Australian Government

Department of Health

RATIFIED PICO

Application 1618:

Testing of tumour prostate tissue to detect *BRCA1/2* or *ATM* pathogenic gene variants, in patients with metastatic castration-resistant prostate cancer, to determine eligibility to PBS-listed olaparib

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

***Please note*: In line with gender-neutral policies and practices, references to 'men' have been changed to 'patients'.**

Component	Description
Patients	**Test:** Patients with metastatic castrate-resistant prostate cancer (mCRPC). **Treatment:** Patients with metastatic castrate-resistant prostate cancer who have failed first- or second-line enzalutamide or abiraterone treatment and have pathogenic *BRCA1/2* or *ATM* variants in tumour tissue.
Prior tests	• Tests to diagnose mCRPC (could include physical examination and medical history, digital rectal examination, a blood test to check for prostate-specific antigen, a transrectal ultrasound, magnetic resonance imaging). • Biopsy of tumour tissue.
Intervention	**Test:** Testing of prostate tumour tissue to detect pathogenic *BRCA1/2* (BReast CAncer gene) or *ATM* (Ataxia-Telangiesctasia Mutated) gene variants, to determine eligibility for olaparib (Lynparza®). **Treatment:** • In those found to be positive for a pathogenic *BRCA1/2* or *ATM* variant: olaparib treatment after failed treatment with enzalutamide or abiraterone. • In those found to be negative for a pathogenic *BRCA1/2* or *ATM* variant: no olaparib treatment (the patient would receive the same treatment as they would have received without *BRCA1/2* or *ATM* testing).
Comparator	**Test:** No genetic testing. **Treatment:** The comparator for olaparib in second-line patients with a detected pathogenic *BRCA1/2* or *ATM* gene variant **is** enzalutamide (if first-line treatment was abiraterone); abiraterone (if first-line treatment was enzalutamide); In third-line patients, the comparator would be enzalutamide (if second-line treatment was abiraterone); or abiraterone (if second-line treatment was enzalutamide).
Reference standard (for analytical validity)	The reference standard would be testing of high quality DNA obtained from fresh tissue (if the testing was performed on FFPE blocks).
Outcomes	**Direct outcomes** ***Effectiveness (primary outcomes)*** • health-related quality of life • mortality **Test-related outcomes** ***Safety*** • physical and/or psychological harms from testing or no testing, adverse events from testing • adverse events associated with biopsy/re-biopsy for patients with inadequate tissue

Component	Description
	Analytical validity • test failure rate • sensitivity (FFPE blocks compared to fresh tissue) • specificity (FFPE blocks compared to fresh tissue) • unsatisfactory or uninterpretable results • diagnostic yield • concordance with other tumour tissue *BRCA1/2* and/or *ATM* test methods ***Clinical validity*** Prognostic effect of pathogenic *BRCA1/2* or *ATM* variants in mCRPC ***Clinical utility*** Treatment effect modification of olaparib in mCRPC ***Other test-related considerations*** • re-biopsy rates • test turn-around time Drug-related outcomes • overall survival • progression-free survival • health-related quality of life • adverse events such as nausea and anaemia Healthcare system outcomes • cost of testing per patient, cost-effectiveness of genetic testing • financial implications (financial impact, overall healthcare costs, etc.)

Assessment questions

Direct evidence

- What is the safety, effectiveness and cost-effectiveness of testing of tumour prostate tissue to detect pathogenic *BRCA1/2* or *ATM* gene variants in patients with mCRPC to determine eligibility for olaparib, compared with no testing (and no olaparib)?

Linked evidence

- What is the analytical validity of *BRCA1/2* and *ATM* testing on FFPE tumour samples compared to fresh tissue in patients with mCRPC?
- [What is the concordance of the evidentiary standard with the range of *BRCA1/2* and *ATM* test options likely used in Australia for patients with mCRPC if listed on the Medicare Benefits Schedule (MBS)?] *(if relevant, i.e. if the test used in the key study does not reflect the range of tests which would potentially be able to use the proposed item number if listed).*
- Is there a change in management in patients with mCRPC who are found to have pathogenic *BRCA1/2* or *ATM* variants?
- What is the safety and effectiveness of olaparib treatment after failed treatment with enzalutamide or abiraterone in patients with mCRPC, compared with treatment with enzalutamide, abiraterone, or cabazitaxel (depending on patient/disease characteristics and intolerances)?

- Is *BRCA1/2* or *ATM* variant status a treatment effect modifier for olaparib in patients with mCRPC?

PICO or PPICO rationale for therapeutic and investigative medical services only

Please note: As per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016), the term 'variant' should be (and has been) used to replace the outdated term 'mutation'.

Where 'mutated' is part of an existing gene variant name or TGA listing, it has been retained, with [variant] presented in brackets, if practicable.

POPULATION

An integrated codependent submission to MSAC/PBAC is proposed for *BRCA 1/2* and *ATM* gene testing of tumour tissue, to help determine PBS access to olaparib in patients with metastatic castrate-resistant prostate cancer (mCRPC).

Background

It was estimated that 19,508 males would be diagnosed with prostate cancer in 2019. This is 25% of all new male cancer cases diagnosed in 2019 (1 in 4). An estimated 3,306 deaths occurred from prostate cancer in 2019, which was 12% of all male deaths from cancer.

Prostate cancer was the most commonly diagnosed cancer in Australia in 2015, and the most commonly diagnosed cancer among males (Cancer Australia 2019). One in seven males will be diagnosed with prostate cancer by the age of 85. The disease is more common among the elderly, with 63% diagnosed in males older than 65 years (Cancer Council 2019). On average, prostate cancer in males is diagnosed before Stage II (average RD stage 1.8). In 2011, 35.9% of cases were diagnosed at Stage I, 46.1% at Stage II, 11.2% at Stage III and 4.2% at Stage IV (metastatic disease). 2.6% of cases were diagnosed at an unknown stage (Australian Institute of Health and Welfare 2019).

When prostate cancer is localised, it can be cured with surgery or radiotherapy, however some patients will relapse with overt metastases or an isolated rise in prostate specific antigen (PSA). A local relapse may be able to be treated with salvage therapy (generally radiation). Patients with advanced disease usually undergo medical management. Advanced (metastatic) disease is considered incurable, but not untreatable (Body et al. 2018).

Prostate cancer growth and proliferation are primarily dependent on androgens. Androgen deprivation therapy aims to limit the growth of cancer cells in the prostate by decreasing the level of testosterone. Prostate cancer is called 'castrate resistant' when the disease progresses despite the patient undergoing continuous androgen deprivation therapy. When this happens, further treatment is needed to maintain control of the disease (Body et al. 2018).

