



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application 1618 – Testing of tumour prostate tissue to detect BRCA1/2 pathogenic gene variants in people with metastatic castration-resistant prostate cancer to help determine eligibility for PBS olaparib***

**Applicant:** AstraZeneca Pty Ltd

**Date of MSAC consideration:** MSAC 83rd Meeting, 25-26 November 2021

#### **1. Purpose of application**

The streamlined codependent resubmission requested:

- Medicare Benefits Schedule (MBS) listing of next generation sequencing (NGS) for the evaluation of *BRCA1/2* pathogenic or likely pathogenic gene variants (abbreviated to pathogenic gene variants hereafter) to help determine eligibility for treatment with olaparib in patients with metastatic castration resistant prostate cancer (mCRPC); and
- Pharmaceutical Benefits Scheme (PBS) Section 85 General Schedule with Authority Required Telephone (initial) and Authority Required Streamlined (continuing) listing for treatment with olaparib for the treatment of mCRPC in patients who have evidence of *BRCA1/2* pathogenic gene variants.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new MBS item for testing for *BRCA1/2* pathogenic variants in tumour tissue from people with metastatic castration-resistant prostate cancer to determine eligibility for olaparib treatment. MSAC also supported a new MBS item for testing germline *BRCA1/2* pathogenic variants when testing of tumour tissue is not feasible. MSAC advised that the fee for MBS items to test for pathogenic variants in only the *BRCA1* and *BRCA2* genes should be reduced from \$1,200 to \$1,000 as the cost of this testing has decreased.

MSAC supported the creation of the following MBS items, with inserted or changed text from that proposed in bold.

Category 6 – Pathology Services
<p>MBS item XXXX Group P7 – Genetics</p> <p>A test of tumour tissue from a patient with metastatic castration-resistant prostate cancer (and <b>characterisation of germline gene variants, should tumour tissue testing be inconclusive</b>), requested by a specialist or consultant physician, to determine eligibility relating to <i>BRCA</i> status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS).</p> <p>Applicable once per primary tumour diagnosis</p>
<p>Fee: <b>\$1,000</b> Benefit: 75% = <b>\$750.00</b> 85% = <b>\$912.10</b></p>
Category 6 – Pathology Services
<p>MBS item YYYY Group P7 – Genetics</p> <p>Detection of germline <i>BRCA1</i> or <i>BRCA2</i> pathogenic or likely pathogenic gene variants, in a patient with metastatic castration-resistant prostate cancer, for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS).</p> <p>Applicable once per lifetime</p>
<p>Fee: <b>\$1,000.00</b> Benefit: 75% = <b>\$750.00</b> 85% = <b>\$912.10</b></p>
<p>Explanatory notes</p> <p>Patients who are found to have a pathogenic or likely pathogenic variant in <i>BRCA1</i> or <i>BRCA2</i> should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or clinical geneticist.</p>

<p><b>Consumer summary</b></p>
<p>This application was from AstraZeneca Pty Ltd for listing genetic testing for <i>BRCA1/2</i> pathogenic gene variants on the Medicare Benefits Schedule (MBS) for people with metastatic castration-resistant prostate cancer who have been already treated with hormone treatment. If the genetic test result is positive, the person could then be eligible to receive a medicine called olaparib on the Pharmaceutical Benefits Scheme (PBS). Olaparib has been shown to improve survival in people with this type of prostate cancer and who have <i>BRCA1/2</i> variants.</p> <p>Metastatic castration-resistant prostate cancer is prostate cancer that has spread to other areas of the body and is not responding to hormone therapy. Genetic testing involves sending a piece of the tumour to a laboratory for <i>BRCA1/2</i> testing. If the tumour is positive for a <i>BRCA1/2</i> pathogenic variant, the laboratory would also test to see if the patient had a germline (heritable) variant by doing the same test on a blood sample. Germline variants mean that the person’s family could also be affected. If the person has a germline <i>BRCA1/2</i> variant, their immediate family members could also be tested to see if they carry the same variant (this is called cascade testing).</p> <p>MSAC considered that testing people with this type of prostate cancer would accurately identify <i>BRCA1/2</i> variants and thus help determine eligibility for olaparib. In November</p>

### Consumer summary

2021, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing olaparib on the PBS as requested.

