have Stage 1 or 2 disease at diagnosis with a high chance of cure using loco-regional treatments such as radical prostatectomy and radiotherapy. Five-year survival rates are currently in excess of 95% for patients with Stage 1-3 disease. For patients diagnosed with prostate cancer in 2011, only 4% of patients had Stage IV disease (distant metastases) that is currently incurable, leading to a reduction in 5 year survival to 36% in this group.

Men with prostate cancer are living longer, but not necessarily living well. Quality of life declines over time with 35–40% of men experiencing poorer physical and mental quality of life outcomes and life satisfaction 10 years after the diagnosis due to effects of the disease and treatment. Depression, anxiety, urinary incontinence, and impairments in sexual and bowel function are common.

The cost of treating prostate cancer is also high, estimated to be \$500 million in 2013 for persons diagnosed between 2009 and 2013 and this doesn't include costs paid by patients themselves. These estimates also do not incorporate the cost of more advanced and more expensive androgen deprivation drugs introduced into clinical practice in the last 5 years.

### **25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

Three primary populations that would be targeted for PSMA PET/CT imaging are men with:

- Prostate cancer that is biopsy proven with intermediate or high-risk features and where loco-regionally directed curative intent ablative therapy is planned
- Prostate cancer with biochemical recurrence and for whom active therapy is likely to be considered

- Patients with proven metastatic prostate cancer currently receiving therapy or in whom systemic or localised therapy is being considered and where PSMA PET/CT imaging will provide superior prognostic information and treatment guidance

### **Presentation for diagnostic imaging**

Irrespective of MBS funding, patients with prostate cancer will be referred for this service when their attending specialist medical practitioners believes the patient's disease management will be favourably influenced by incremental knowledge provided by PSMA PET/CT imaging.

This pattern of referral has already been established in the 5 years since the technique has been available in Australia. Cyclotek Pty Ltd alone has supplied more than 8000 doses to date in Australia under SAS provisions and in New Zealand since late 2016.

Most commonly the information sought will pertain to the extent of prostate cancer and the exact location of tumour sites to decide whether loco-regional curative intent treatments are feasible and, if so, to guide those treatments to incorporate all sites of disease. In a much smaller number of patients, information about the magnitude and homogeneity of PSMA expression will be required to weigh the potential benefits of radionuclide targeted therapy or to gauge the response of prostate cancer metastases to other systemic therapies such as chemotherapy or androgen deprivation therapy.

From the perspective of personalising cancer care with a view to achieving optimal individual patient outcomes it is proposed that patients with prostate cancer should be eligible for MBS funded PSMA PET/CT imaging whenever this intervention is judged to have greater clinical and cost utility than comparator imaging techniques or alternative management approaches

### **Primary staging**

Patients are likely to be referred for PSMA PET/CT imaging by surgeons and radiation oncologists following PSA testing, prostate biopsy and multiparametric MRI when intermediate and high-risk prostate cancers are detected and loco-regionally directed curative intent ablative therapies offer optimal outcomes for patients with truly loco-regionally confined cancer.

### **Biochemical recurrence**

Patients are also likely to be referred by surgeons and radiation oncologists for PSMA PET/CT imaging when biochemical recurrence of prostate cancer is detected following prior loco regional ablative procedures. In this common clinical scenario further (salvage) loco-regional ablative procedures may improve oncological outcomes or achieve cure particularly when guided by the PSMA PET/CT to cover appropriate regions rather than given "blind". If extra pelvic metastatic disease is present the patient may be best treated with systemic therapies.

### **Evaluation of therapeutic response and guiding therapy**

Patients will be referred by surgeons, radiation oncologists and medical oncologists for PSMA PET/CT imaging to evaluate therapeutic response at all stages of the disease when they judge that PSMA PET/CT imaging will provide superior prognostic information and treatment guidance to comparator diagnostic strategies including comparator imaging tests.

Patients will be referred by surgeons, radiation oncologists and medical oncologists if progressive prostate cancer patient symptoms indicate that more information about the location and extent of prostate cancer is required to consider treatment change if there is evidence of progression or targeted therapy for limited, symptomatic disease and the attending specialists judge that for PSMA PET/CT imaging is a more beneficial approach than comparator imaging technologies.

### **Co-dependent therapy**

Patients will be referred by surgeons, radiation oncologists and medical oncologists for PSMA PET/CT imaging if they judge that radionuclide PSMA therapy may be the most effective therapy. It is worth noting that approximately 1000 radionuclide PSMA therapies have already been given in Australia.