Biomarkers

Specific variants in several genes which are involved in DNA damage repair can make patients more susceptible to prostate cancer. Around 24-30% of patients with mCRPC have loss of function variants in homologous recombination repair (HRR) genes involved in DNA damage response (DDR). Pathogenic variants in HRR genes have been associated with response to poly (ADP-ribose) polymerase (PARP) inhibitors in prostate cancer (Chung et al. 2019). The most prevalent pathogenic HRR variants occur in the *BRCA1/2* (BReast CAncer) gene, or *ATM* (Ataxia-Telangiesctasia Mutated) gene (Chung et al. 2019).

BRCA1 and *BRCA2* proteins play a role in DNA repair, in the homologous recombination repair (HRR) pathway, which is responsible for effective repair of double strand DNA breaks. A lack of functional *BRCA1* or *BRCA2* proteins means that double strand breaks cannot be effectively repaired using the HRR pathway. Instead, alternative (more error-prone) pathways are activated, such as the non-homologous end-joining pathway, leading to increased genomic instability and the cells becoming cancerous.

The *BRCA1/2* genes are large, with 23 exons (consisting of 5,592 bp), encoding 1,863 amino acids for *BRCA1;* and 27 exons (10,257 bp), encoding 3,418 amino acids for *BRCA2*. Sequence changes causing loss of function of the BRCA1/2 proteins can occur anywhere within the *BRCA1/2* genes. This includes the exon-intron splice sites, and can be either germline or somatic in origin.

More than 1800 distinct variants (causing intronic changes), missense variants (single nucleotide variants [SNVs]), and small insertions or deletions (INDELs), have been reported in *BRCA1,* and 2000 have been reported in *BRCA2* (Couch, Nathanson & Offit 2014).

The *ATM* gene encodes a protein that helps control the rate at which cells grow and divide, located primarily in the nucleus of cells. The ATM protein also assists cells in the recognition of broken or damaged DNA, and coordinates DNA repair (Genetics Home Reference 2020). The *ATM* gene consists of 146,619 bases. It codes for a 350 kDa protein, consisting of 3,056 amino acids.

While extending beyond the scope of this application (1618), it is worth noting that the National Comprehensive Cancer Network (NCCN) guidelines[1] state patients with mCRPC can be considered for microsatellite instability (MSI) or mismatch repair deficiency (sMMR); and considered for germline and tumour testing to check for variants in HRR genes (i.e. *BRCA1, BRCA2, ATM, PALB2, FANCA*). *See NCCN Guidelines Version 1.2020 (from MS-57):*

Testing population

The target population for testing prostate tumour tissue to detect *BRCA1/2* or *ATM* gene variants are patients with mCRPC, to determine eligibility for treatment with the PARP inhibitor, olaparib.

PASC confirmed the proposed population is to be tested on diagnosis of metastatic castrate-resistant prostate cancer rather than waiting for evidence of progression following the first line of therapy of this stage of cancer.

It is estimated that 10-20% patients diagnosed with prostate cancer develop CRPC within approximately 5 years (Kirby, Hirst & Crawford 2011). Evidence from a small study suggests around 84% of patients with CRPC have bone metastases (Kirby, Hirst & Crawford 2011). The average length of survival of patients, from time of diagnosis of CRPC, is 14 months (varying from 9 to 30 months) (Kirby, Hirst & Crawford 2011).

[1] Available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx

Table 1 Expected prevalence/incidence of mCRPC

Population	Expected prevalence/incidence/%
Expected new cases of prostate cancer in 2019	19,508
Patients with prostate cancer developing CRPC within 5 years of follow-up	10-20%
Patients with CRPC expected to have metastases at diagnosis of CRPC	≥ 84% (84%-95%)
Expected number of patients with mCRPC per year	**3277 - 3707**

To estimate the number of patients diagnosed with mCRPC per year, the following calculation was done (for expected prevalence/incidence, see Table 1):

> Expected new cases of prostate cancer * (upper limit of percentage of patients with prostate cancer developing CRPC/100) * (percentage of patients with CRPC expected to have metastases/100) = number of patients with mCRPC (per year).

The upper limit of the estimated percentage of patients with prostate cancer developing CRPC within 5 years was used, as it was expected that some patients would still progress to CRPC after 5 years (see Table 1). It was estimated that between 84 and 95% of patients with CRPC were expected to have metastatic disease. Therefore, the expected range of patients diagnosed with mCRPC per year was between 3277 and 3707.

PASC agreed with the applicant that the eligible test population with metastatic castrate-resistant prostate cancer (mCRPC) would likely be approximately 3,000 patients per year.

PASC noted that around 50% of homologous recombination repair gene variants detectable in tumour tissue constitute germline variants, and considered that there is a clinical rationale to offer germline testing to a patient with a positive tumour test. Current germline testing for BRCA 1/2 is only offered to patients with high-risk breast cancer or ovarian cancer (MBS items 73295 and 73296); testing of patients with prostate cancer would require adaptation of the current MBS items, or creation of a new item number specific for prostate cancer. The estimated financial costs should factor this in: if the estimated test population is 3,000 patients, and the BRCA/ATM positivity rate is 20%, then up to 600 patients would need a second germline test for a known variant, at approximately **REDACTED** *per test. Related genetic counselling would also need to be provided by the requester of these services.*

Similarly, PASC considered that there is a clinical rationale to extend this to cascade testing of the population of family members of those shown to have a germline variant. Implementing this would also require an amendment of the related cascade testing MBS items. Additional costs for this cascade testing would also need to be estimated.

As also discussed under "Outcomes" below, PASC also advised that the integrated codependent submission would need to provide evidence regarding the clinical utility and cost-effectiveness of this extension into predisposition testing of the requested and cascade populations.

The applicant confirmed, the flow-on consequences of germline/cascade testing will be included in the codependent submission, as requested by the PASC.

Drug population

Patients with mCRPC, who are found to have pathogenic *BRCA1/2* or *ATM* variants after tumour testing (either somatic or germline), would be eligible for olaparib if they meet the other proposed PBS criteria to access treatment, and if they progress on first- or second-line enzalutamide or abiraterone. The benefit for patients with pathogenic *ATM* variants should be reported separately from those with pathogenic *BRCA1/2* variants to validate its inclusion in the test.

The proposed PBS criteria for olaparib state that patients must have progressed or failed treatment following a prior new hormonal agent (enzalutamide or abiraterone) treatment

Patients with mCRPC with a HRR pathway (e.g. pathogenic *BRCA2* variant) are known to have a poorer prognosis and overall survival compared with patients with a functional HRR pathway. However, patients with a germline or somatic sequence variant deactivating the HRR pathway are more likely to respond to treatment with PARP inhibitors, such as olaparib, than those with a functional HRR pathway.