#### MSAC's advice to the Commonwealth Minister for Health

MSAC considered the test to be safe, effective and cost-effective, and supported the requested MBS listing for people with metastatic castration-resistant prostate cancer, to help find people who should access olaparib.

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

MSAC noted that this was a codependent application, from AstraZeneca, for the detection of *BRCA1/2* variants to determine eligibility for treatment with olaparib of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair *BRCA1/2* gene variants (somatic and/or germline) who have progressed following a prior novel hormonal agent (NHA). MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) recommended olaparib for such patients at its November 2021 meeting.

MSAC recalled that this submission was originally reviewed at its 81st meeting in March–April 2021, when MSAC had determined that the testing was safe, effective and cost-effective. However, MSAC had deferred its decision and had advised that it would rapidly reconsider the application if PBAC recommended olaparib for this group of patients.

MSAC considered that there is a clinical need for this testing and treatment, as patients with metastatic prostate cancer who are resistant to hormone therapy and have a *BRCA1/2* pathogenic or likely pathogenic variant clinically respond to olaparib.

MSAC noted the proposed Medicare Benefits Schedule (MBS) item descriptor and fee. MSAC agreed with the proposed additional text stating that the fee included both tumour (somatic) and germline testing where tumour testing had failed, and that laboratories should not be able to claim twice for tumour and germline testing if tumour testing fails. MSAC noted that most of the cost of *BRCA1/2* testing is for sequencing. If the DNA quality is poor from the FFPE extraction, laboratories should not sequence the sample and instead request germline testing using a blood sample. Thus, failed somatic testing is not expected to increase the cost of testing to determine eligibility for olaparib.

MSAC noted that no amendment would be required for MBS item 73302. MSAC queried both the proposed fee of \$1,200 and the current fee for germline and somatic *BRCA1/2* testing alone, noting that the fee for *BRCA1/2* testing when included as part of larger panel testing was also \$1,200, making the fee for *BRCA1/2* testing alone appear to be high. MSAC considered that the *BRCA1/2* genes are very large and complex to sequence and that the other genes sequenced in panels alongside *BRCA1/2* are generally smaller and less complex. MSAC advised the Department consider reducing the fee to \$1,000 noting that the cost of sequencing had decreased since the \$1,200 fee was established. MSAC noted that other *BRCA1/2* testing items for olaparib access (MBS item 73295) would also have to be reviewed, to ensure consistency among fees. MBS item 73296 is testing for *BRCA1/2* cancer predisposition, not access to olaparib, and MSAC recommended that this fee can remain at \$1,200 as it requires testing of at least three genes. The Department agreed to review all *BRCA1/2* testing fees.

MSAC noted the new concordance data, which showed there was high concordance (100%) between the FoundationOne®CDx (F1CDx) test used in the PROfound trial and the QIASeq Targeted DNA Panel sequencing test offered by an Australian pathology provider.

MSAC noted that data from the key clinical trial (PROfound) reported tumour testing may fail in approximately 31% of patients, due to poor tissue sample quality and other factors. Patients who cannot have tumour testing can have blood testing for germline (heritable) variants. However, approximately half of *BRCA1/2* variants are somatic only variants and will not be detected by germline testing. This reduces the effective test sensitivity to 76% because germline testing will miss patients who are tumour-positive but germline-negative for *BRCA1/2*. The pre-MSAC response contended that the test sensitivity (and specificity) should be calculated based on successful samples. The pre-MSAC response highlighted that the local test returned a result in 20 of 21 (95%) samples compared with 16 of 21 (76%) for the F1CDx test. The pre-MSAC response claimed that the F1CDx test has very strict and unusually high tumour tissue area, section number and cellularity metrics for the assay which preclude a large number of patient samples from testing. Therefore, the failure rate in Australian clinical practice will likely be lower than what was observed in the trial. MSAC accepted that the failure rate in Australian clinical practice will likely be much lower than what was observed in the trial.