**26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

The clinical algorithms developed are attached to the application. Two clinical management algorithms are presented – each shows current and proposed algorithm for patients with biopsy proven prostate cancer with intermediate or high-risk features in the staging setting and patients with biochemical recurrence of prostate cancer.

**Staging**

Patients with suspected prostate cancer would usually have been referred due to an elevated PSA level to a surgeon. Initial staging by MRI scan is often performed to assess for a primary lesion and local nodal spread. Prostate biopsy then may follow depending on the PSA level, MRI findings and clinical assessment. Intermediate and high risk is based on tumour staging, biopsy results and PSA level as per the NCCN guidelines (with slight differences for those following EAU guidelines). Patients with increased risk of extra prostatic disease would then be referred for PSMA PET/CT to establish whether there is evidence of progression beyond the prostate gland.

**Biochemical recurrence**

Patients treated with loco-regional ablative procedures are typically monitored by serial PSA measures. When there is an increasing level of PSA, a PSMA PET/CT is usually the next imaging procedure performed due to its higher yield than CT or MRI. The PET/CT gives information on site and extent of recurrence guiding local or systemic therapy selection.

**Therapeutic monitoring and guidance**

As noted above, there is less but increasing evidence available for this indication. Specialists managing their patients are often faced with the need to gauge therapeutic response to assess treatment efficacy and the need for ongoing administration of often expensive pharmaceuticals. An unexpected rise in PSA levels, particularly when conventional imaging shows no change, would trigger a search for disease progression on PSMA PET/CT. A patient who develops localised symptoms with negative conventional imaging would also be referred for PSMA PET/CT to allow targeted therapy where appropriate.

When patients with prostate cancer have progressive prostate cancer that is not amenable to other systemic treatments, they would be eligible for PSMA PET/CT imaging if radionuclide PSMA therapy is judged to have potential benefits. Such patients would most often have been treated with and have failed or not tolerated androgen deprivation therapy (ADT), and chemotherapy, and these treatments would have been monitored by PSA testing and likely comparator diagnostic imaging. In this clinical setting baseline PSMA PET/CT imaging is vital for assessing the uniformity and intensity of PSMA expression at cancer sites to guide radionuclide PSMA therapy treatment planning. Post therapy imaging to assess therapeutic response is often necessary in guiding further treatment.

**PART 6b – INFORMATION ABOUT THE INTERVENTION**

**27. Describe the key components and clinical steps involved in delivering the proposed medical service:**

The overall procedure for PSMA PET/CT scanning is very similar to currently MBS funded PET/CT procedures, although fasting is not required.

When men are referred for a PSMA PET/CT scan, the clinical need for the diagnostic procedure is verified by an experienced healthcare professional and if the request is valid an appointment is made so that supply of the short-lived radiotracer can be organised for an appropriate time. The patient is given details about the scan and necessary preparation.

On the day of the scan the radiotracer is administered intravenously and 45-120 minutes later a PET/CT scan is performed. The imaging time is approximately 30 minutes during which time the patient can lie comfortably on the scanning bed. Upon completion the patient can leave the imaging facility without further requirements. Adverse events are extraordinarily rare when these diagnostic agents are administered

The scan is interpreted by an appropriately credentialed specialist and their report is provided to the referring specialist who incorporates the information gained into the patient's management plan

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

No

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

Not applicable.

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

The supply of radioactive tracers in Australia is regulated by the Therapeutic Goods Act, administered by the Therapeutic Goods Administration which is a Commonwealth Government agency. Radiation safety aspects of radiotracer supply and usage is regulated by State Authorities and at a Commonwealth level by Australian Radiation Protection and Nuclear Safety Agency (ARPANSA).

The small dose of radiation delivered by the procedure is not a limitation to use in this population group, particularly considering the average age. The dose is similar to that from other PET/CT studies and other CT only procedures. Most patients will receive a single study for staging or a small number of studies for recurrence assessment (usually years apart).

PSMA radiotracers are limited mainly by the short half-life of the radionuclide component of the radiotracer, and in general sterile therapeutic goods have an expiry time of 12 hours or less. Access to these tracers is currently by either by in house production of gallium 68 based pharmaceuticals or commercial provision of the longer lasting fluorine based tracers.

Access to PSMA PET/CT scans is limited by the number of PET/CT sites (currently approximately 91 sites throughout Australia).