Table 2 Prevalence of pathogenic variants in *BRCA1/2* or *ATM* genes in patients with prostate cancer and mCRPC

Study	Population	Pathogenic variants in			Total % patients with pathogenic variants
		BRCA1	*BRCA2*	*ATM*	
Chung et al. (2019)	Patients with prostate cancer (n=3,476)	1.4%	9.8%	5.2%	In HRR gene: 31.0% In *BRCA* or *ATM* genes: 16.4%
Mateo et al. (2015)	Patients with mCRPC (n=49)	2.0%	14.3%	10.2%	In *BRCA* or *ATM* genes: 26.5%
Robinson et al. (2015)	Patients with mCRPC (n=150)	-	-	-	In *BRCA* or *ATM* genes: 19.3%

Table 2 shows the occurrence of pathogenic variants in the *BRCA1, BRCA2* and *ATM* genes in different studies. The study by Robinson et al. (2015) stated that aberrations of *BRCA1/2* or *ATM* were observed at substantially higher frequencies in patients with mCRPC, compared to patients with primary prostate cancer (Robinson et al. 2015).

In this study, 29/150 mCRPC patients (19.3%) had pathogenic variants in *BRCA1/2* or *ATM.* Based on the studies shown above, it is estimated that around 20% of mCRPC patients would have a pathogenic *BRCA1/2* or *ATM* variant identified by tumour testing, and this would mean an estimated 655 - 741 (20% of 77 – 3707) mCRPC patients would technically be eligible for olaparib per year. *PASC agreed with the above estimate and considered that around 20% (rather than 16% as estimated by the applicant) of mCRPC patients would have a pathogenic BRCA1/2 or ATM variant identified by tumour testing.*

However, given not all patients will undergo genetic tumour testing, and olaparib would only be prescribed after failed treatment with enzalutamide or abiraterone, not all patients would receive olaparib. It was estimated that only around 55% of patients diagnosed with mCRPC will be successfully tested for *BRCA1/2* and *ATM* variants[2], and *PASC noted that it is estimated that less than 5% of patients with mCRPC will have second-line treatment after receiving abiraterone or enzalutamide in first line.*

Abiraterone and enzalutamide are used more often as a second-line treatment after docetaxel. It is estimated that >15% of patients with mCRPC go on to a third-line treatment, after receiving abiraterone or enzalutamide in second line (Drug Utilisation Sub-Committee 2016). If 55% of patients are estimated to be successfully tested, and 20% of patients with a pathogenic *BRCA1/2* or *ATM* variant receive olaparib in second or third line, this equates to around 72-81 mCRPC patients a year receiving olaparib.

Rationale

There are many other genes in the HRR family of genes (e.g. *CDK12, CHEK2, PALB2, FANCA, CDK12, PPP2R2A, CHECK1*), and patients with a pathogenic variant in these genes are also likely to respond to olaparib. The occurrence of pathogenic HRR variants in these genes are lower (0 - 1.8%), however if it is decided to expand tumour testing to more genes, this would mean that more mCRPC patients would

[2] Estimated by the applicant (Teleconference 25/2/2020).

potentially be eligible for olaparib. The reason for exclusion of other HRR pathogenic variants should be discussed.

Prior tests

Prior to genetic testing for somatic or germline pathogenic *BRCA1/2* and *ATM* gene variants, patients would have undergone tests as part of their prostate cancer diagnosis. Some of the common tests include physical examination and medical history, digital rectal examination, a blood test to check for PSA, a transrectal ultrasound, multiparametric magnetic resonance imaging (MRI), and/or a prostate biopsy.

After the patient is diagnosed with prostate cancer, the following tests can be used to determine the stage of cancer: (1) transrectal ultrasound, (2) biopsy or removal of lymph nodes, (3) a bone scan, and/or (4) imaging like computerised tomography, MRI or other.

Patients with mCRPC would be eligible for testing for pathogenic *BRCA1/2* and *ATM* gene variants after undergoing a biopsy of tumour tissue.

Prior treatments

Patients with mCRPC would be treated with enzalutamide, abiraterone, or docetaxel in first line. According to the PBS restrictions, abiraterone and enzalutamide are only to be used as a first-line therapy if the patient is unsuitable for treatment with docetaxel due to resistance or predicted intolerance. Abiraterone and enzalutamide interfere with androgen stimulation of prostate cancer growth, whereas docetaxel is a taxane chemotherapy.

Cabazitaxel (also a taxane) is used as a second-line treatment. It is a synthetic taxane derivative developed to have activity in patients who progress after treatment with docetaxel. The clinical benefit rate is shown to be greater with cabazitaxel compared to enzalutamide and abiraterone, although this is counterbalanced by a significantly worse toxicity profile for cabazitaxel. Cytotoxic chemotherapy with a taxane is generally reserved for patients with relatively rapidly progressing symptomatic disease, for which less toxic approaches are not an appropriate option. Either docetaxel or cabazitaxel are an appropriate choice if chemotherapy is initially used. In a large trial, cabazitaxel was equivalent to docetaxel in efficacy, with less neuropathy and alopecia. Cabazitaxel is preferred for patients who have progressed after treatment with docetaxel, as it has been shown to prolong survival in this setting (Dawson et al. 2019).

Enzalutamide has limited activity in patients with CRPC who have previously been treated with both docetaxel and abiraterone. As an example, in a retrospective case series, approximately 10% of such patients had a ≥50% decrease in serum PSA during treatment with enzalutamide.

According to Dawson et al. (2019), androgen deprivation therapy (ADT) is generally continued in most patients with CRPC in conjunction with secondary therapies.

INTERVENTION

The codependent intervention is testing for *BRCA1/2* and *ATM* variants in tumour tissue, and in those with pathological variants, use of olaparib (and in those without *BRCA1/2* or *ATM* variants, standard care).

Testing for *BRCA1/2* or *ATM* pathogenic variants in tumour tissue

The evidentiary standard test should be defined in this subsection, against which the likely alternative test options (available in Australia) should be compared. This should describe how the testing

option(s) were performed in the key clinical study/studies, to be used as the evidentiary basis for the codependency. This should specify aspects like:

- the assay performed;
- the type of tumour tissue (e.g. fresh or archived); and
- the processing of tissue (e.g. fresh frozen or FFPE).

The proposed investigative medical service is testing of tumour prostate tissue to detect pathogenic *BRCA1/2* or *ATM* gene variants, to determine eligibility for olaparib. The test is proposed to be performed at diagnosis of mCRPC, due to the relatively long turnaround time of the test (estimated 4-6 weeks).

PASC confirmed that the intervention was appropriate, noting it would not be pathologist determinable as there is also a need to know patient characteristics to determine eligibility for the test.