MSAC noted that clinicians advised that re-biopsy is not appropriate for patients with mCRPC. Re-biopsy at a stage of late treatment is invasive and not practicable at the mCRPC stage of the patient journey. MSAC also noted that newer technologies allowed improved yield from formalin-fixed, paraffin-embedded (FFPE) tissue, increasing the success rates of extracting high-quality DNA from such samples. MSAC was satisfied there was little concern that the availability of an MBS item number would result in increased re-biopsy rates.

MSAC noted the resubmission included a new stepped economic evaluation based on the PROfound trial. The revised economic model assumed 100% test sensitivity and did not include the cost of cascade testing. The incremental cost-effectiveness ratio (ICER) increased from \$55,000 to < \$75,000 to \$55,000 to < \$75,000 when test sensitivity is decreased to 76% and the costs of cascade testing are included, which MSAC accepted. MSAC noted the updated sensitivity analysis which showed that if genetic testing is omitted and 9.7% (prevalence of *BRCA1/2* pathogenic variants) of the patients are randomly allocated olaparib, the ICER increases to \$155,000 to < \$255,000 from the base case of \$55,000 to < \$75,000 . MSAC considered this supported the value proposition of the requested codependent testing. MSAC noted that if 11% prevalence is used as suggested by the minor overview, the ICER decreases to \$55,000 to < \$75,000 .

MSAC noted the revised financial estimates, which now include:

- updated eligible population by using an incidence approach
- archival tissue sample retrieval
- cascade testing for patients found to have a germline mutation.

MSAC noted the net cost to the MBS was approximately \$20 million to < \$30 million over six years. MSAC noted that no cost for potential re-biopsy was included, as per expert advice and considered these estimates were reasonable.

#### **4. Background**

At its March-April 2021 meeting, MSAC considered Application 1618. MSAC deferred its decision regarding testing for *BRCA1/2* pathogenic gene variants in tumour tissue from men

with metastatic castration resistant prostate cancer. MSAC foreshadowed that it would rapidly reconsider this testing if the Pharmaceutical Benefits Advisory Committee (PBAC) recommends olaparib for those patients in this population in whom a *BRCA1/2* pathogenic gene variant is detected ([MSAC Application 1618 Public Summary Document \[PSD\]](#), p4.

The applicant submitted a minor resubmission for MSAC consideration. However, the major submission to PBAC presented additional evidence including:

- prognostic evidence (4 studies)
- analytical performance evidence
- biomarker prevalence data
- a revised economic model with a test-treatment structure.

## 5. Prerequisites to implementation of any funding advice

On 19 March 2019, the Therapeutic Goods Administration (TGA) approved olaparib for the following indication:

LYNPARZA® (olaparib) is indicated as monotherapy for the treatment of adult patients with BRCA-mutated (germline and/or somatic) metastatic castration-resistant prostate cancer who have progressed following prior therapy that included a new hormonal agent. BRCA mutation status should be determined by an experienced laboratory using a validated test method.

The resubmission stated that there are currently four National Association of Testing Authorities (NATA) accredited laboratories providing locally validated TGA notified Class 3 *in-vitro* diagnostic medical devices (IVD) homologous recombination repair (HRR) tumour panel testing covering *BRCA1* and *BRCA2*. These are Peter MacCallum Cancer Centre Melbourne; NSW Health Pathology North, Newcastle; PathWest, Perth WA; Genomics for Life, Brisbane QLD. Additionally, another four laboratories are in the process of validating their assays and obtaining accreditation.

## 6. Proposal for public funding

The requested MBS item descriptors were unchanged from the previous MSAC consideration (see Table 1).

**Table 1: Requested MBS item descriptor (unchanged from previous MSAC consideration)**

Category 6 – PATHOLOGY SERVICES	
MBS item XXXX	Group P7 - Genetics
<b>New tumour tissue testing (or amendment of item 73301)</b>	
A test of tumour tissue from a patient with metastatic castration-resistant prostate cancer, requested by a specialist or consultant physician, to determine eligibility relating to <i>BRCA</i> status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS).	
Applicable once per primary tumour diagnosis	
Fee: \$1,200.00 Benefit : 75% = \$900.00 85% = \$1,115.30	
Category 6 – PATHOLOGY SERVICES	
MBS item XXXX	Group P7 - Genetics
<b>New MBS item for germline testing (or amendment of item 73295)</b>	
Detection of germline <i>BRCA1</i> or <i>BRCA2</i> pathogenic or likely pathogenic gene variants, in a patient with metastatic castration-resistant prostate cancer, for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS).	
Fee: \$1,200.00 Benefit : 75% = \$900.00 85% = \$1,115.30	

#### Explanatory notes

Patients who are found to have a pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2* should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or clinical geneticist.

