



**Australian Government**

**Department of Health**

# Application Form

## Testing of tumour prostate tissue to detect BRCA1/2 or ATM gene mutations in men with metastatic castration-resistant prostate cancer to determine eligibility for PBS olaparib

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 – APPLICANT DETAILS

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

Corporation / partnership details (where relevant): N/A

Corporation name: AstraZeneca Pty Ltd

ABN: 54009682311

Business trading name: AstraZeneca Pty Ltd

### Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

### Alternative contact name: REDACTED

Alternative 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

Testing of tumour prostate tissue to detect BRCA1/2 (Breast Cancer gene) or ATM (Ataxia-Telangiectasia Mutated) gene mutations in men with metastatic castration-resistant prostate cancer (mCRPC), to determine eligibility for PBS subsidised treatment with olaparib.

### 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)

In 2019 in Australia, it is estimated that prostate cancer will be the most commonly diagnosed cancer in males, with an estimated 19,508 new cases and 3,306 deaths. On average, prostate cancer in males is diagnosed before Stage II, and in 2011, 4.2% of total prostate cancer cases were diagnosed at Stage IV. In 2011, prostate cancer had close to 100% 5-year relative survival when diagnosed at Stage I. At Stage IV, the 5-year relative survival rate fell to 36% (Australian Institute of Health and Welfare, 2019).

When localised, prostate cancer can be cured with surgery or radiotherapy, but some patients will relapse with either overt metastases or an isolated rise in prostate-specific antigen (PSA). There is also a proportion of men who have metastases when the prostate cancer is first diagnosed. Prostate cancer is termed 'castrate resistant' when the disease progresses despite continuous androgen deprivation therapy. After this, further treatment is needed to maintain disease control (Body A, 2018).

This application concerns the metastatic disease, which is a small part of the overall disease and is furthermore targeted at those patients with genetic mutations in their homologous recombination repair (HRR) genes. A small percentage of prostate tumours have loss of function mutations in candidate genes involved in HRR of DNA. BRCA1, BRCA2, or ATM are the most well characterised and/or frequently mutated HRR genes in prostate cancer. The overall mutation frequency for these three genes together range from 13% to 26.5% in metastatic castration resistant prostate cancer (mCRPC) (Armenia, 2018); (Chung, 2019) (Kumar A, 2016); (Mateo J, 2015); (Robinson D, 2015).

### 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)

To enable timely decision-making this application presents two scenarios for consideration.

**SCENARIO 1 (preferred medical service):** The proposed medical service is testing of prostate tumour tissue to detect BRCA1/2 (Breast Cancer gene) or ATM (Ataxia-Telangiectasia Mutated) gene mutations in men with metastatic castration-resistant prostate cancer (mCRPC) to determine eligibility for treatment with olaparib. An in-house test has been developed and is currently undergoing validation in Australian laboratories.

**SCENARIO 2 (alternative medical service):** An alternative medical service to the above is testing of prostate tumour tissue to detect BRCA 1 or BRCA 2 gene mutations in men with metastatic castration-resistant prostate cancer (mCRPC) to determine eligibility for treatment with olaparib.

Tumour testing for BRCA1/2 mutations is also under consideration by MSAC as part of Application 1554 to determine eligibility for olaparib maintenance therapy in newly diagnosed patients with platinum-sensitive high grade epithelial ovarian cancer.

Tumour testing breast and ovarian tissue is currently being performed in a number of commercial and research pathology laboratories in Australia. Please refer to Part 3 for further information.

Germline BRCA1/2 testing to determine eligibility for olaparib maintenance therapy in patients with platinum-sensitive, relapsed high grade serous ovarian cancer (HGSOC) is listed on the MBS (Item 73295) and PBS (Items 11503K & 11522K – 100 mg tablets; 11528R & 11539H – 150 mg tablets; 11050N 50 mg capsules) (refer to co-dependent MSAC/PBAC Application 1380). Germline BRCA testing is also established to screen for mutations in at risk patients with ovarian or breast cancer (MBS Item 73296) and for familial cascade testing (MBS Item 73297).

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:

N/A

(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:

Insert description of other public funding mechanism here

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):

N/A

(c) 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

Insert PBAC submission item number here N/A

An integrated co-dependent submission to MSAC/PBAC is proposed.

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

Trade name: Lynparza®  
Generic name: olaparib

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

- Yes  
 No

Not applicable

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

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses 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

As per MSAC Application 1538/1554, the only single or multi-use consumables for in-house developed in-vitro diagnostic (IVD) assays would be kits which may be used for DNA extraction or quality assurance, or any kit for PCR amplification methods.

## 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: Pharmaceutical product: LYNPARZA® (olaparib)  
 Manufacturer's name: AstraZeneca Pty Ltd  
 Sponsor's name: AstraZeneca Pty Ltd

Type of therapeutic good: In-vitro diagnostic test: In-house developed  
 Manufacturer's name: **REDACTED**

Sponsor's name: **REDACTED**

**SCENARIO 1:**  
**REDACTED**

**SCENARIO 2:**  
 Currently tumour BRCA 1 and BRCA 2 testing is available at the Australian laboratories listed in Table 1.

**Table 1 Australian molecular pathology service providers that offer tumour BRCAm testing on a commercial basis**

Molecular pathology service provider (State)	Method	QAP involvement
Genomics for Life (QLD)	NGS + MLPA	EMON via RCPAQAP, Collaborators in Belgium
Pathology North (NSW)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
Peter MacCallum Cancer Centre (VIC)	NGS + MLPA	EMON via RCPAQAP
Genomics Diagnostics (VIC-national network)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality Assurance Programs

Abbreviations: EDTA, ethylenediaminetetraacetic acid; EMQN, European Molecular Genetics Quality Network; MLPA, multiplex ligation-dependent probe amplification; NGS, next-generation sequencing; QAP, quality assurance programme; RCPAQAP, Royal College of Pathologists of Australasia Quality Assurance Programs Pty Ltd

The most similar tests to the proposed service would be the currently MBS-listed germline BRCA gene mutation tests (Items 73295, 73296 and 73297).

MBS Item 73295 relates to germline BRCA1/2 testing to determine eligibility for olaparib, while MBS Items 73296 and 73297 include germline BRCA1/2 testing in patients with ovarian cancer at high risk (>10%) of harbouring a mutation, and testing for their biological relatives.