BRCA1/2 and *ATM* testing of tumour tissue would be performed in a pathology laboratory. Tumour tissue specimens can be obtained as either fresh tissue following primary tumour debulking surgery or from formalin-fixed paraffin-embedded (FFPE) tissue block (which can be stored for many months or years). DNA is extracted from the tissue samples in the pathology laboratory, purified and may be quantified using the laboratory's preferred kits. Polymerase chain reaction (PCR) amplification, including multiplex ligation-dependent probe amplification (MLPA) would likely be used to prepare sequencing libraries and quality of the library could be assessed at this point. The libraries would be sequenced using next generation sequencing (NGS)-based methods and compared to reference libraries in order to identify sequence variants. Gene panels like the BROCA cancer risk panel identify all different classes of sequence variants (e.g. single base substitutions, deletions, small insertions, and large gene re-arrangements). Most Australian laboratories perform next-generation sequencing using the Illumina MiSeq system, however some laboratories use Illumina NextSeq. Results of the test would be sent to the requesting physician. *PASC noted that there is a quality assurance program (QAP) in place for BRCA1/2 testing but not yet for ATM.*

If archived specimens are used for the test (FFPE blocks), the retrieval of these samples may add an extra two weeks to the test turnaround time. Also the preparation, extraction and interpretation may add extra time (possibly weeks). The applicant states that costs (**REDACTED**) will be incurred for retrieving archived samples and forwarding (if required) to the testing laboratory.

If degradation of DNA in the archived specimen has occurred, or if neo-adjuvant chemotherapy resulted in significant tumour shrinking and debulking surgery did not provide viable tumour tissue, a re-biopsy may be required. There may be safety issues associated with the re-biopsy.

PASC noted the 7% attrition rate for all types of prostate tumour testing, and that laboratories obtain good results from FFPE samples. PASC concluded that obtaining suitable tissue for testing should therefore not be an issue.

If a pathogenic variant is found, a genetic counselling appointment would be planned in which the results would be delivered. Patients with class 4 (likely pathogenic) or class 5 (known pathogenic) variants would then be referred to Genetics Services/Familial Cancer Centres for further counselling. If a patient has a variant of unknown significance (class 3) or a strong family history should also be referred for further counselling.

If the patient tests positive for pathogenic *BRCA1/2* or *ATM* variants on a tumour test, they have around a 50% chance of the variant being germline. Therefore, patients with a Class 4 or 5 pathogenic variant (identified by the somatic test) would be referred for genetic counselling (where results would be delivered to the patient).

These patients could then also be referred for germline testing if appropriate, to determine whether the somatic variant is heritable. It was noted the USA's National Comprehensive Cancer Network (NCCN) guidelines[3] state that if mutations [variants] in HRR genes (i.e. *BRCA1*, *BRCA2*, *ATM*, *PALB2*) are found, and/or there is a strong family history of cancer, the patient is to be referred to genetic counselling for confirmatory germline testing:
Patients with a variant of unknown significance may also be referred for post-test counselling. Germline testing in patients with prostate cancer is currently not listed on the MBS, and if the decision is made to list this, adaptation of the current MBS items for germline *BRCA1/2* variant testing or the creation of a new MBS item would be required, including for consequential cascade testing.

Evidence supporting the addition of for germline cascade testing should be provided, noting that the outcomes for relatives with germline pathogenic *ATM* variants will differ from those with *BRCA1/2* variants as most pathogenic *ATM* variants will not increase risk of breast cancer.

If a pathogenic *BRCA1/2* or *ATM* variant is found in the patient's prostate tumour tissue, the treating physician would prescribe olaparib to the patient (after failed enzalutamide or abiraterone treatment), if he meets all other criteria for access to treatment.

For the estimated number of patients diagnosed with mCRPC per year, see Table 1. It is proposed that testing of tumour tissue for *BRCA1/2* or *ATM* gene variants be conducted once per patient. However, it may be useful to consider MSAC's advice in the Public Summary Document (PSD) for Application 1554. MSAC changed this type of wording to: "once per primary tumour diagnosis" [page 5 of PSD]. MSAC's ESC considered the restriction of 'once per lifetime testing' for somatic testing was unnecessary [page 18 of PSD].

If all patients were to undergo genetic testing as soon as mCRPC was diagnosed, the expected number of tests per year would be up to the range 3277 – 3707 (see Table 1). However, it is unlikely ALL eligible patients would take up genetic testing. The applicant estimated that 80% of patients diagnosed with mCRPC would take up genetic tumour testing, therefore the estimated number of tests per year would be 2621 – 2966.

Testing for pathogenic germline *BRCA1/2* variants to determine eligibility for olaparib is currently reimbursed through MBS item 73295, for patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer. The November 2019 MSAC meeting supported an extension of this listing to include tumour testing in these cancers (MSAC Application 1554). No MBS items for testing tumour tissue for *BRCA1/2* variants of any tumour type are currently available.

The 'in-house' developed in vitro diagnostic medical devices (IVDs) for testing of tumour tissue for *BRCA1/2* or *ATM* gene variants had not yet been submitted to the TGA at the time of the application. However, the laboratories indicated they will submit to the TGA once they receive NATA accreditation. According to the applicant[4], the Peter MacCallum Cancer Centre in Melbourne would start using the test in March 2020.

[3] Available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx
[4] Teleconference with the Australian Government Department of Health and the applicant on 25/02/2020.

Evidence base for testing of pathogenic BRCA1/2 or ATM variants in prostate tumour tissue

Ten studies were presented by the applicant, as 'diagnostic evidence'.

However, none of these studies included the intervention (testing for *BRCA1/2* or *ATM* pathogenic variants in prostate tumour tissue). The first study presented the landscape of germline DNA repair gene variants in Chinese patients with prostate cancer (not specific to mCRPC) (Wei et al. 2019). Two other studies did include patients with mCRPC, but they also only included germline testing (no tumour testing was done) (Antonarakis et al. 2018; Pritchard et al. 2016).

Two studies and two conference abstracts included testing for plasma cell-free DNA in patients with mCRPC, but not tumour tissue testing (Annala et al. 2017; Annala et al. 2018; Wyatt, Annala, Beja, et al. 2016; Wyatt, Annala, Parimi, et al. 2016).

Some studies or conference abstracts were not conducted in humans (Xu et al. 2019), or it was unclear which test was performed due to the use of unexplained abbreviations (Hussain et al. 2017; Hussain et al. 2016). None of the 'diagnostic studies' provided by the applicant mentioned tumour testing.

In addition to 'diagnostic studies', the applicant provided a link to a phase II trial that performed whole-exome sequencing and transcriptome studies on DNA from fresh-frozen tumour-biopsy samples obtained before treatment; germline whole-exome sequencing was performed on DNA from saliva samples (Mateo et al. 2015). This trial provides data on diagnostic yield and should be included.