Source: Table 6, p61 of the resubmission to PBAC.

At its March/April 2021 consideration, MSAC considered that germline testing might be necessary after inconclusive tumour testing. MSAC advised that an explanatory note be included in the MBS item, stating that the fee (\$1,200) included both tumour (somatic) and germline testing where tumour testing had failed, and that laboratories should not be able to claim twice for somatic and germline testing for the same patient. Additionally, the wording of the proposed item descriptor for germline testing does not account for germline testing when tumour testing has failed, only when testing of tumour tissue is not feasible. The failure rate in PROfound was 31%, of which 42.5% was due to failure in DNA extraction from FFPE samples (refer to Test failure rate).

The minor resubmission did not adopt the aforementioned recommendations in the proposed item descriptors. The minor resubmission indicated that the sponsor is willing to work with the MSAC to finalise the MBS item descriptors.

The minor resubmission also presented MBS item 73302 (Table 2) as an item that will be affected by the codependent submission as it covers flow on germline testing for patients who have a pathogenic or likely pathogenic *BRCA1/2* variant identified by tumour testing. No amendment has been requested for this item. At its March/April 2021 consideration, MSAC considered that for the germline test after a positive somatic test, the laboratory would only have to test for the same variant that was identified in the somatic test and so billing the separate item 73302 for this purpose would be appropriate.

**Table 2: MBS item for germline testing**

	Category 6 – Pathology Services
MBS item 73302 (no amendment required)	Group P7 - Genetics
Characterisation of germline gene variants including copy number variants, in <i>BRCA1</i> or <i>BRCA2</i> genes, in a patient who has a pathogenic or likely pathogenic variant identified in either gene by tumour testing and who has not received a service to which items 73295, 73296, 73297 applies, requested by a specialist or a consultant physician.	
Applicable once per primary tumour diagnosis	
Fee: \$400.00 Benefit : 75% = \$300.00 85% = \$340.00	

Source: Table 6, p61 of the resubmission.

## 7. Summary of public consultation feedback/consumer Issues

Consultation feedback was received from five consumer organisations - Advanced Prostate Cancer Support Group Australia, Prostate Cancer Foundation of Australia, Albury Wodonga Prostate Cancer Support Group (consumer organisation), Ballarat Prostate Cancer Support Group, Tamworth and District Prostate Cancer Support Group. The feedback highlighted the physical impacts, financial stress, anxiety, and depression in men with mCRPC as well as their families. The feedback was supportive of *BRCA1/2* or *ATM* gene variants detection in men with mCRPC and treatment with olaparib, as it increases affordability of testing and treatment for affected patients, informs treatment pathways and options to improve outcomes for men living with the disease, as well as providing greater awareness for their family members of their own risk of developing cancer through cascade testing.

The feedback from Advanced Prostate Cancer Support Group Australia indicated that archived biopsy and radical prostatectomy samples are often old with poor DNA extraction, or become unavailable, particularly with recurrent prostate cancer. Further, the ideal requirement of testing fresh metastatic prostate cancer tumours for germline sampling may be unrealistic, as a high percentage of prostate cancer metastasise to the bone, making biopsy and extraction of useable DNA samples difficult. The secondary most common metastatic sites are the lymph nodes; however, these sites are often inaccessible to biopsies performed safely. The feedback expressed that when more generally feasible, running somatic testing in conjunction with germline testing rather than sequentially would be more efficient, informative and more economical.

The organisational feedback collectively expressed that the proposed codependent technologies (*BRCA/ATM* tumour 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 feedback stated that most other major comparable international jurisdictions support this service and treatment approach.