- (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

All Australian molecular pathology service providers that currently perform BRCAm testing use in-house developed testing methods (as opposed to commercial test kits). Under the 2010 TGA regulatory framework, BRCAm tests that are used to determine eligibility for olaparib are classified as in-house developed Class 3 in vitro diagnostic medical devices (IVDs). The TGA framework requires laboratories that deal with Class 3 IVDs to provide the TGA with a declaration of conformity that the in-house IVDs comply with the essential principles and describe the 'kinds' of IVDs manufactured.

**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

The in-house developed IVDs have not yet been submitted to the TGA (see Q.15 below).

The co-dependent pharmaceutical product Lynparza® (olaparib) is currently registered on the ARTG with the following ARTG details:

ARTG ID: 288614 Lynparza 150mg tablets  
ARTG ID: 288613 Lynparza 100mg tablets

Please note that an application for the treatment of prostate cancer will not be made for the Lynparza 50mg capsules.

The current indications for Lynparza tablets are as follows:

**Ovarian Cancer**

Lynparza® is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced BRCA-mutated (germline or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. BRCA mutation status should be determined by an experienced laboratory using a validated test method.
- maintenance treatment of adult patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.

**Breast Cancer**

Lynparza® is indicated as monotherapy for the:

- treatment of adult patients with germline BRCA-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.

TGA approved purpose(s), if applicable: Not applicable

**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: **REDACTED**

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

The labs developing in-house IVDs will submit to TGA once they receive NATA accreditation.

## 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.*

	Type 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***
<b>Phase II trials</b>					
1.	Phase II trial	DNA-repair defects and olaparib in metastatic prostate cancer	Fifty patients with metastatic castration-resistant prostate cancer were treated with olaparib tablets at a dose of 400 mg twice a day. The primary endpoint was the response rate. Targeted next-generation sequencing, exome and transcriptome analysis, and digital polymerase-chain-reaction testing were performed on samples from mandated tumour biopsies.	<a href="https://www.nejm.org/doi/full/10.1056/NEJMoa1506859">https://www.nejm.org/doi/full/10.1056/NEJMoa1506859</a>	2015
<b>Diagnostic studies</b>					
2.	Diagnostic study	Germline DNA Repair Gene Mutation Landscape in Chinese Prostate Cancer Patients	Landscape of 18 germline DNA repair gene mutation in 316 Chinese patients with prostate cancer.	<a href="https://www.sciencedirect.com/science/article/abs/pii/S0302283819304531">https://www.sciencedirect.com/science/article/abs/pii/S0302283819304531</a>	2019
3.	Diagnostic study	Germline DNA-repair Gene Mutations and Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Receiving First-line Abiraterone and Enzalutamide	To determine whether and how germline DNA-repair gene mutations influence clinical outcomes to abiraterone or enzalutamide in patients with castration-resistant prostate cancer using germline genotyping for 50 DNA-repair genes using blood samples from 172 patients with CRPC beginning first-line systemic therapy with abiraterone or enzalutamide.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6045965/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6045965/</a>	2018

	<b>Type 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>
4.	Diagnostic study	ATM deficiency promotes progression of CRPC by enhancing Warburg effect	Report on ATM mutation contributing to the CRPC progression through a metabolic rather than DNA repair mechanism, and ATM deficiency generated by CRISPR/Cas9 editing promoted CRPC cell proliferation and xenograft tumour growth.	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30400006">https://www.ncbi.nlm.nih.gov/pubmed/30400006</a>	2019
5.	Diagnostic study	Treatment Outcomes and Tumor Loss of Heterozygosity in Germline DNA Repair-deficient Prostate Cancer	To determine the clinical response of 319 mCRPC patients with germline DNA repair defects to androgen receptor-directed therapies and to establish whether biallelic DNA repair gene loss is detectable in matched circulating tumour DNA.	<a href="https://www.ncbi.nlm.nih.gov/pubmed/28259476">https://www.ncbi.nlm.nih.gov/pubmed/28259476</a>	2017
6.	Diagnostic study	Inherited DNA-repair gene mutations in men with metastatic prostate cancer	Multicentre study that recruited 692 men with metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis. Germline DNA was isolated and used multiplex sequencing assays to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes.	<a href="https://www.nejm.org/doi/full/10.1056/NEJMoa1603144">https://www.nejm.org/doi/full/10.1056/NEJMoa1603144</a>	2016
7.	Diagnostic study	Circulating tumor DNA (ctDNA) burden and actionable mutations in treatment-naive metastatic castration-resistant prostate cancer (mCRPC)	Collection of baseline cfDNA samples from 36 chemotherapy-naive mCRPC patients enrolled in an ongoing randomised phase II crossover trial of abiraterone vs enzalutamide (NCT02125357) and performed deep targeted sequencing using a custom NimbleGen SeqCap EZ Choice panel of 72 mCRPC-related genes.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01267739/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01267739/full</a>	2016
8.	Diagnostic study	Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer	Randomisation of 202 patients with treatment-naïve mCRPC to abiraterone or enzalutamide for whole exome and deep targeted 72 gene sequencing of plasma cell free DNA prior to therapy.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01610686/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01610686/full</a>	2018

	Type 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***
9.	Diagnostic study	Abiraterone + prednisone (Abi) +/- veliparib (Vel) for patients (pts) with metastatic castration-resistant prostate cancer (CRPC): NCI 9012 updated clinical and genomics data	148 patients had metastatic disease biopsy, stratified by IHC-ETS status and randomised to Abi (Arm A) or Abi + Vel (Arm B). Primary endpoint: PSA response rate (RR >= 50% decline). Secondary endpoints: safety, objective RR (ORR), progression free survival (PFS), and molecular analysis including if DNA repair gene deficiency (DRD: BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C) predicts response.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01750310/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01750310/full</a>	2017
10.	Diagnostic study	Genomic alterations in circulating tumor DNA (ctDNA) are associated with clinical outcomes in treatment-naive metastatic castration-resistant prostate cancer (mCRPC) patients commencing androgen receptor (AR)-targeted therapy	Deep targeted sequencing of 72 mCRPC-related genes in baseline cfDNA from 62 chemotherapy-naïve mCRPC patients enrolled in an ongoing randomised phase II trial of abiraterone vs enzalutamide (NCT02125357). Genomic alterations in cfDNA were examined for association with clinical variables including time on treatment.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01295966/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01295966/full</a>	2016
11.	Diagnostic study	Co-targeting androgen receptor (AR) and DNA repair: a randomized ETS gene fusion-stratified trial of abiraterone + prednisone (Abi) +/- the PARP1 inhibitor veliparib for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) (NCI9012)-A University of Chicago phase II consortium trial	148 eligible mCRPC pts underwent metastatic disease biopsy, were stratified by ETS status and randomised to Abi (Arm A) or Abi + Veliparib (Arm B). The primary endpoint was confirmed PSA response rate. Secondary endpoints included safety, objective RR (ORR), progression free survival (PFS), and if DNA repair gene deficiency (DRD; homozygous deletions or deleterious mutations: BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C) predicts response.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01733597/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01733597/full</a>	2016
<b>Other studies</b>					