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

None

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

Nuclear Medicine Technologists

Medical Physicists

Radiochemists and radiopharmacists

Nuclear Medicine Physicians

Radiologists

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

No

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

Supplied only by medical specialists who are credentialed to deliver PET services, only on referral by a specialist medical practitioner.

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

See above

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

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

The service will be provided in facilities specifically licensed to undertake PET/CT imaging.

These are located in public and private hospitals as well as stand alone facilities throughout Australia.

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

The service will be provided where there is an accredited provider and these are variously located as indicated above.

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

- Yes
- No – please specify below

**PART 6c – INFORMATION ABOUT THE COMPARATOR(S)**

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

At initial presentation with biopsy proven prostate cancer, many patients with intermediate or high-risk features will undergo CT and Whole Body Bone Scan (WBBS) (with MRI used to clarify uncertainty) to determine if the disease is loco-regionally confined or if distant metastases are present. In patients with biochemical recurrence of prostate cancer, PSA testing alone or used in conjunction other comparator diagnostic imaging tests, particularly CT but often WBBS with SPECT/CT is used in an attempt to identify metastatic disease that may render curative intent treatment futile. Comparator imaging is also used in the hope that identification of the sites of disease will enable tightly directed incremental increase in the local radiation dose.

The following comparator tests are all stand alone diagnostic procedures that are currently funded through the MBS and do not require additional healthcare resources for most men with prostate cancer.

- CT scan of the head/neck/thorax/abdomen and pelvis with contrast
- Whole Body Bone Scan with SPECT/CT
- PSA testing

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

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

MBS Item Number	Description
56507*	Computed tomography ( abdomen and pelvis)
61425	Bone study (for bone scintigraphy)
61505	CT (with SPECT, for localisation / correction)
61719	CT (with SPECT, for localisation / correction)
66656	Prostate specific antigen (PSA) testing

\*Less commonly 56807 including chest

**40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):**

As described previously in response 26, the clinical algorithms attached to this application include current and proposed algorithms for patients with biopsy proven prostate cancer with intermediate and high-risk features in the primary staging setting and patients with biochemical recurrence of prostate cancer. The algorithms also indicate where PSMA/PET CT can also be substituted in the therapeutic monitoring setting.

**Overview**

The management of men with prostate cancer over the course of their disease is highly variable due to the wide range of factors to be considered including co-morbidities and general life expectancy, their treatment preferences and tolerance to potential adverse treatment effects. In addition, the behaviour of their cancer and it's response to treatment at different stages is variable . Hence this overview and the attached flow charts are necessarily indicative in nature.

Clinicians have already clinically accepted the superiority of PSMA PET/CT imaging over MBS funded existing standard of care diagnostic imaging comparators for defining the location and extent of active prostate cancer. This has led to rapid adoption of PSMA PET/CT despite lack of federal support. Many clinicians and patients have decided that pre-PSMA PET/CT management pathways are no longer tenable and now routinely use PSMA PET/CT in those who can arrange funding.

**Clinical Pathways in which comparator imaging tests are used to direct prostate cancer patient management.**

**Primary staging**

At initial presentation with possible prostate cancer (palpable nodule or elevated PSA) patients will typically progress to prostate MRI. Based on these findings, a biopsy may be performed. In patients with biopsy proven prostate cancer, patients with low volume, low grade disease may move to active surveillance or surgery/radiotherapy. Patients at intermediate risk and high risk of metastatic disease will typically undergo CT of the abdomen and pelvis and WBBS to determine if the disease is loco-regionally confined or if distant metastases are present. Some may require a regional MRI to elucidate findings on the CT/bone scan studies. Accurate staging guides and supports successful choice of management therapy. Loco-regionally confined disease will be managed with radical prostatectomy, external beam radiotherapy or brachytherapy. ADT will most often be used for a period of 2 years in conjunction with radiotherapy.



Patients in whom metastatic disease is detected will most often receive systemic therapy, most commonly ADT and in those with less than 5 metastases on comparator WBBS, radiotherapy may also be given to the prostate primary tumour in view of evidence that this group of patients can achieve improved overall survival.

In post radical prostatectomy patients who show high risk features for recurrence (involved surgical margins, high grade disease, extracapsular extension, pelvic nodal spread) adjuvant radiotherapy to the prostate bed and/or pelvic lymphatics may be applied as this has been shown in several randomised trials to improve oncological outcomes and, in one study, to improve overall survival. If this treatment pathway is followed a planning CT will be used to define radiation fields according to empiric guidelines.