Ten consumer feedback were received, consisting of nine individuals and 1 care giver. The feedback was supportive of *BRCA1/2* or *ATM* gene variants detection in men with mCRPC and treatment with olaparib. The feedback highlighted the need of new targeted therapies for improved outcomes in patients with mCRPC who are unresponsive to standard hormonal treatments and chemotherapy, and the importance of reduction of out-of-pocket costs for diagnosis and treatment.

## 8. Proposed intervention's place in clinical management

### *Description of proposed intervention*

Unchanged from the previous MSAC consideration, the proposed medical service is testing of prostate tumour tissue to detect *BRCA1/2* pathogenic or likely pathogenic gene variants in patients with metastatic castration-resistant prostate cancer to determine eligibility for treatment with olaparib.

The minor resubmission reaffirmed that if somatic testing fails, germline testing would occur rather than re-biopsy. The reasons for this was that re-biopsy is invasive and there is increasing utilisation of complex multiparametric testing modalities including MRI and systemic biopsy to improve diagnostic power. Further, re-biopsy is not part of an optimal surveillance schedule.

The resubmission did not discuss the potential for discordance between tumour and germline testing, and the potential for missing patients who are tumour-positive but germline-negative for *BRCA1/2*. A recent analysis of the TOPAR-B study<sup>1</sup> reported that 59.4% (19 of 32) of *BRCA1/2*-positive patients had tumour-only pathogenic alterations. This would increase the number of false negatives and reduce the sensitivity of the test, which would impact the base case ICER where the sensitivity and specificity were assumed to be 100%.

### *Description of medical condition(s)*

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. There

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<sup>1</sup> Carreira S, Porta N, Arce-Gallego S, Seed G, Llop-Guevara A, Bianchini D, Rescigno P, Paschalis A, Bertan C, Baker C, Goodall J, Miranda S, Riisnaes R, Figueiredo I, Ferreira A, Pereira R, Crespo M, Gurel B, Nava Rodrigues D, Pettitt SJ, Yuan W, Serra V, Rekowski J, Lord CJ, Hall E, Mateo J, de Bono JS. Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPAR-B Trial. *Cancer Discov.* 2021 May 27;candisc.0007.2021. doi: 10.1158/2159-8290.CD-21-0007

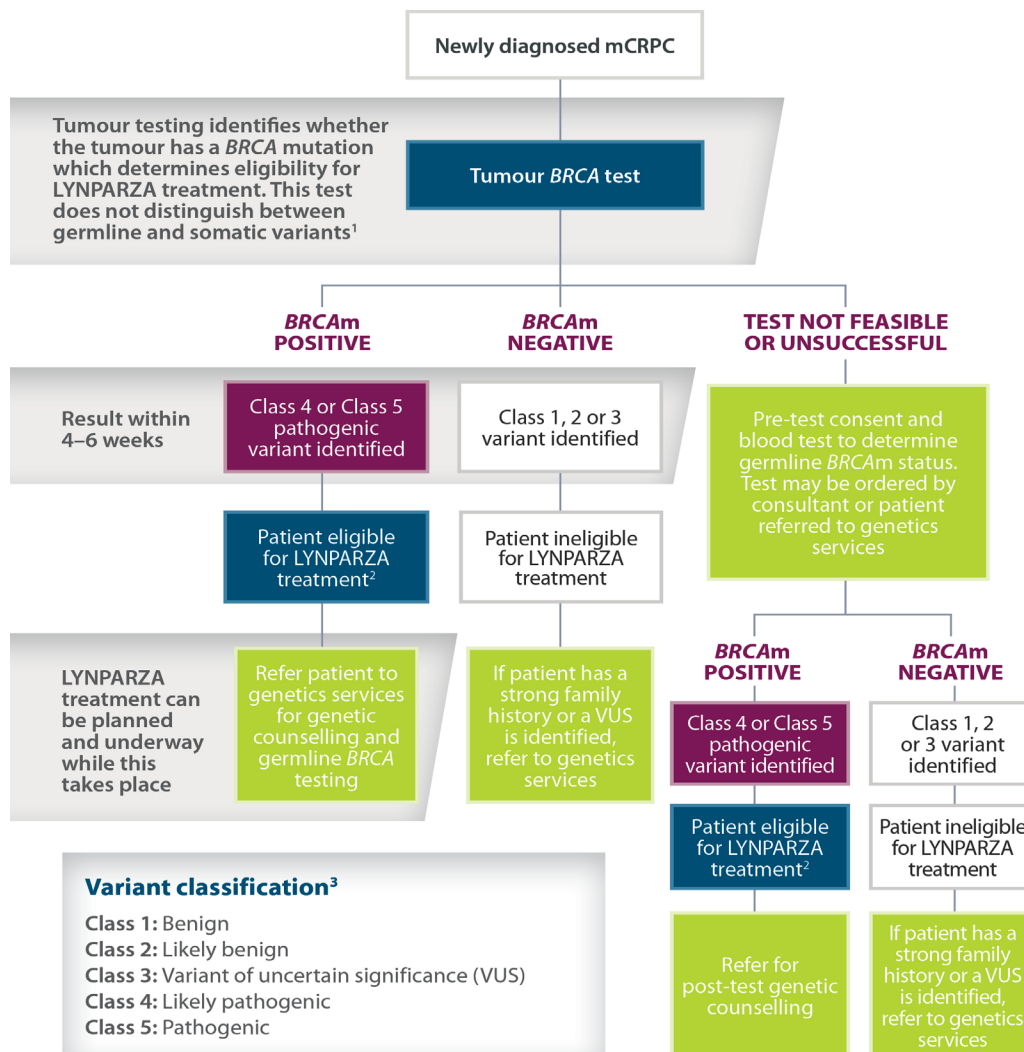
is also a proportion of men who have metastases when the prostate cancer is first diagnosed. Prostate cancer is termed 'castrate resistant' when the disease progresses despite continuous androgen deprivation therapy. After this, further treatment is needed to maintain disease control.