Olaparib (Lynparza®) treatment

Olaparib is a potent PARP enzyme inhibitor (including PARP1, PARP2 and PARP3 enzymes). PARP enzymes are involved in DNA transcription, cell cycle regulation, and DNA repair. The anti-tumour effect of PARP inhibitors is dependent on an underlying defect in a cancer cell's DNA damage response (DDR) mechanisms. These defects in DDR mechanisms come from pathogenic variants causing HRR deficiency, of which *BRCA1/2* and *ATM* pathogenic variants are subtypes. At the sites of single-strand DNA damage, olaparib can trap PARP and prevents both their dissociation from the DNA and DNA repair. (Murai et al. 2012) These DNA-PARP blocks lead to double-strand DNA breaks during DNA replication, which are normally repaired by the HRR pathway (Lord & Ashworth 2016; Pommier, O'Connor & de Bono 2016). Tumours in patients with *BRCA1/2*, *ATM* or other HRR gene pathogenic variants have HRR deficiency and cannot accurately repair the DNA damage, leading to increasing DNA instability, which can become potentially lethal to tumour cells (Lord & Ashworth 2016). Therefore, biological plausibility suggests that in HRR-deficient tumours, olaparib would offer a more effective cancer treatment, compared with taxane-based chemotherapy. Some studies have indicated that treatment with olaparib is effective in mCRPC patients, particularly those with a pathogenic HRR gene variant (such as a *BRCA1, BRCA2* or *ATM* variant) (Mateo et al. 2015; Mateo et al. 2020).

There is no proposed change in treatment for those without pathogenic variants in the *BRCA1/2* or *ATM* genes.

ARTG registration

The pharmaceutical product Lynparza® (olaparib) is currently registered on the ARTG for the current indications:

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

An application has been made to the TGA to extend the registration of olaparib to include patients with mCRPC and a detected pathogenic *BRCA1/2* or *ATM* variant.

PBS listing

Olaparib is currently PBS-listed for platinum sensitive relapse patients with high grade serous ovarian, fallopian tube or primary peritoneal cancer, who also have germline *BRCA1/2* pathogenic variant (PBS items: 11503K; 11522K – 100 mg tablets; 11528R;11539H – 150 mg tablets; 11050N – 50 mg capsules). Olaparib is not currently listed for patients with mCRPC.

If olaparib is listed on the PBS for mCRPC, mCRPC patients who progress on first- or second-line enzalutamide/abiraterone would be eligible for second- or third-line treatment with olaparib, respectively, if a pathogenic *BRAC1/2* or *ATM* gene variant is detected in the tumour tissue. It is expected that around 5% of patients with mCRPC receive abiraterone or enzalutamide in first line and will then progress to second-line treatment (Drug Utilisation Sub-Committee 2016). It is estimated that >15% of patients with mCRPC go on to a third-line treatment after receiving abiraterone or enzalutamide in second line.

Evidence base for olaparib treatment in patients with mCRPC and a pathogenic BRCA1/2 or ATM variant

In the summary of evidence section in the Application Form, the applicant provided the study by Mateo et al. (2015) as a key trial (Mateo et al. 2015). Also presented were links to information about 'yet to be published' research (the PROfound Study, the PROpel study, and one trial comparing abiraterone + prednisone with olaparib and abiraterone, prednisone + olaparib in patients with mCRPC).

The Mateo et al. (2015) study (TOPARP-A) provides data on whether pathogenic *BRCA1/2* and *ATM* variants are treatment effect modifiers for olaparib in patients with mCRPC. It reported that 14 of 16 biomarker-positive patients (88%) had a response to olaparib, compared with 2 out of 33 biomarker-negative patients (6%). TOPARP-B was conducted after TOPARP-A. Results of this study were published in 2020 (Mateo et al. 2020). TOPARP-B was designed to validate the observed antitumour activity of olaparib in patients with mCRPC presenting with different DDR gene aberrations. It was reported that 25/30 patients with pathogenic *BRCA1/2* variants (83%) had an overall response to olaparib treatment, and 7/19 (37%) in those with pathogenic *ATM* variants.

Results of the PROfound study have not yet been published, however this study may have evidence to answer the question regarding the effectiveness of olaparib treatment in patients with mCRPC compared with comparator treatments (e.g. enzalutamide, abiraterone).

The other studies (PROpel study and the study by Northwestern University) may not be eligible for inclusion as these studies were done in the wrong study population (patients with mCRPC who have not received prior chemotherapy (or new hormonal agents) for mCRPC). In these studies, olaparib is used as a first-line treatment which is outside the scope of this application.

COMPARATOR

Testing

The nominated comparator for the medical service of testing of tumour tissue to detect *BRCA1/2* or *ATM* gene variants in patients with mCRPC is no genetic testing. In the absence of genetic testing, patients are treated with enzalutamide, abiraterone, docetaxel and/or cabazitaxel, depending on patient/disease characteristics and intolerances (type of treatment decided by the treating physician, (see current and proposed clinical management algorithm).

PASC confirmed the comparator for the test.

The reference standard would be testing of high quality DNA obtained from fresh tissue (if the testing was performed on FFPE blocks). As discussed above (see "Testing for BRCA1/2 or ATM pathogenic variants in tumour tissue"), the evidentiary standard test should also be defined and compared against the likely alternative test options available in Australia.

Treatment

The comparator for olaparib in second line in mCRPC patients with a detected pathogenic *BRCA1/2* or *ATM* gene variant is enzalutamide (if first-line treatment was abiraterone), abiraterone (if first-line treatment was enzalutamide) and/or palliative care.

Patients who received docetaxel in first line and enzalutamide or abiraterone in second line would be eligible for olaparib in third line (if they have a pathogenic *BRCA1/2* or *ATM* variant). As per second-line treatment, the comparator for olaparib in this group would be enzalutamide (if second-line treatment was abiraterone) or abiraterone (if second-line treatment was enzalutamide) treatment (see Figure 2).

Olaparib is proposed to replace these second- or third-line treatments in patients with detected *BRCA1/2* or *ATM* gene variants in tumour tissue.

PASC agreed with the applicant's view that cabazitaxel does not need to be considered as a comparator for the codependent medicine, because only approximately 7% of patients receive this treatment after docetaxel (or in second line), and no patients are using cabazitaxel in first line. These estimates were taken from the applicant's updated analysis of the 10% Medicare Data for PBS scripts from January-December 2019 (see applicant-revised proposed algorithm in Figure 2). PASC also noted the applicant did not consider palliative care to be an additional comparator for the codependent medicine as this typically occurs after drug treatment at end of life.

The Applicant confirmed its view that cabazitaxel does not need to be considered as a comparator for the codependent medicine and considered that cabazitaxel and palliative care should be removed as comparators to olaparib in both the second line and third line treatment settings within in the PICO.

The Applicant also agreed that, the figures presented in Appendix A of the Applicant response to the Draft PICO (Figures 1 and 2 below) will be the referenced clinical management algorithm in the submission.