All patients following curative intent therapy for primary prostate cancer are kept under surveillance with PSA testing most commonly without imaging initially.

A percentage of patients- perhaps 50% overall- are indeed cured as indicated by complete PSA response as defined respectively for radical prostatectomy or radiotherapy. The remainder of patients will have a PSA that either remains “detectable” or becomes detectable after an interval of months to years (biochemical recurrence).

### **Biochemical recurrence**

Significant PSA rises after definitive treatment are termed a “biochemical recurrence” (BCR). This occurs in advance of related symptoms. At very low PSA levels, observational studies suggest that curative intent treatments are effective. Comparator imaging approaches have been demonstrated to be less sensitive in BCR, with sensitivity related to PSA levels. On this basis patients may be offered “salvage” radiotherapy (SRT) to the pelvic lymph node pathways and/or prostate bed, with the field of treatment determined empirically and template defined. Despite the low yield, many men will be offered the comparator diagnostic imaging tests, particularly CT but often WBBS also, in an attempt to identify metastatic disease that may render curative intent treatment futile. Comparator imaging is also used in the hope that identification of the sites of disease will enable localised increases in radiotherapy dose. SRT may be undertaken with or without the addition of ADT.

“Salvage” curative intent surgery is advocated in some situations and some surgical practices if no extra pelvic metastases are detected and resectable disease in the prostate bed and/or pelvic lymph nodes is identified.

If extra pelvic metastatic disease is identified, stereotactic radiotherapy (SRS) may be undertaken in addition to standard pelvic radiation to these areas in the hope of increasing the number of men achieving cure or other improved outcomes.

If the only disease sites detected are outside conventional loco-regional ablative fields, SRS only may be undertaken again with the objective of increasing the number of men achieving cure or improving oncological outcomes.

### **Therapeutic monitoring**

The treatment outcomes of SRS, SRT and salvage surgery whether used alone or in combination are assessed by PSA response, and often WBBS and/or CT if these imaging tests had previously identified sites of prostate malignancy.

If PSA fails to respond, patients will most often be deemed unsuitable for further attempts at loco-regional therapy and systemic therapy will be instituted, most often ADT, but this may be deferred until a clear pattern of rising PSA suggests a substantial bulk of prostate cancer has likely developed. Comparator imaging is often used in this situation to further quantify the bulk of active malignancy and to act as a baselined for future comparison.

Patients who experience a substantial or complete response to “salvage” therapies will usually be followed with PSA testing alone without imaging.

If PSA begins to rise again, comparator imaging will often be performed to restage the patient and guide local versus systemic therapy. If local therapies are considered unlikely to offer significant benefit, the patient will be directed to systemic therapy, most commonly ADT initially, sometimes after a period of PSA surveillance to confirm disease progression.

Following the introduction of ADT most men have a significant, and in some cases complete, PSA response, and comparator imaging will often only be undertaken near the PSA nadir to help define the extent of remission of previously identified prostate cancer.

Most men will experience a rise of PSA despite continued ADT and castrate levels of testosterone, signifying that the patient has moved into a “castrate resistant” state. At this stage comparator imaging tests will often be undertaken to again assess the extent of imaging defined prostate cancer and to form a baseline for assessment of response to a range of second-line systemic therapies including advanced drugs that target the androgen hormone signalling pathways, or several lines of taxane family chemotherapy.

At variable timepoints in the treatment of castrate resistant patient’s comparator imaging will be undertaken to provide a more complete understanding of the patient’s treatment response.

Also, at variable timepoints throughout the course of an individual’s prostate cancer treatment comparator diagnostic imaging may be undertaken to determine the cause of symptomatic deterioration to assist in directing the patient to optimal therapy.

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

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

**(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

**Primary staging and biochemical recurrence**

In the settings of primary staging and biochemical recurrence when ablative loco regional therapies are the treatments that offer the best opportunity for improved oncological outcomes the substitution is expected to be near complete for the purposes of detecting pelvic nodal and distant metastatic disease.

**Therapeutic monitoring and guidance**

In the setting of therapeutic monitoring it is estimated that there will be minimal substitution unless an evidence base is developed that demonstrates that use of PSMA PET/CT imaging better answers to the question that define treatment planning.