	Type 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***
12.	Prospective report	Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition	A report on prospectively planned, serial, cfDNA analyses from patients with metastatic prostate cancer treated on an investigator-initiated phase II trial of olaparib. These analyses provide predictive, prognostic, response, and resistance data with "second hit" mutations first detectable at disease progression.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143169/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143169/</a>	2017
13.	Case series	Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors	Identification of BRCA2 reversion mutations associated with olaparib and talazoparib resistance in prostate cancer patients.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5581695/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5581695/</a>	2017
<b>Reviews (2018-2019)</b>					
14.	Review	PARP inhibitors in prostate cancer- The preclinical rationale and current clinical development	Overview of published and ongoing trials exploring PARP inhibitors in treatment of prostate cancer and discuss the underlying biology.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723995/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723995/</a>	2019
15.	Review	Recent advances in prostate cancer research: Large-scale genomic analyses reveal novel driver mutations and DNA repair defects	Review of the recent advances in prostate cancer research, including understanding the genetic alterations that drive the disease and how specific mutations can sensitise tumours to potential therapies.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073096/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073096/</a>	2018
16.	Review	A decade of clinical development of PARP inhibitors in perspective	Summary of a decade of PARP inhibitor clinical development.	<a href="https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz192/5520938">https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz192/5520938</a>	2019

	Type 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***
17.	Review	DNA repair defects in prostate cancer: impact for screening, prognostication and treatment	Review covers the relationship between DNA repair defects and prostate cancer, highlighting the prevalence of mutations in key genes and their controversial association with clinical outcomes.	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30281887">https://www.ncbi.nlm.nih.gov/pubmed/30281887</a>	2019
18.	Review	Targeting DNA Repair Defects for Precision Medicine in Prostate Cancer	Review of the current knowledge on DNA repair defects in prostate cancer and an overview of how these alterations can be targeted towards a personalised prostate cancer management.	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30919167">https://www.ncbi.nlm.nih.gov/pubmed/30919167</a>	2019
19.	Review	DNA damage repair: An emerging strategy in metastatic prostate cancer	Review in prostate cancer discussing DNA repair abnormalities which mainly correspond to somatic or constitutional mutations of the BRCA2 and ATM genes. Therapeutic management of metastatic castration-resistant prostate cancer (mCRPC) is currently based on new hormonal therapies and taxane-type chemotherapy.	<a href="https://www.ncbi.nlm.nih.gov/pubmed/30278883">https://www.ncbi.nlm.nih.gov/pubmed/30278883</a>	2018

\* 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***
<b>Pivotal study</b>					
1.	Randomised Phase III trial	<b>PROfound:</b> a randomized Phase III trial evaluating olaparib in patients with metastatic castration-resistant prostate cancer and a deleterious homologous recombination DNA repair aberration  ClinicalTrials.gov Identifier: NCT02987543	The purpose of this study is to evaluate the efficacy and safety of olaparib versus enzalutamide or abiraterone acetate in subjects with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01467396/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01467396/full</a>	2019-2021  Presented at ESMO Sept 2019
2.	Randomised Phase III trial	Study of Olaparib (Lynparzaâ„¸) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer ( <b>PROfound</b> Study)  ClinicalTrials.gov Identifier: NCT02987543	The purpose of this study is to evaluate the efficacy and safety of olaparib versus enzalutamide or abiraterone acetate in subjects with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01883757/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01883757/full</a>	2019-2021  Presented at ESMO Sept 2019
3.	Phase III study	Study on Olaparib Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer  <b>PROpel</b>  ClinicalTrials.gov Identifier: NCT03732820	The purpose of this study is to evaluate the efficacy and safety (including evaluating side effects) of combination of olaparib and abiraterone versus placebo and abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) who have received no prior cytotoxic chemotherapy or new hormonal agents (NHAs) at metastatic castration-resistant prostate cancer (mCRPC) stage.	<a href="https://clinicaltrials.gov/ct2/show/NCT03732820?term=propel&amp;cond=prostate+cancer&amp;rank=2">https://clinicaltrials.gov/ct2/show/NCT03732820?term=propel&amp;cond=prostate+cancer&amp;rank=2</a>	2021-2022

	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.	Randomised, open-label, multicentre, Phase II study	Abiraterone/Prednisone, Olaparib, or Abiraterone/Prednisone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects  ClinicalTrials.gov Identifier: NCT03012321	This is a biomarker preselected, randomized, open-label, multicenter, phase II study in men with metastatic castration resistant prostate cancer (mCRPC). Patients with tumors that have ATM, BRCA1 and/or BRCA2 mutations/deletions/loss of heterozygosity will be randomized in a 1:1:1 fashion to each arm. Patients with mutations in noncanonical DNA repair genes including FANCA, PALB2, RAD51, ERCC3, MRE11, NBN, MLH3, CDK12, CHEK2, HDAC2, ATR, PMS2, GEN1, MSH2, MSH6, BRIP1, or FAM175A defects will be assigned to Arm IV with single agent olaparib.	<a href="https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01592458/full">https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01592458/full</a>	2021-2022

\* 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):

REDACTED

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

Not applicable

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

REDACTED

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

There is no single sponsor for tumour BRCA/ATM mutation testing in Australia.

Only one know laboratory, Genomics for Life offers panel testing to identify BRCA1/2 and ATM (along with 8 other gene mutations) on somatic (tissue) or germline sample.

There are several different Australian molecular pathology service providers that offer germline BRCA mutation testing and more recently tumour BRCA testing on a commercial basis. BRCA 1, BRCA 2 and ATM germline testing is offered by laboratories in each State as part of existing ovarian or breast cancer panels.