OUTCOMES

PASC advised that 'flow-on consequences for germline/cascade testing' should be added to 'Other test-related considerations' As also discussed under "Population" above, PASC advised that it would be necessary for the integrated codependent submission to provide evidence to inform MSAC on how the estimated extent of health outcome benefit (clinical utility) and cost-effectiveness consequences would compare for an index case with prostate cancer (as proposed) rather than breast or ovarian cancer (as already funded); and for an ATM pathologic variant rather than a BRCA1/2 pathologic variant. This additional information is needed to enable MSAC to judge whether to support the extra funding for these other consequences of the requested testing.

PASC considered testing for germline status of BRCA1/2 positive mCRPC patients and testing of biological relatives of mCRPC patients who are found to have a germline BRCA1/2 variant should also be included as part of the healthcare system outcomes.

PASC confirmed that the other outcomes were appropriate.

The Applicant confirmed the flow-on consequences of germline/cascade testing will be included in the codependent submission, as requested by the PASC. The Applicant also agreed to provide evidence to inform MSAC on how the estimated extent of health outcome benefit (clinical utility) and cost-effectiveness consequences would compare for an index case with prostate cancer (as proposed) rather than breast or ovarian cancer (as already funded).

Test-related outcomes

Safety

Physical and/or psychological harms from testing or no testing

Adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing

Effectiveness (primary outcomes)

Health-related quality of life

Mortality

Analytical performance

Test failure rate, unsatisfactory or uninterpretable results, diagnostic yield

Sensitivity (FFPE blocks compared to fresh tissue)

Specificity (FFPE blocks compared to fresh tissue)

Positive predictive value

Negative predictive value

Concordance with other tumour tissue *BRCA1/2* and/or *ATM* test methods

Clinical validity and utility

Prognostic effect of somatic pathogenic *BRCA1/2* or *ATM* variants in mCRPC

Treatment effect modification of olaparib in mCRPC

Other test-related considerations

Re-biopsy rates

Test turn-around time

Flow-on consequences for germline/cascade testing

Healthcare system

If testing of tumour tissue for pathogenic *BRCA1/2* or *ATM* variants and treatment with olaparib becomes available to eligible patients with mCRPC, the resulting healthcare resources and costs will relate to:

- testing for somatic pathogenic *BRCA1/2* and *ATM* variants
- pathologists' time and materials required for interpreting and reporting the results
- treating adverse events from testing and treatment
- any additional procedures (e.g. laparoscopy and laparotomy) when re-biopsy is required
- treatment with olaparib for patient with a pathogenic somatic *BRCA1/2* or *ATM* variant

Drug-related outcomes

Progression-free survival (PFS)
Overall survival (OS)
Objective response rate (ORR)
Health-related quality of life (HRQoL)

Safety

Safety and tolerability of olaparib treatment as assessed by adverse events (AEs), physical examinations, laboratory findings, and vital signs.

Current and proposed clinical management algorithms for identified population

PASC noted the clinical management algorithms were revised several times by the applicant, most recently due to the its updated analysis using patient numbers from the 10% Medicare PBS data (Appendix A in the applicant's comments on the draft PICO).

PASC confirmed that this is the correct proposed clinical management algorithm for the codependent aspect of the application, and noted for consistency, that the latest current algorithm in Figure 1 should also be updated for the 10% Medicare PBS data.

The Applicant agreed that the updated clinical management algorithm included in Appendix A of the Draft PICO Applicant Response, noted above, would be the referenced algorithm in the submission.

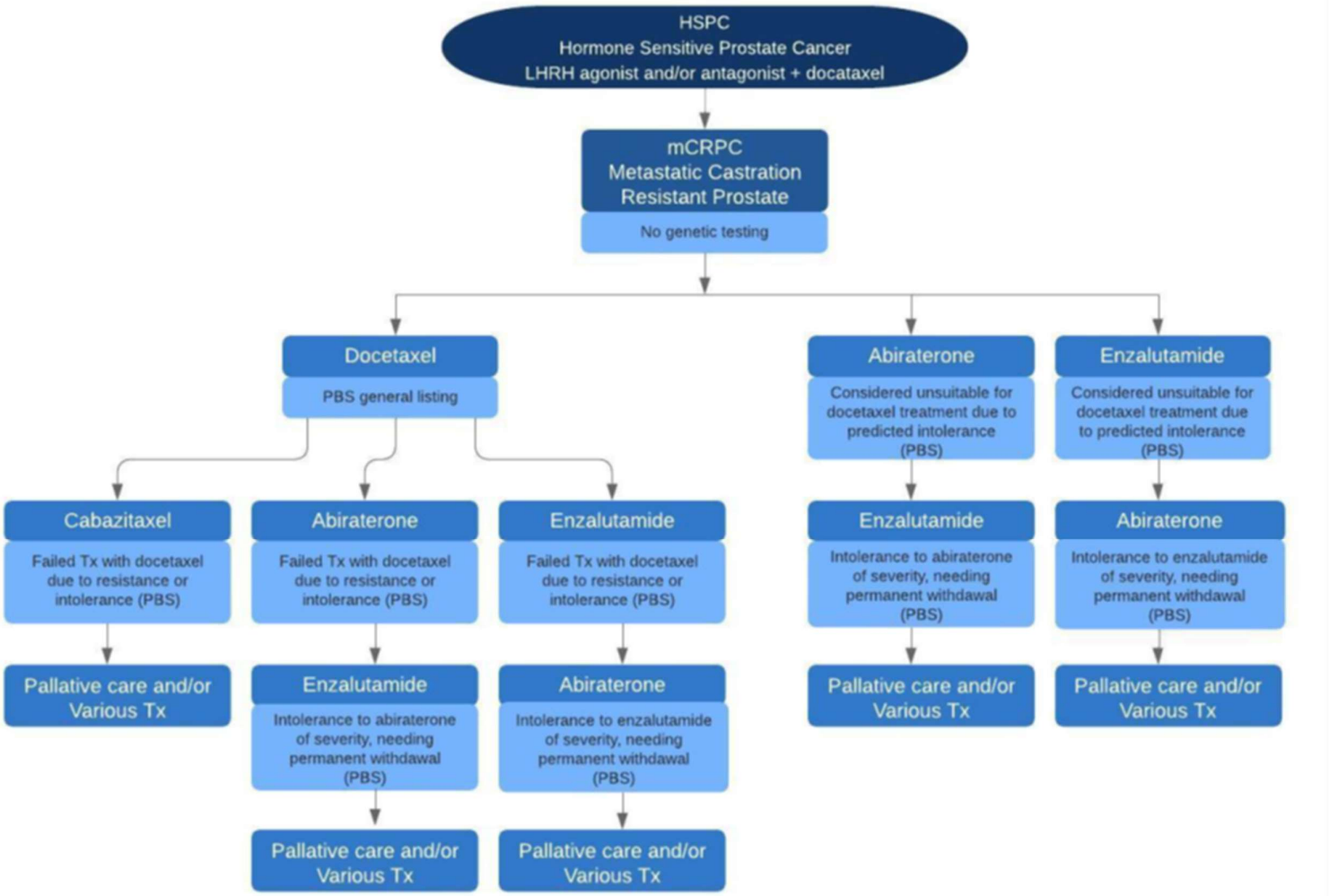

Figure 1 Current management algorithm for patients diagnosed with mCRPC, provided by the applicant