**42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources):**

**Primary Staging and biochemical recurrence**

PSMA PET/CT imaging provides considerably more accurate information about the extent of prostate cancer than current standard of care diagnostic techniques that are routinely applied to guide clinical decision making in patients undergoing initial treatment for prostate cancer and in men who experience recurrent prostate cancer whether this is biochemical or clinical recurrence.

With that context the clinical management pathways following the substitution of PSMA PET/CT imaging for comparator diagnostic imaging techniques *are predominantly the same* as those following application of comparator diagnostic imaging techniques that are MBS funded for these purposes.

However, the superior ability of PSMA PET/CT to detect sites of prostate cancer has been demonstrated to decrease the number of futile curative intent loco-regional ablative procedures, resulting in a saving of the healthcare resources that would otherwise have been unnecessarily consumed.

The ability to localise sites of prostate cancer within empirically or comparator imaging defined treatment fields is not anticipated to cause a significant change in the use of healthcare resources. Radiotherapy is the dominant salvage treatment used and altering radiation fields to include all sites of PSMA PET/CT defined prostate cancer and/or to intensify radiation dose at sites of PSMA PET/CT defined prostate cancer will not consume significantly greater healthcare resources.

The superior ability of PSMA PET/CT to detect sites of prostate cancer will upstage many patients however this may lead to little change in the number of metastasis directed therapies. Patients diagnosed as limited metastatic disease following comparator imaging assessment will be upstaged and hence no longer suitable for these therapies while other patients thought to have local disease only will be upstaged and now become suitable for these therapies. The number of patients having local curative intent therapies will decrease.

PSMA PET/CT is not predicted to increase the overall use of systemic therapies. Patients in whom comparator imaging tests currently fail to identify prostate cancer sites outside loco-regional treatment fields will ultimately not benefit from those treatments and relapse requiring the same systemic therapies. This will mean that they have received futile therapy, with their attendant adverse health and economic effects. The PSMA PET/CT will bring forward the use of systemic therapy, so there may be a transient spike. It is anticipated that better targeting of curative intent loco-regional ablative therapies based upon PSMA PET/CT imaging will result in a greater number of men being cured and thus lead to an overall decreased need for systemic therapies.

Available data does not suggest that PSMA PET/CT will replace or be used in addition to comparator diagnostic imaging techniques for monitoring conventional pharmacotherapy response in late stage castrate resistant prostate cancer as frequently clonal diversity develops and metastases that express little or no PSMA on their cell surface develop and these cannot be detected with great sensitivity by PSMA PET/CT imaging.

#### **Guiding ongoing therapy and therapeutic options**

As noted previously, PSMA PET/CT has limited evidence currently available in the therapeutic monitoring setting however data is rapidly becoming available. For the near future, it is not predicted that routine use of PSMA PET/CT instead of, or in addition to comparator diagnostic imaging techniques for assessing therapeutic response in early stage systemic treatments for metastatic prostate cancer would be appropriate. The clinical utility of using PSMA PET/CT imaging in early stage systemic treatments with ADT remains unclear even though current evidence indicates that responses to ADT in particular may be discordant with PSA responses and as such PSMA PET/CT may be useful for detecting early castrate resistant clones that require some form of treatment intensification. PSMA PET/CT also provides an easy method for quantification of total functional tumour burden and this is not readily achievable with comparator diagnostic imaging techniques, but there is insufficient evidence to assess whether this use of PSMA PET/CT has incremental healthcare benefits.

Where therapeutic PSMA targeting radionuclide therapy is either assessed or has been implemented, PSMA PET/CT imaging is mandatory as comparator imaging techniques are not helpful. Currently the evidence supporting the utility of PSMA based radionuclide therapy is confined to very late stage castrate resistant prostate cancer. Expanded use of radionuclide therapy for prostate cancer will entail an increase in the use of PSMA PET/CT and FDG PET/CT to enable proper patient selection, dose calculation and response assessment.

#### **PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME**

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

##### **Overall clinical claims for primary populations**

In patients with biopsy proven prostate cancer with intermediate and high-risk features, PSMA PET/CT imaging is superior to CT and WBBS with SPECT/CT imaging in terms of analytic validity, clinical validity and clinical utility.

In patients with biochemical recurrence of prostate cancer, PSMA PET/CT imaging is superior to CT and WBBS with SPECT/CT imaging in terms of analytic validity, clinical validity and clinical utility.

## Background

PSMA PET/CT scanning is a safe whole-body imaging test, with a margin of improved safety compared to diagnostic CT as iodinated contrast administration is omitted or given at a lower dose.