The test for SCENARIO 1 will specifically sequence BRCA 1, BRCA 2 and ATM in prostate cancer tumour tissue and require separate validation.

As noted above, under SCENARIO 2 tumour testing for BRCA 1/2 gene mutations is currently available and being performed predominantly on breast and ovarian tissue.

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: REDACTED

Name of expert 2: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

*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:**

Prostate cancer occurs when abnormal cells develop in the prostate. These abnormal cells can continue to multiply in an uncontrolled way and sometimes spread outside the prostate into nearby or distant parts of the body (Prostate Cancer Foundation of Australia, 2014).

Prostate cancer is generally a slow growing disease and the majority of men with low grade prostate cancer live for many years without symptoms and without it spreading and becoming life-threatening. However, high grade disease spreads quickly and can be a significant cause of morbidity and mortality (Prostate Cancer Foundation of Australia, 2014).

Early (localised) prostate cancer refers to cancer cells that have grown but do not appear to have spread beyond the prostate. Advanced prostate cancer can either be local or metastatic (Cancer Council Australia, 2019):

- locally advanced prostate cancer where the cancer has spread outside the prostate to nearby parts of the body or glands close to the prostate
- metastatic prostate cancer where the cancer has spread to distant parts of the body.

The most common place for prostate cancer to spread to is the bones. It may also spread to lymph nodes outside the pelvis or rarely to the liver or the lungs. It is not possible to cure metastatic prostate cancer. Metastatic prostate cancer may develop in men who have previously been treated for prostate cancer. In some men, prostate cancer is first diagnosed when cancer has already reached an advanced stage (National Institute for Health Research, April 2019).

Prostate cancer growth and proliferation are primarily dependent on androgens, and androgen deprivation therapy (ADT) is an effective means of controlling the disease. However, some men develop resistance to androgen deprivation, resulting in the development of castration-resistant prostate cancer (CRPC) (National Institute for Health Research, April 2019).

Although the cause of prostate cancer is unknown, a man's risk of developing prostate cancer depends on many factors such as age, ethnicity, being overweight or obese, genetics and family history, lifestyle factors, and other medical conditions. Patients might have specific symptoms depending on where cancer has spread. Prostate cancer does not usually cause any symptoms until cancer has grown large enough to put pressure on the urethra. Symptoms of prostate cancer can include: needing to urinate more frequently, often during the night, needing to rush to the toilet, difficulty in starting to urinate, straining or taking a long time while urinating, weak flow, feeling that your bladder has not emptied fully, blood in urine or in semen, fatigue, feeling generally unwell, and have weight loss for no known reason (National Institute for Health Research, April 2019).

Inherited mutations in several genes involved in DNA damage repair have been reported to predispose men to prostate cancer. Between 24% to 30% of mCRPCs have loss of function mutations in genes involved in homologous recombination repair (HRR) of DNA damage response (DDR) (Abida, 2017), (Armenia, 2018), (Chung, 2019), (Mateo J, 2015) (Robinson D, 2015). Mutations in the breast cancer susceptibility genes (BRCA1 and/or BRCA2) are the most prevalent HRR gene mutations in mCRPC (with BRCA2 more prevalent than BRCA1) with ATM (ataxia telangiectasia mutated) the second most frequently mutated HRR gene in mCRPC (Armenia, 2018), (Chung, 2019), (Mateo J, 2015), (Robinson D, 2015). Together the prevalence of BRCA1/2 and ATM mutations in mCRPC ranges from 13% to 26.5%. The next most prevalent HRR gene mutated (HRRm) genes in mCRPC are CDK12 (1.3% to 8%), CHEK2 (1.4% to 4%)

and PALB2(0.3%to3%), PPP2R2A (5% in one dataset) and CHEK1 (0.9% to 2%). The prevalence of other HRR genes is very low (0%to1.8%).

Prostate cancer is a significant cause of morbidity and mortality in men, especially in those over the age of 75 years and impacts on their daily lives, particularly physical and emotional health, relationships and social life (National Institute for Health Research, April 2019).

In 2019 in Australia, it is estimated that prostate cancer will be the most commonly diagnosed cancer in males, with an estimated 19,508 new cases and 3,306 deaths. On average, prostate cancer in males is diagnosed before Stage II. The high proportion of cases diagnosed in Stage I or II is most likely attributed to prostate-specific antigen (PSA) testing. In 2011, 4.2% of total prostate cancer cases were diagnosed at Stage IV (Australian Institute of Health and Welfare, 2019).

Approximately 10% to 20% of men with prostate cancer will progress to castration resistant prostate cancer (CRPC) within 5 years, and ≥84% of those will have metastases at the time of CRPC diagnosis (Kirby M, 2011); (Wade CA, 2018).

In 2011, prostate cancer had close to 100% 5-year relative survival when diagnosed at Stage I. At Stage IV, the 5-year relative survival rate fell to 36%. (Australian Institute of Health and Welfare, 2019).

When localised, prostate cancer can be cured with surgery or radiotherapy, but some patients will relapse with either overt metastases or an isolated rise in PSA. A proportion of these patients are found to have a local relapse and can have salvage therapy (generally radiation), but the remainder of cases are considered to have incurable advanced disease. There is also a proportion of men who have metastases when the prostate cancer is first diagnosed. The management of advanced disease is predominantly medical. While the cancer is incurable, it is not untreatable. Prostate cancer is termed 'castrate resistant' when the disease progresses despite continuous androgen deprivation therapy. After this, further treatment is needed to maintain disease control (Body A, 2018).

**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:**

The proposed medical service is testing of tumour prostate tissue to detect BRCA1/2 (Breast CAncer gene) or ATM (Ataxia-Telangiectasia Mutated) gene mutations in men with metastatic castration-resistant prostate cancer (mCRPC) to determine eligibility for treatment with olaparib.

An outline of investigations, management and referral of patients within the Australian healthcare system prior to being eligible for the proposed service is provided below.

Patients with mCRPC do not currently undergo genetic testing as part of their diagnosis, although this is currently performed for breast and ovarian cancer.