HSPC = hormone sensitive prostate cancer; LHRH = Luteinizing hormone-releasing hormone; mCRPC = metastatic castrate-resistant prostate cancer; PBS = Pharmaceutical Beneifits Scheme; Tx = treatment

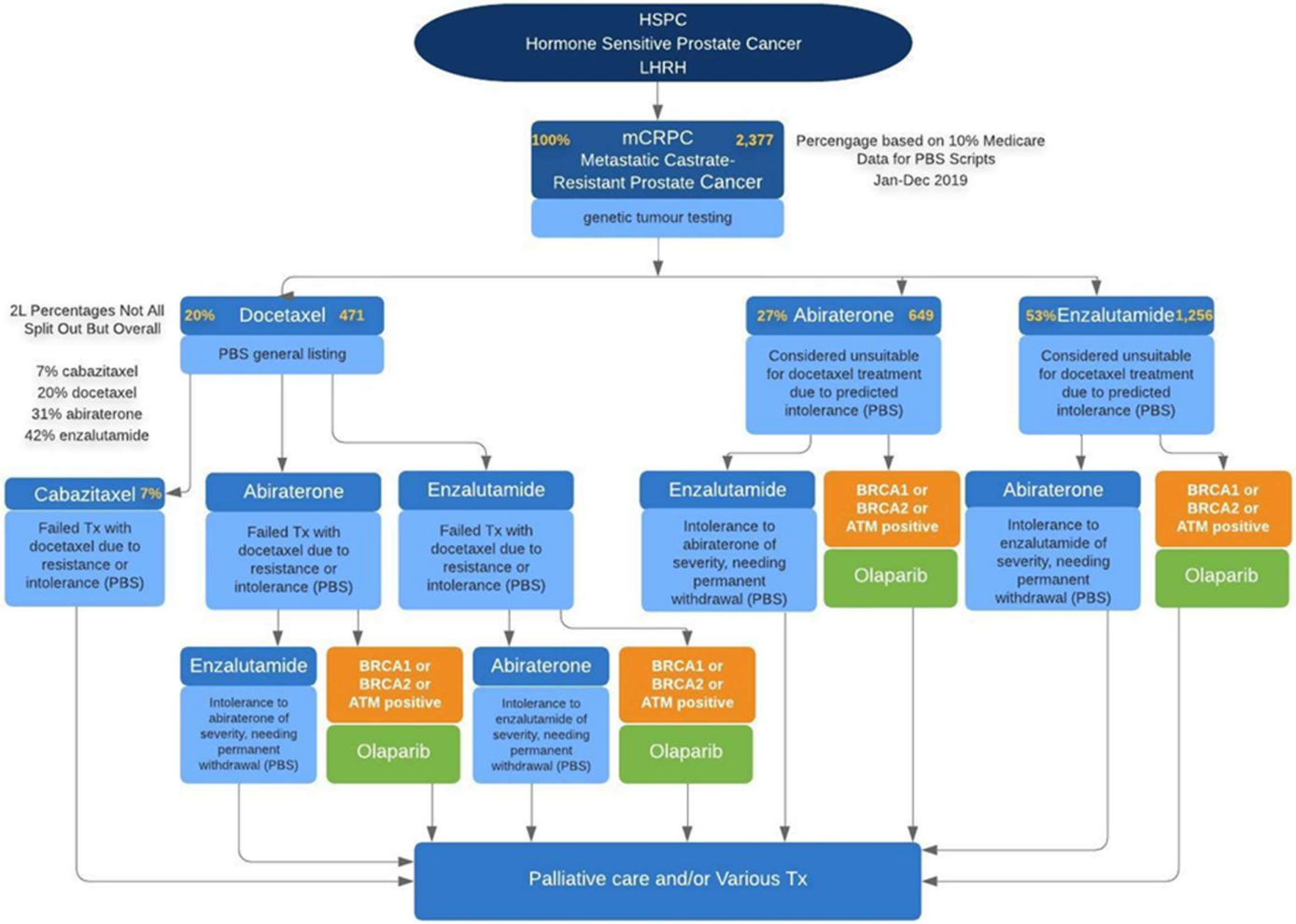

Figure 2 Proposed clinical management algorithm for patients diagnosed with mCRPC, provided by the applicant

ATM = (Ataxia-Telangiesctasia Mutated gene; BRCA1/2 = breast cancer genes 1 and 2; HSPC = hormone sensitive prostate cancer; LHRH = Luteinizing hormone-releasing hormone; mCRPC = metastatic castrate-resistant prostate cancer; PBS = Pharmaceutical Beneifits Scheme; Tx = treatment

PASC advised that the proposed algorithm (Figure 2) needs to be updated to include the flow on to germline and cascade testing and explicitly depict that tumour testing leads to germline testing (after counselling, if tumour testing is positive), followed by cascade testing (after counselling, if germline testing is positive).

Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (testing for pathogenic *BRCA1/2* or *ATM* variants in tumour tissue and treatment with olaparib in second or third line) are **superior** in terms of comparative effectiveness versus the main comparator (no genetic testing and treatment with cabazitaxel, enzalutamide or abiraterone in second/third line) in patients with mCRPC. Given the claim of clinical superiority, a cost-effectiveness or cost-utility analysis should be presented.

PASC confirmed that, given the claim of clinical superiority, a cost-effectiveness or cost-utility analysis should be presented.

PASC advised that the costs of additional germline testing including cascade testing of relatives where mCRPC are found to have a germline BRCA1/2 variant, should be factored in (see 'Testing Population' (p.6)), at approximately **REDACTED** *per test for 600 patients, as well as estimating the likely extent of flow on to cascade testing with its associated costs. PASC further advised that these should be extended into an economic evaluation as appropriate.*

The Applicant confirmed a cost utility analysis will be presented. The Applicant also confirmed that the cost of additional germline testing including cascade testing of relatives where mCRPC are found to have a germline BRCA1/2 variant, will be factored in, and cost and number of patients re-confirmed. An estimate of the likely extent of flow-on to cascade testing with its associated costs will also be included in the economic model.

Proposed MBS item descriptor and MBS fee

The proposed MBS item descriptor as presented in the Application Form *and amended based on a request from PASC*[5] is shown below.