PSMA is present in low concentrations in normal prostate and other body tissues, but found at much higher concentrations on the surface of prostate adenocarcinoma, especially more aggressive forms of the disease. PSMA PET/imaging is notable for highlighting the location of prostate tumours throughout the body, even before any anatomical disruption is detectable.

The key improvement in healthcare outcomes resulting from the substitution of comparator techniques with PSMA PET/CT imaging are directly related to its higher sensitivity and specificity compared to standard imaging allocating patients with greater accuracy to appropriate stages. This ensures that critical treatment decisions are based on the most accurate available data.

### Primary Staging:

Contemporary prostate cancer management is highly dependent upon knowledge of the actual location of prostate cancer in the body, and the quantity of active cancer that is present. Understanding the true extent of disease is a fundamentally important determinant of prognosis, in large part because loco regional ablative procedures are currently the only therapies capable of curing men with prostate cancer. Distant metastases indicate a poorer prognosis because this situation often precludes the application of curative treatments. Loco-regional nodal metastases have an intermediate prognostic impact because the application of curative intent therapies is not contraindicated, but much less likely to be successful. This, in part, may be due to the underestimation of the true extent of disease burden by conventional imaging rendering efforts at cure fruitless.

The importance of staging explains why diagnostic imaging, and particularly contrast CT and WBBS with SPECT/CT, are used routinely to guide decision making in patients with prostate cancer. Currently funded comparators suffer from significant false negative rates leading to frequent under staging of patients and inappropriate allocation to management regimes.

In patients with intermediate and high risk primary prostate cancer who require diagnostic imaging because of an increased risk of extra prostatic malignancy, PSMA PET/CT imaging provides greater accuracy than comparator imaging tests, demonstrating both independent and incremental accuracy benefits. The additional information provided by PSMA PET/CT has been documented to result in significant management changes.

When reported by suitably experienced specialists PSMA PET/CT has very low false positive rate (near perfect specificity in histopathologically validated studies) as well as sensitivity for detecting sites of significant active prostate cancer that is both superior to standard imaging comparators and demonstrably clinically useful.

*The pivotal finding in clinical studies of comparative accuracy is that PSMA PET/CT very often detects disease sites that are completely inapparent on standard imaging studies, but the opposite situation is rare.*

Since PSMA/PET scanning was introduced into clinical practice in 2013 in Germany and from 2014 onwards in Australia, tens of thousands of men with prostate cancer have been studied with PSMA PET/CT imaging. PSMA PET/CT is now widely regarded by clinicians as the imaging test of choice in many clinical indications related to prostate cancer management. Increasingly PSMA PET/CT is being incorporated as a recommended procedure in reputable practice guidelines.

Failure to include all sites of prostate cancer in the treatment field negates the logical basis of curative intent loco regional ablative therapies. Better staging will allow patients to avoid futile attempts at loco-regional ablative treatment. These patients will be spared futile therapies and associated side effects and be offered appropriate therapy for their stage at an earlier timepoint.

In addition to allowing more patients to avoid futile treatments as a direct result of the increased true positive fraction of PSMA PET/CT imaging, intensified therapies may be applied to those identified sites of disease or effective therapy with an entirely different intent may be applied.

**Biochemical recurrence:**

Biochemical recurrence occurs in between 30-50% of prostate cancer patients initially treated with radical prostatectomy or radiation therapy and presents a therapeutic dilemma in thousands of men with prostate cancer annually. Cure is still feasible if the disease is loco-regionally confined but the probability of cure is significantly lower than at the time of primary treatment. Comparator diagnostic imaging tests are very insensitive particularly at PSA values less than 1 nanogram/ml where available evidence suggests that salvage radiotherapy or surgery provide the best opportunity for cure or improved oncological outcomes.

PSMA PET/CT has been repeatedly shown to detect additional sites of disease that leads to altered management even at very low levels of PSA. In approximately 20% of patients the sites of disease identified lead to revised treatment plans that prevent patients from undergoing futile curative treatment with the attendant adverse health and economic consequences.

When diagnostic imaging is required to optimise treatment selection in patients with biochemical recurrence the evidence strongly supports choosing PSMA PET/CT as the first line investigation. CT, whole body bone scan and MRI rarely provide clinically useful incremental information.