A number of tests may be performed to investigate symptoms of prostate cancer and confirm a diagnosis. Some of the more common tests include (Australian Government, Cancer Australia, 2017):

- physical examination and medical history
- digital rectal examination
- blood test to check for prostate-specific antigen (PSA), a protein produced by the prostate. The level of PSA can be higher than normal in people with prostate cancer (but also in people with other prostate conditions that are not cancer)
- transrectal ultrasound – where a probe is inserted into the rectum that uses sound waves to create a picture of the prostate inside the body
- magnetic resonance imaging (MRI)
- biopsy – where a small sample of tissue is removed to be examined under a microscope. The biopsy results include a Gleason score – a score from 2 to 10 used by the pathologist that indicates the likelihood of the tumour spreading outside the prostate (2 is least likely to spread, and 10 is most likely to spread).

Following diagnosis, tests to determine the stage of prostate cancer can include (Australian Government, Cancer Australia, 2017):

- transrectal ultrasound
- biopsy or removal of lymph nodes – where tissue from the lymph nodes is taken to be examined under a microscope
- bone scan
- CT, MRI or other scans

Treatment and care of people with cancer is usually provided by a multidisciplinary team and depends on stage of the disease, location of the cancer and severity of the symptoms.

When localised, prostate cancer can be cured with surgery or radiotherapy, but some patients will relapse with either overt metastases or an isolated rise in PSA. A proportion of these patients are found to have a local relapse and can have salvage therapy (generally radiation), but the remainder of cases are considered to have incurable advanced disease. There is also a proportion of men who have metastases when the prostate cancer is first diagnosed. The management of advanced disease is predominantly medical. While the cancer is incurable, it is not untreatable. Prostate cancer is termed ‘castrate resistant’ when the disease progresses despite continuous androgen deprivation therapy. After this, further treatment is needed to maintain disease control (Body A, 2018).

A small percentage of prostate tumours have loss of function mutations in candidate genes involved in homologous recombination repair (HRR) of DNA. BRCA1, BRCA2, or ATM are the most well characterised and/or frequently mutated HRR genes in prostate cancer. The overall mutation frequency for these three genes is expected to be less than 15% (Kumar A, 2016); (Mateo J, 2015); (Robinson D, 2015).

**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):**

Management options for prostate cancer include watchful waiting, acute surveillance, prostatectomy, radiotherapy, cryosurgery, hormone therapy, chemotherapy or immunotherapy (Australian Government, Cancer Australia, 2017).

The Australian treatment pathway for mCRPC is presented in Figure 1 (attached). There are no published Australian specific treatment guidelines, however consultation with local clinical experts confirmed that treatment is driven by international guidelines (e.g. The European Society for Medical Oncology (ESMO) clinical practice guidelines for cancer of the prostate (Parker C, 2015) and the NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 2.2019 (Mohler JL, 2019)). These guidelines are implemented with regard to the prescribing restrictions applied to PBS-funded access (summarised in Australian Prescriber (Body A, 2018)).

Hormone sensitive prostate cancer is treated with androgen deprivation therapy. Luteinising hormone releasing hormone (LHRH) agonists or antagonists and/or bicalutamide are most often prescribed in Australia (see Figure 1). Prostate cancer is termed ‘castrate resistant’ when the disease progresses despite continuous androgen deprivation therapy.

While ESMO and NCCN guidelines position the “novel hormonal agents” (NHA) abiraterone and enzalutamide as an alternative to docetaxel in the first line treatment of mCRPC, the PBS restrictions for these agents assume that patients will receive docetaxel first line unless their treating physician predicts docetaxel will not be tolerated. Docetaxel monotherapy is therefore an alternative first line treatment. Patients will be trialled on the alternative first line therapy as the second line of therapy given the sequential use of abiraterone and enzalutamide is PBS-restricted. Cabazitaxel is also considered at second line, however it is less well tolerated than docetaxel or the NHA.

The most common pathways through the treatment algorithm are indicated with heavier lines in the attached Figure 1.

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

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

The current key components and clinical steps involved in delivering a tumour BRCA/ATM mutation test under both scenarios are as follows:

1. Patient's tumour sample is taken and sent to a pathology laboratory where BRCA/ATM testing is performed. Tumour tissue specimens for BRCA/ATM testing for the target patient population may be obtained as either a fresh tissue or an archived tissue specimen as formalin-fixed paraffin-embedded (FFPE) blocks, following primary tumour debulking surgery. Macro- or micro-dissection of the specimen may be required to increase the proportion of tumour tissue. DNA is extracted, purified and may be quantified using the laboratory's preferred commercially available kits. PCR amplification methods, including multiplex ligation dependent probe amplification (MLPA) may be used. Hybridisation capture baits may also be used. Libraries for sequencing are prepared and library quality may be evaluated at this step. Some gene panels (e.g. BROCA) identify all classes of mutations including single base substitutions, small insertions and deletions and large gene re-arrangements. Variants are called using comparison to reference libraries. Next-generation sequencing is performed at most Australian laboratories using the Illumina MiSeq platform, although some laboratories have moved to Illumina NextSeq. Sequencing results are then reported to the requesting specialist or consultant physician. Tumour tissue specimens obtained as FFPE blocks may have been archived for many months or years prior to tumour testing. Retrieval of archived samples may add up to 2 weeks to the turnaround time for the test, and preparation, extraction and then interpretation can add several additional weeks. It is likely that specialists and consultants may prefer to obtain new tissue samples. However, in some circumstances (such as a long period in archive or issues with the FFPE process) there may be degradation of the DNA in the specimen and a re-biopsy may be necessary. A fresh biopsy may also be required in cases where initial neo-adjuvant chemotherapy resulted in significant tumour shrinkage and tumour debulking surgery did not provide any viable tumour tissue. Costs (\$88 for block retrieval) will be incurred for retrieving samples from archive and possibly for forwarding them on to the specialist molecular diagnostic laboratories who are able to analyse the tissue. There may be additional harms to patient due to the need for re-biopsy in some cases.
2. The results are sent to the treating medical practitioner. If a mutation is detected, a face-to-face post-test counselling appointment with the patient and their family is arranged to deliver the results. Individuals identified as harbouring a pathogenic mutation (Class 4 or 5) are referred to Genetics Services/Familial Cancer Centres for post-test counselling. Patients with a VUS or strong family history should also be referred for post-test counselling.
3. Based on a positive mutation for BRCA or ATM, the medical practitioner will consider prescribing olaparib to the patient if they meet the PBS criteria to access treatment.

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

Registered trademarks may be held by the various commercial kits used at the different stages of the testing process outlined in Q27 above, for example for DNA extraction, quality assurance, quantification, PCR amplification, as well as the NGS platform itself.