The applicant originally proposed a separate MBS item descriptor for each of its two proposed scenarios:

- Scenario 1 (applicant-preferred) = BRCA1/2 or ATM; or
- Scenario 2 = BRCA1/2.

The applicant advised that Scenario 1 would be followed in its assessment report/submission. The applicant was encouraged to seek advice from the RCPA regarding *ATM* tesing in Australia, including implementation of a quality assurance program, which does not yet exist.

The applicant proposed an MBS fee of **REDACTED**. This fee is based on the proposed fee for tumour *BRCA1/2* variant testing in Application 1554, which was **REDACTED**, with provision for additional costs of **REDACTED** for testing the *ATM* gene.

[5] The proposed item initially included the restriction 'after first or second line enzalutamide or abiraterone treatment', and PASC confirmed that this wording was PBS specific and not necessary in the descriptor.

Category 6 – Pathology Services **(applicant proposed MBS item descriptor)**	
MBS item XXXX	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 requirements relating to *BRCA* or *ATM* variant status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. MBS Fee: **REDACTED**	

Category 6 – Pathology Services **(revised MBS item descriptor)**	
MBS item XXXX	Group P7 - Genetics
Tumour testing for detection of pathogenic *BRCA1, BRCA2* or *ATM* gene variants, in 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* variant status for access to olaparib ~~(after first or second line enzalutamide or abiraterone treatment)~~ under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. "Maximum one test per lifetime" OR "Once per primary tumour diagnosis" ***(as per earlier MSAC advice in PSD 1554)*** MBS Fee: **REDACTED**	

PASC noted the original applicant-proposed descriptor for tumour tissue testing (first MBS item XXXX descriptor above) did not make clear the necessity to test all three genes; however, this was rectified in the applicant's comments on the draft PICO.

PASC also noted the applicant did not support the inclusion of a 'once in a lifetime testing' limitation, indicating that re-testing after the progression of disease should be funded, for example, for reversions or resistance emergence. PASC noted that such changes were rare, and considered that re-testing should not be performed for a patient receiving olaparib to check for emergent resistance in order to influence the decision to stop olaparib. PASC advised that a stronger case should be made in the integrated codependent submission should the applicant still wish to omit this limitation from the item descriptor.

The Applicant agreed with the red text included in the revised MBS item XXXX descriptor above.

PASC considered the applicant-proposed fee for tumour tissue testing, noting that:

- *germline testing in breast and ovarian cancer involving BRCA 1/2 is funded* **REDACTED** *(MBS items 73295 and 73296).*
- *MSAC application 1554 requested* **REDACTED** *for somatic (i.e. tumour tissue) BRCA testing in ovarian tumour tissue than for existing germline BRCA testing, but this was not supported by the November 2019 MSAC meeting.*
- *the current application requests* **REDACTED** *for testing the ATM gene as well as BRCA 1/2 in tissue.*

The applicant advised PASC that **REDACTED** *for including the ATM gene is because it is a complex and large gene (66 exons). PASC considered that the rationale for the fee increase should be clearly presented in the integrated codependent submission. The Applicant confirmed the rationale for the fee* **REDACTED** *will be clearly presented in the integrated codependent submission.*

For patients who are found to have a pathogenic somatic *BRCA1/2* or *ATM* gene variant, a known variant test on a blood sample for germline variants could be performed. This would help distinguish between somatic and germline variants, and allow cascade testing for family members. This test is not listed on the MBS. If MSAC supports testing for (known) pathogenic germline *BRCA1/2* or *ATM* variants (in addition to somatic testing), a new MBS item would be needed. The proposed MBS item for this test is shown below.

Category 6 – Pathology Services	
MBS item YYYY	Group P7 - Genetics
Characterisation of germline gene variants, requested by a specialist or consultant physician, including copy number variation in the *BRCA1*, *BRCA2* or *ATM* gene, in a patient who has had a pathogenic variant identified in one or more of the genes specified above, from tumour testing (MBS item XXXX). Maximum one test per lifetime. Fee: **REDACTED**	

Currently, family members of a patient with a known pathogenic germline *BRCA1* or *BRCA2* variant can be tested through MBS item 73297. This item would need a minor amendment to include family members of a patient with a known pathogenic germline *ATM* variant, and reference the new mCRPC item, if cascade testing is supported for this population.

PASC advised that related MBS items would need to be developed or amended for the associated consequential germline and cascade testing.

Regarding the assessment group- proposed MBS item YYYY for germline testing in patients found to be positive on somatic testing, PASC advised that, currently, family members of a patient with a known pathogenic germline BRCA1/2 variant can be tested through MBS item 73297. This item would also need a minor amendment to include family members of a patient with a known pathogenic germline ATM variant, and reference the new mCRPC item, if cascade testing is supported for these additional populations.

The Applicant agreed with the PASC that MBS item YYYY would need include family members of a patient with a known pathogenic germline ATM variant, and reference the new mCRPC item, if cascade testing is supported for these additional populations.

Consultation feedback

- Pathology provider with experience in genetic basis of inherited cancer:

  Archival tumour blocks used for HRR testing may not be the most appropriate tissue to test for two reasons. First, subsequent somatic alterations may be acquired only in the metastatic setting such that by testing a primary tumour a treatable metastatic tumour may be missed. Second, BRCA2 reversion mutations have been reported and these would only be apparent in metastatic disease. Although these patients are rare, they will be resistant to PARP inhibitor treatment.

- Royal College of Pathologists of Australia

  The College generally is supportive of BRCA/ATM mutation testing for prostate cancers in tissues. The use of the test is consistent with the updated National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology and American Society of Clinical Oncology (ASCO) 2018 Recommendations.

  Note that the application does not include testing of individuals with a strong family history at initial diagnosis of prostate cancer.

- Patient Advocacy Group

  They are supportive of the need for testing to identify likely responders to PARP inhibitor treatment and note the potential to help define benefit of routine germline genetic testing of patients with prostate cancer

- Patient Support Group:

  They are generally supportive but indicated that there will likely be a financial impact of testing costs on (frequently) elderly patients

PASC noted the generally supportive consultation feedback. PASC also noted the feedback from a pathology provider indicating that archival specimens may not be the most appropriate tissue to test because somatic alterations may be acquired only in the metastatic setting such that by testing a primary tumour a treatable metastatic tumour may be missed, and BRCA2 reversion mutations have been rarely reported and these would only be present in metastatic disease. PASC considered that if available, using the most recent biopsy would be preferable.

PASC agreed with the feedback regarding the importance of appropriate genetic counselling.

Next steps

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

PASC noted the applicant elected to progress its application as an ADAR (applicant-developed assessment report) in the form of an integrated codependent submission.

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(Please note: Where publication titles include 'mutation' or 'mutations', these have been retained, noting the current correct terms are 'variant' or 'variants')

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