The resubmission included an updated testing algorithm (Figure 1), including flow-on cascade testing with referral to genetic services and further germline testing following a positive tumour test. The updated clinical management algorithm did not show how the test would change clinical management. The change in management was illustrated in the clinical management algorithm considered by MSAC at its March-April 2021 consideration (PSD, p14), noting the treatment comparator has been updated in the minor resubmission.

The resubmission to PBAC presented updated clinical management algorithms for the treatment of mCRPC. These depicted three lines of treatment in mCRPC; with novel hormonal agents (NHA = either enzalutamide or abiraterone) or docetaxel as first-line; BSC, NHA, cabazitaxel or docetaxel in second-line; followed by BSC or cabazitaxel in third-line. In the proposed algorithm, in addition to current options, olaparib can be used as an alternate first-, second- or third-line therapy. The PBAC had previously considered that the appropriate clinical place for olaparib was as third-line treatment following failure on docetaxel and failure on an NHA (paragraph 7.3, olaparib PSD, March 2021). This was echoed by the recently updated NCCN 2021 guidelines, which state the preferred regimen for those with prior NHA but no prior docetaxel would be docetaxel, and the preferred regimens in mCRPC patients who received prior NHA and prior docetaxel would be cabazitaxel and docetaxel rechallenge. Olaparib is an option after NHA irrespective of whether the patient has failed prior docetaxel.



# PROPOSED BRCA<sub>m</sub> TESTING ALGORITHM TO DETERMINE ELIGIBILITY FOR LYNPARZA TREATMENT IN mCRPC



*BRCA<sub>m</sub>*=*BRCA* mutation; mCRPC=metastatic castration-resistant prostate cancer.

**References:** 1. Cheng HH *et al. J Natl Compr Canc Netw* 2019;17(5):515–521. 2. LYNPARZA (olaparib) Tablets Product Information. 3. Radice P *et al. Ann Oncol* 2011;22(1):i18-i23.

**Figure 1: Tumour and Germline testing algorithm– flow on consequences**

Source: Figure 4, p60 of the resubmission to PBAC

*BRCA*=breast cancer genes (1 and 2); mCRPC=metastatic castration resistant prostate cancer; VUS=variant of uncertain significance

## 9. Comparator

The comparator for the *BRCA1/2* testing was unchanged. The comparator for olaparib treatment was changed from sequential novel hormonal agents (NHAs) to best supportive care (BSC) and cabazitaxel as the secondary comparator.