The drug name LYNPARZA is a registered trademark.

**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?**

N/A

**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):**

For both Scenarios, tumour testing approach to identify BRCA/ATM mutations is relatively new and is not reimbursed on the MBS. **REDACTED**. The NGS platforms allow for high throughput so turnaround times with two initial laboratories should not be impacted.

It is unlikely that a patient would require more than one tumour BRCA/ATM test in their lifetime.

**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:**

Approximately half of homologous recombination repair (HRR) gene mutations detectable in tumour tissue constitute germline mutations (the other half being somatic in nature, i.e., exclusively occurring in tumour tissue (Mateo J, 2015). Therefore, if a patient tests positive on a tumour test, they have a 50% chance of the mutation being in the germline and should be offered subsequent germline testing to determine if the genetic mutation detected in the tumour is hereditary. Current germline testing for the BRCA 1/2 genes are offered to patients with high risk breast cancer or ovarian cancer. Germline testing of prostate patients would require adaptation of the current MBS items, or creation of a new item number specific for prostate cancer.

If a patient is referred for a germline test, genetic counselling will also be required.

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

Testing to identify BRCA/ATM gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

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

N/A

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

Testing to identify BRCA/ATM gene mutations in patients with mCRPC should be based on a referral request from a specialist or consultant physician and should not be pathologist determinable.

**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:**

Testing to identify BRCA/ATM gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

**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 medical service proposed in both Scenarios will be conducted in pathology laboratories which may be private companies or may be domiciled within private or public research institutes or hospitals. All laboratories are accredited to the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs. For further information please refer to the website: <https://www.rcpaqap.com.au/home-page>

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

N/A

**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):**

**SCENARIO 1 (preferred):**

The nominated comparator for the medical service of testing tumour prostate tissue to detect BRCA1/2 or ATM gene mutations in men with metastatic castration-resistant prostate cancer to determine eligibility for treatment with olaparib, is no testing.

**SCENARIO 2 (alternative):**

The nominated comparator for the medical service of testing tumour prostate tissue to detect BRCA1/2 gene mutations in men with metastatic castration-resistant prostate cancer to determine eligibility for treatment with olaparib, is no testing.

Treatment of mCRPC is not currently dependent on BRCA or ATM mutation status, as outlined in Question 26.

The nominated comparator for olaparib treatment in mCRPC depends on the line of treatment. As outlined in the current treatment pathway presented in Figure 1, there is no current standard of care. First line treatment for mCRPC includes treatment with a new hormonal therapy (enzalutamide or abiraterone) or docetaxel monotherapy. Patients are trialled on an alternative first line therapy at the second line, or given cabazitaxel.

**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

No medical service has been nominated as the comparator.

**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):**

Not applicable. The comparator for tumour BRCA/ATM testing is currently “no test.” Consequently, the algorithm provided at Q26 describes the current clinical management for metastatic castrate resistant prostate cancer.

Changes to the treatment algorithm after introduction of tumour BRCA/ATM mutation testing are described in answer to Q42. A patient with mCRPC who has been identified to have a BRCA/ATM gene mutation is eligible to access treatment with olaparib if all other PBS criteria are met.

Olaparib is a potent oral human polyadenosine 5'diphosphoribose polymerisation (PARP) inhibitor (PARP-1, -2 and -3) whose anti-tumour effects are dependent on an underlying defect in a cancer cell's DNA damage response (DDR) mechanisms, rather than a direct interaction with a mutated gene or protein (McCabe N, 2006), to preferentially kill cancer cells with these deficiencies compared to normal cells. These defects in DDR mechanisms arise from mutations that cause homologous recombination deficiency, of which BRCA mutations are only one subtype. Olaparib traps PARP at the sites of single-strand DNA damage and prevents their repair (Murai, 2012). During replication, the single-strand breaks where PARP is trapped are converted to double-strand DNA breaks, which are normally repaired by a high fidelity process known as HRR (Ashworth, 2016), (Pommier, 2016). Tumours with homologous recombination deficiency, such as mCRPC in patients with BRCA1, BRCA2, ATM or other HRR gene mutations, cannot accurately repair the DNA damage, which may become lethal to tumour cells as it accumulates (Ashworth, 2016). In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available taxane-based chemotherapy regimens.

Tumours with homologous recombination deficiency are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Hay, 2009), (Rottenberg, 2008) and in the clinic (Fong, 2009), (Tutt, 2010). Clinical studies suggest that single agent olaparib is effective in mCRPC patients, particularly those with a HRR gene mutation (such as BRCA1, BRCA2 or ATM) (Mateo J, 2015), (Mateo, 2019).

**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)

The proposed medical service (i.e. tumour mutation testing) will be used instead of the comparator (no tumour mutation testing).

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

It could be assumed that up to 100% substitution of no testing (the comparator) with testing for BRCA and ATM mutations will occur for men with mCRPC, to determine patient eligibility for treatment with olaparib. The availability of a new treatment option will increase uptake of tumour BRCA/ATM mutation testing. However, it is unlikely that all eligible patients will take up testing due to cultural and religious beliefs.

A patient can only access olaparib based on a positive mutation status. Patients without the BRCA or ATM mutation will not be eligible for olaparib therapy and will follow current standard of care.

**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 (Refer to Question 39 as baseline):**

Changes to the current clinical management pathway following introduction of tumour BRCA/ATM mutation testing are outlined in Figure 2 in the Attachment to this form.

In summary, no changes to first line treatment of mCRPC will occur in response to BRCA/ATM tumour testing. However, patients who progress on first line enzalutamide/abiraterone will be eligible for 2<sup>nd</sup> line treatment with olaparib, if a BRCA1/2 or ATM gene mutation is detected in the tumour tissue, it is proposed that the BRCA/ATM test is performed on patients as they are diagnosed with mCRPC, rather than at the point they progress after first line treatment.



**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):**

The overall clinical claim is that the proposed co-dependent technologies (BRCA/ATM tumour mutation testing and olaparib therapy) are superior in terms of comparative effectiveness versus the main comparator (no testing and current standard of care) in patients with mCRPC following prior treatment with a new hormonal agent.