**Therapy monitoring:**

Although evidence is less well developed for PSMA PET/CT usage in other indications, the available evidence indicates that PSMA PET/CT provides unique information in patients where diagnostic imaging is necessary to assess response to therapy. PSMA PET/CT has been shown to identify sites of residual active malignancy despite a complete PSA response, and PSMA PET/CT can reveal where residual structural abnormalities, particularly in the skeleton, are inactive and likely healed as a consequence of prior treatment. That this should occur is consistent with experience obtained in several malignancies with FDG PET/CT.

**Therapy guidance:**

PSMA PET/CT is a mandatory examination for planning radionuclide therapy with PSMA targeting radiotherapeutic agents such as <sup>177</sup> Lutetium PSMA 617 and <sup>177</sup> Lutetium PSMA I&T. These therapies have been shown to produce biochemical and sometimes symptomatic response in more than 50% of patients when applied to patients with uniformly high PSMA expression at sites of prostate cancer metastatic disease. Randomised controlled trial evidence may indicate that outcomes from treatment using <sup>177</sup> Lutetium PSMA 617 are superior to second-line standard of care chemotherapy with carbazitaxol. When this evidence becomes available, a separate submission will be completed.

In summary, PSMA PET/CT provides higher accuracy of primary staging and restaging in the setting of biochemical recurrence. It therefore allows patients to be appropriately allocated to best practice treatment regimens and avoid many futile procedures. It has no harms in comparison to standard comparators with lower radiation exposure and no significant risk of adverse reactions.

Substitution of PSMA PET/CT will have minimal financial impact as it will replace staging CT and WBBS.

**44. Please advise if the overall clinical claim is for:**

- Superiority  
 Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

**Safety Outcomes:**

The technique is safe - adverse events are an extreme rarity in conjunction with the administration of diagnostic PSMA targeting PET radiotracers.

Radiation dose delivered is lower than comparator tests CT and WBBS with SPECT/CT and the characteristic low radiation doses have no demonstrable adverse health effects

**Clinical Effectiveness Outcomes:**

PSMA PET/CT has been repeatedly demonstrated to detect sites of prostate cancer throughout the body that cannot be identified using comparator MBS funded diagnostic techniques, with a very low rate of false positive localisations.

The superior diagnostic accuracy of PSMA PET/CT PET for detecting metastatic prostate cancer sites significantly improves the ability to predict disease outcomes, as well as to select, plan and conduct treatment for individual patients.

By virtue of superior diagnostic accuracy PSMA PET/CT has been demonstrated to, or can be imputed to, improve a range of health care outcomes for individual patients.

PSMA PET/CT results in *significantly fewer patients being subjected to futile loco regional interventions* applied with the intent of improving oncological outcomes. PSMA PET/CT has been repeatedly demonstrated to detect sites of prostate cancer outside fields of intervention planned empirically or on the basis of comparator diagnostic imaging techniques. A decrease in deleterious healthcare effects of such futile healthcare interventions occurs in direct proportion to the number of patients avoiding such procedures in each clinical indication. Beneficial outcomes occur particularly in the clinical contexts of primary staging for intermediate and high-risk prostate cancer patients and biochemical recurrence.

PSMA PET/CT use facilitates improved treatment delivery for patients in whom loco-regional ablative procedures applied with curative intent are deemed optimal therapy. Radiation oncologists can develop treatment fields that have a significantly higher probability of incorporating all sites of active prostate cancer, and radiation doses that have a greater probability of achieving tumour ablation can be employed with lower risk of increased toxicity to surrounding normal tissues. Surgical procedures can similarly be optimised if the surgeon knows the location of lymph node metastases as these are often identifiable outside empirically determined pelvic nodal dissection fields yet remain technically resectable.

PSMA PET/CT imaging facilitates metastasis directed therapy applied with the intent of improving oncological outcomes because these therapeutic approaches are only feasible if metastatic sites are identifiable.

PSMA PET/CT use facilitates earlier detection of treatment non-response or progression and so reduces adverse health and economic effects of prolonging treatments that are not or no longer effective in that patient, and facilitates earlier transition of those patients to more effective treatment methods.

# PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

## 46. Estimate the prevalence and/or incidence of the proposed population:

### Primary staging

With approximately 20,000 new cases of prostate cancer per annum, it is proposed that approximately 10,000 cases will be at intermediate at high risk of adverse prostate cancer outcome and require PSMA PET/CT staging for more individualised prognosis assessment and treatment planning.

### Biochemical recurrence

As approximately 50% of patients who undergo curative intent ablative procedures experience biochemical recurrence, it is estimated that 80% of these patients, or 4000 men will be benefited by PSMA PET/CT assessment.