## 10. Comparative safety

The resubmission did not include further information on adverse events from testing or from changes in management. This was reasonable as there were no outstanding concerns related

to the comparative safety of tumour or germline *BRCA1/2* testing or changes in clinical management.

## 11. Comparative effectiveness

### *Prognostic evidence*

The resubmission presented an updated literature search which identified four studies (including a subgroup analysis of PROfound).

**Table 3: Prognostic evidence reported in the included studies**

Study/design	Population	Comparison	Outcome measures	Comments
PROfound P3 RCT	mCRPC, N=387, <i>BRCA1/2</i> , n=58 Cohort B (proxy <i>BRCAwt</i> ), n=48	<i>BRCA1/2</i> vs. non-carriers	rPFS, OS	Re-analyses of PROfound data comparing the <i>BRCA1/2</i> in Cohort A vs. Cohort B (other HRR genes)
Castro 2019 Prospective cohort	mCRPC, N=419: <i>gBRCA2</i> , n=14 <i>gATM/BRCA1/BRCA2/PALB2</i> , n=26 <i>gDDR</i> , n=68 non-DDR carriers, n=351	<i>gBRCA2</i> vs. non-carriers	CSS, PFS2	The study only included germline pathogenic variants and the subgroup of interest ( <i>gBRCA2</i> ) did not include <i>gBRCA1</i> . Treatment was at the discretion of the treating physician.
Kohli 2020 Prospective cohort	mCRPC N=166: <i>BRCA2</i> , n=13 <i>ATM+BRCA1/2</i> , n=23	<i>BRCA2</i> vs. non-carriers	OS	The study used ctDNA and cfDNA to determine <i>BRCA1/2</i> status, in addition to germline testing. Treatment strategies were not accounted for in the survival analysis.
Mateo 2018 Retrospective cohort	mPC N=390 <i>gDDR</i> , n=60 <i>gBRCA2</i> , n=37 non-carriers, n=330	<i>gBRCA2</i> vs. non-carriers	OS (from CRCP) PFS (for mCRPC)	Retrospective analysis of mPC patients with/without DDR pathogenic variants. In mCRPC, Only <i>BRCA2</i> PFS is evaluated, but number of patients with mCRPC was not reported.

Source: Constructed during the evaluation

ATM=ataxia telangiectasia mutated, *BRCA1/2*= breast cancer gene 1 and 2; *BRCAwt*=*BRCA1/2* wild-type (negative), cfDNA=circulating free DNA, ctDNA=circulating tumour DNA, CSS=cancer-specific survival, DDR= DNA damage response and repair, g=germline, HRR=homologous recombination repair, mCRPC=metastatic castration-resistant prostate cancer, mPC=metastatic prostate cancer, OS=overall survival; P3=phase 3, *PALB2*=partner and localizer of *BRCA2*, PFS=progression-free survival, RCT=randomised controlled trial; rPFS=radiographic progression-free survival

The resubmission did not appraise the quality of the included prognostic studies. The PROfound trial was considered to be at low risk of bias. The remaining studies were not RCTs and at potentially high risk of bias.