The Phase III PROfound trial compared the efficacy of the PARP inhibitor, olaparib, and physician's choice of new hormonal agent treatment with enzalutamide or abiraterone in two groups of men with mCRPC. Those in Cohort A had alterations in BRCA1, BRCA2 or ATM genes while those in Cohort B had alterations in any one of 12 other genes known to be involved in DNA repair, including among them CDK12. In Cohort A, median progression free survival (PFS) was 7.39 months with olaparib compared to 3.55 months with hormonal treatment (hazard ratio [HR] 0.34,  $p < 0.0001$ ). In the overall population (Cohort A+B), median PFS was 5.82 vs 3.52 months respectively (HR 0.49,  $p < 0.0001$ ).

Although insufficient deaths had occurred for a conclusive result, interim overall survival analysis in Cohort A showed that median overall survival was 18.5 months with olaparib compared to 15.11 with hormonal treatment (HR 0.64,  $p = 0.0173$ ). Median overall survival in the overall population (Cohort A+B) was 17.51 vs 14.26 months (HR 0.67,  $p = 0.0063$  [nominal]) with olaparib vs hormonal treatment respectively. Adverse events were more common with olaparib than with hormonal treatment, though median treatment duration was longer with olaparib (7.4 months) than hormone treatment (3.9 months). In the olaparib group, 16.4% of patients discontinued treatment due to adverse events, compared to 8.5% with hormonal treatment.

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

- Superiority  
 Non-inferiority

**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:** Safety and tolerability of olaparib treatment assessed by adverse events and collection of clinical chemistry/haematology parameters

**Clinical Effectiveness Outcomes:**

**Test outcomes**

*Trial based (evidentiary standard) analytical performance:*

Sensitivity, Specificity, Positive predictive value, Negative predictive value

*Clinical utility of test:*

Prognostic effect of BRCA1/2 or ATM mutation in mCRPC

Treatment effect modification of olaparib in patients with mCRPC following prior treatment with a new hormonal agent

*Other test-related considerations:*

Re-biopsy rates

Test turnaround time

Estimated number of patients being tested

Cost of testing per patient

**Drug outcomes**

Radiographic progression-free survival (rPFS)

Overall survival (OS)

Objective response rate (ORR)

Time to pain progression

## PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

In “Cancer in Australia, 2019”, the AIHW estimate 19,508 new cases and 3,306 deaths in 2019. These estimated numbers are projected from observed cases between 2006 and 2015 (Australian Institute of Health and Welfare, 2019). An alternative estimate was reported in the AIHW cancer predictions 2011-2020 (AIHW 2012), in which 29,840 prostate cancer diagnoses were predicted for 2019, rising to 31,000 in 2020.

A review of CRPC epidemiology (Kirby M, 2011) reports a range of 10% to 20% of men with prostate cancer will progress to castration resistant prostate cancer within 5 years. The study population in the UK Health Information Network (THIN) appears most relevant to this application (11.2% of patients diagnosed with prostate cancer developed castrate resistant cancer within 5 years).

(Wade CA, 2018) reports that  $\geq 84\%$  of patients will have metastases at the time of CRPC diagnosis, although this is based on a relatively small study in Japanese men.

#### ***For the year 2020, it is estimated that:***

31,000 patients will be diagnosed with prostate cancer (using the higher estimates from AIHW),

2,838 patients will be diagnosed with castrate-resistant disease, of which,

**2,384** will have metastatic disease.

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

Testing to determine tumour BRCA or ATM gene mutation status would be conducted only once per patient in most cases. Some patients with metastatic pancreatic cancer may already know their gBRCAm status via testing under existing MBS item codes for breast/ovarian cancer or cascade testing due to an established familial risk.

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

Tissue testing to determine BRCA or ATM gene mutation status is not required for routine monitoring of a patient. The substantial majority of patients should only require testing once per lifetime to detect BRCA or ATM gene mutations.

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

The number of patients utilising the proposed medical service is dependent on the number of patients diagnosed with metastatic prostate cancer (which is estimated in Question 46).

If the BRCA/ATM test is administered at the time of diagnosis of mCRPC, then up to 2,384 newly diagnosed patients could be eligible for the test in 2020. However, it is unlikely that all eligible patients would take up testing.

A detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

### 49. 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 not anticipated that there would be any supply or demand issues as the overall number of patients requiring testing to detect BRCA or ATM gene mutations is manageable even if the number of laboratories conducting testing does not increase. Risk of leakage is expected to be low given the specific details of the proposed item descriptor.

A detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

## PART 8 – COST INFORMATION

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

The current MBS fee for detection of germline BRCA1 or BRCA2 mutations according to Item 73295 or Item 73296 is \$1,200.00.

Tumour testing to detect somatic BRCA1/2 may have additional complexity over blood-based tumour testing as FFPE tumour specimens may need to be retrieved from archive and transported to the testing laboratory. Macro or micro-dissection of the tumour specimen may be required and DNA quality assurance may be carried out prior to next generation sequencing. Depending on the quality and quantity of the specimen, multiplex ligation-dependent probe amplification (MLPA) may be required. The proposed fee for tumour BRCA1/2 testing in MSAC application 1554 is \$1,400, which would apply to Scenario 2 of this application.

To make provision for the additional costs with the inclusion of ATM, an MBS fee of **REDACTED** is proposed for tumour testing to detect tumour BRCA1/2 and ATM mutations for Scenario 1.

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

Tumour testing to detect somatic BRCA1/2 mutations takes 6-8 weeks from request to reporting. This includes time for the request and time to transport the tumour specimen to a specialist laboratory, if needed (7-10 days). Testing in the laboratory may require several hours of activity to perform plus run time for automated processes depending on instrumentation and procedures being followed and could take up to 4 weeks. Reporting results to the requesting specialist or consultant physician takes a further 1-2 days. A similar timeframe would apply to BRCA/ATM testing.

**52. 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.**

This application requests the creation of a new MBS item for both Scenarios.