### Therapeutic monitoring and guidance

The population in whom PSMA PET/CT would be required rather than comparator imaging for treatment response assessment of systemic treatments disease is thought to be small currently, even though this clinical indication is common.

The population in whom PSMA PET/CT would be required for evaluating suitability for PSMA based radionuclide therapy is potentially all men in whom other systemic therapies have failed and in whom symptomatic treatment is required or in whom disease amelioration is considered likely to be beneficial.

This population is a significant percentage, perhaps 10%, of the 90000 men estimated to be living with prostate cancer.

## 47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Most commonly 1, maximum 2-3 and PSMA PET/CT would not be used in most years when a patient is living with prostate cancer

## 48. How many years would the proposed medical service(s) be required for the patient?

The proposed medical service may be required for 15 years or longer with anticipated improvements in therapy for prostate cancer.

However, as the clinical course of prostate cancer varies greatly in different men this is not a question that has a single answer.

Approximately 50% of men overall will be cured by initial therapy and in these men only a single staging PSMA PET/CT scan will be required as cure will be documented by repeated PSA testing.

In men who experience biochemical recurrence this may be detected at an interval of months to many years after initial curative intent therapies. PSMA PET/CT scanning may be applied to assist determination of optimal therapy (loco-regional or systemic) when active therapy rather than surveillance is judged to be required.

PSMA PET/CT may not be undertaken for several years if PSA testing indicates successful disease ablation of initial treatment recurrence.

PSMA PET/CT may be applied at shorter time intervals in patients undergoing systemic therapy for recurrent disease than in those who choose loco regional ablative approaches. However, developing evidence will determine in which clinical situations, if any, PSMA PET/CT evaluation provides better or incremental information for treatment planning than comparator imaging tests.

PSMA PET/CT may be required up to several times a year to guide application of therapeutic PSMA radioligand therapy, however with current therapies the majority of patients have less than 3 applications of this therapeutic agent due to tumour resistance and accumulating toxicity predominantly to salivary glands.

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

It is anticipated that up to 12,000 scans may be performed in the first year

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

It is estimated that the uptake of PSMA PET/CT imaging would increase over 3 years to 18000 scans per annum.

The limited number of PET scanners throughout Australia will constitute a restriction on the number of PSMA PET/CT scan that can be undertaken. Currently there is approximately 91 scanners with another 9 scanners under consideration.

Currently PET scanners are predominantly located in major cities which is likely to reduce uptake for patients in rural and remote areas.

Supply of PSMA radiotracers is expected to be able to increase to meet the projected demand.

Staffing requirements should also be able to increase sufficiently to meet projected demand for PSMA PET/CT services.

With respect to "leakage" this can be minimised through the design of the MBS Item descriptor, development of appropriate use criteria and patient and medical specialist education. It is anticipated that leakage can be contained to less than 1% of services.



## PART 8 – COST INFORMATION

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

\$1400 total.

Radiotracer and transport \$500. PET/CT imaging and report \$900.

**52. Specify how long the proposed medical service typically takes to perform:**

2-3 hours total from injection of radiotracer to completion of the PET/CT imaging.

**53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.**

**Proposed MBS item descriptor**

Our preference for simplicity would be a single item and descriptor

Category 5 – DIAGNOSTIC IMAGING SERVICES
PSMA PET/CT study in patients with proven prostate cancer for the purposes of staging, restaging or altering therapy in patients considered suitable for active therapy
Fee: \$1400

**Alternative MBS item descriptors**

However, noting recent descriptors being more limited, we would suggest the following if a single descriptor is not favoured:

Category 5 – DIAGNOSTIC IMAGING SERVICES
Proposed item descriptor 1: PSMA PET/CT study, performed for the staging of intermediate to high risk prostate cancer, for a patient who is considered suitable for active therapy (R)
Fee: \$1400
Proposed item descriptor 2: PSMA PET/CT study, performed for the evaluation of suspected metastatic or suspected locally or regionally recurrent prostate carcinoma, for a patient who is considered suitable for active therapy (R)
Fee: \$1400
Proposed item descriptor 3: PSMA PET/CT study, performed to allow guidance for systemic or localised therapies in patients with recurrent prostate carcinoma, for a patient who is considered suitable for active therapy, when a specialist or consultant physician judges that PSMA PET/CT imaging will provide superior information (R)
Fee: \$1400