**SCENARIO 1:** testing of tumour prostate tissue to detect BRCA1/2 or ATM gene mutations in men with mCRPC

Category 6 – Pathology Services	
MBS item number	Group P7 - Genetics
A test of tumour tissue from a patient with metastatic castration-resistant prostate cancer requested by a specialist or consultant physician, to determine whether the requirements relating to BRCA or ATM mutation status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Fee: <b>REDACTED</b> Benefit: 75% = <b>REDACTED</b> 85% = <b>REDACTED</b>	

**SCENARIO 2:** testing of tumour prostate tissue to detect BRCA1 or BRCA2 gene mutations in men with mCRPC

Category 6 – Pathology Services	
MBS item number	Group P7 - Genetics
A test of tumour tissue from a patient with metastatic castration-resistant prostate cancer requested by a specialist or consultant physician, to determine whether the requirements relating to BRCA mutation status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Fee: \$1400.00 Benefit: 75% = \$1050.00 85% = \$1190.00	

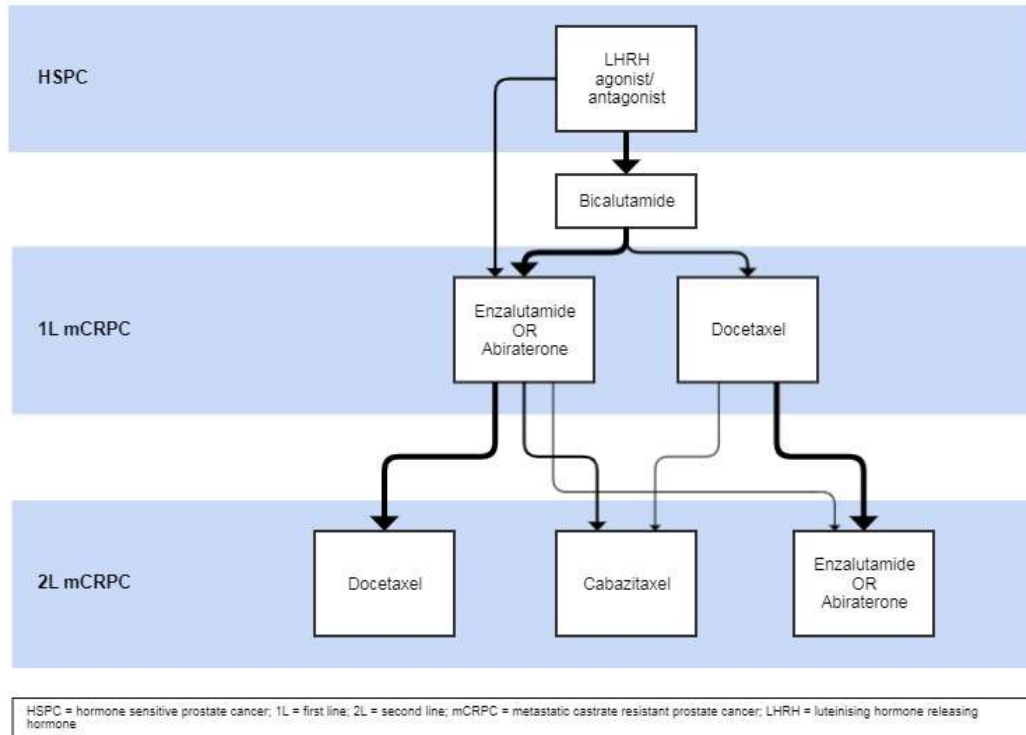
## REFERENCES

- Abida. (2017). Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis*.
- Armenia, J. (2018). The long tail of oncogenic drivers in prostate cancer. *Nat Genet*, 645-51.
- Ashworth, L. a. (2016). BRCAness revisited. *Nat Rev Cancer*, 110-20.
- Australian Government, Cancer Australia. (2017, December 7). Retrieved August 30, 2019, from Prostate cancer: <https://prostate-cancer.canceraustralia.gov.au/diagnosis>
- Australian Institute of Health and Welfare. (2019). *Cancer in Australia*.
- Body A, P. G. (2018). Medical management of metastatic prostate cancer. *Aust Prescr*, 41, 154–159.
- Cancer Council Australia. (2018). *Understanding prostate cancer: a guide for men with cancer, their families and friends*.
- Cancer Council Australia. (2019, May 17). *Prostate cancer*. Retrieved August 29, 2019, from Cancer Council: <https://www.cancer.org.au/about-cancer/types-of-cancer/prostate-cancer/>
- Cheng H, P. J. (2018). Practical Methods for Integrating Genetic Testing Into Clinical Practice for Advanced Prostate Cancer. *ASCO*, 372-381.
- Chung. (2019). Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. *JCO Precis Oncol*, 3.
- DUSC. (June 2016). *Metastatic prostate cancer: predicted versus actual analysis*. Canberra.
- Fong. (2009). Inhibition of poly (ADP-ribose) polymerase in tumors for BRCA mutation carriers. *N Engl J Med*, 123-34.
- Hay. (2009). Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumours in vivo and delays tumor relapse in combination with carboplatin. *Cancer Res*, 3850-5.
- Kirby M, H. C. (2011). Characterising the castration-resistant prostate cancer population: a systematic review. *J Clin Pract*, 65(11), 1180-1192.
- Kumar A, C. I. (2016). Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. *Nat Med*, 22(4), 369-378.
- Mateo. (2019). TOPARP-B: A phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations. *Presented at the American Society of Clinical Oncology 31 May -4 June 2019*, Abstract 5005.
- Mateo J, C. S.-L. (2015). DNA repair defects and PARP inhibition in metastatic prostate cancer. *N Engl J Med*, 373(18), 1697-1708.
- Mohler JL, A. E. (2019). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 2.2019. *J Natl Compr Canc Netw*, 17(5), 479-505.
- Murai. (2012). Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res*, 5588-99.
- National Institute for Health Research. (April 2019). Health Technology Briefing: Olaparib for BRCAm or ATM mutated metastatic castration-resistant prostate cancer.
- Parker C, G. S. (2015). Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 26(Suppl63), v69-v77.
- Pommier. (2016). Laying a trap to kill cancer cells: PARP inhibitors and their mechanism of action. *Sci Transl Med*, 17.
- Prostate Cancer Foundation of Australia. (2014). *What you need to know about prostate cancer*.

- Robinson D, V. A. (2015). Integrative clinical genomics of advanced prostate cancer. *Cell*, 161(5), 1215-1228.
- Rottenberg. (2008). High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci*, 17079-84.
- Tutt. (2010). Oral poly(ADPribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet*, 235-44.
- Wade CA, K. N. (2018). Profiling Prostate Cancer Therapeutic Resistance. *Int J Mol Sci*, 19(904).

# Attachment

**Figure 1 Current clinical algorithm for metastatic prostate cancer**



**Figure 2 Clinical algorithm following introduction of mutation testing for metastatic prostate cancer**