**Table 4: Results from included prognostic studies**

<b>PROfound (NHA arm)</b>	<b>BRCA1/2</b>	<b>BRCAt (Cohort B)</b>	<b>HR (95% CI)</b>
Median rPFS, months	3.0	3.3	NR
Median OS, months (unadjusted)	14.4	13.3	NR
Median OS, months (RPSFTM adjusted)	9.2	12.6	NR
<b>Castro 2019</b>	<b>gBRCA2</b>	<b>BRCAt (Non-DDR carriers)</b>	<b>HR (95% CI)</b>
Median CSS, months	17.4	33.2	2.10 (1.07, 4.10)
Median CSS, months (Taxanes+NHA)	10.7	28.4	4.16 (1.80, 9.62)
Median CSS, months (NHA+Taxanes)	24.0	31.1	0.93 (0.29, 2.95)
Median PFS2, months (Taxanes+NHA)	<b>8.6</b>	<b>17.1</b>	<b>8.16 (3.60, 18.49)</b>
Median PFS2, months (NHA+Taxanes)	18.9	21.1	1.25 (0.51, 3.07)
<b>Kohli 2020</b>	<b>BRCA2</b>	<b>BRCAt (non-carriers<sup>b</sup>)</b>	<b>HR (95% CI)</b>
Median OS, months	<b>13.7</b>	<b>54.6</b>	<b>2.5 (1.3, 5.1)</b>
<b>Mateo 2018</b>	<b>gBRCA2</b>	<b>gBRCAt (non-BRCA2)</b>	<b>HR (95% CI)</b>
Median PFS, months (after 1LNHA)	99.6	99.6	1.09 (0.72, 1.67)
Median PFS, months (after 1L docetaxel)	66	75.6	0.96 (0.64, 1.43)
Median OS, months (from CRPC)	36	38.4	0.83 (0.50, 1.36)

Source: Table 27, p95 of the resubmission. Castro 2019 publication. **bold = statistically significant**

Abbreviations: *BRCA1/2*, Breast cancer susceptibility gene mutation carrier; CI=confidence interval, CSS=cancer-specific survival, *gBRCA*=germline *BRCA* test, HR=Hazard ratio, NHA=novel hormonal agent, OS=overall survival, PFS2=progression-free survival from initiation of 1L to progression to 2L, rPFS, radiographic progression-free survival, RPSFTM, Rank Preserving Structural Failure Time Model, WT=wild type, indicate that patients do not have the pathogenic gene variant.

<sup>a</sup> Cohort B consisted of patients other homologous recombination repair (HRR) pathogenic variants (not *BRCA1/2*)

<sup>b</sup> several pathogenic variants analysed.

The resubmission stated that, overall, the included studies suggested that *BRCA2* was likely associated with worse prognosis in mCRPC patients. The minor overview considered that seemed reasonable, although some of the studies reported non-significant differences in survival between the two groups. The minor overview noted that most studies did not control for treatment received or the sequence of treatment, which might impact survival.

The minor overview highlighted that all studies, except PROfound, focused on *BRCA2* carriers, which were previously shown to have worse prognosis than *BRCA1* carriers (p18, MSAC 1618 PSD, March 2021). However, given the lower proportion of the *BRCA1* pathogenic variant in the mCRPC population (1.0%, de Bono et al. ESMO 2019 poster), the impact of *BRCA1* on these results may be small.

Results from the NHA arm of PROfound did not show significant differences in PFS and unadjusted OS between the two groups, but after adjustment for crossover (patients in the NHA arm who received olaparib treatment) OS was numerically lower in the *BRCA1/2*-positive subgroup.

The minor overview noted that in Kohli 2020, OS was significantly lower in *BRCA2*-positive patients compared to patients without pathogenic variants. Of note, the comparator group in this study included patients without any identified pathogenic variants, which differed from Cohort B in PROfound where patients had other HRR pathogenic variants (not *BRCA1/2*), and may be more representative of *BRCA*-negative patients. However, Kohli 2020 did not include *BRCA1*-positive in the survival analysis and did not specify which treatments were given to mCRPC patients.

Castro 2019 showed poorer cancer-specific survival (CSS) for mCRPC patients with germline *BRCA2* (*gBRCA2*) pathogenic variants compared to those without any DDR

pathogenic variants. The minor overview highlighted that the authors found treatment sequence had a modifying effect on survival. Among *gBRCA2*-positive patients with mCRPC, those treated first with abiraterone/enzalutamide and followed by taxane treatment had better CSS and progression-free survival from initiation of the first survival-prolonging therapy to progression to the second-line treatment (PFS2) than patients who received the reversed treatment sequence.

The minor overview noted that there were no survival differences between the two groups in Mateo 2018. However, the PFS analysis was only conducted after first-line treatments for mCRPC and OS was measured from mCRPC.

#### *Comparative analytical performance*

The resubmission to PBAC presented further evidence comparing the analytical performance of tumour *BRCA1/2* testing using the clinical utility standard, FoundationOne®CDx (F1CDx), with testing performed by an Australian pathology provider (PMCC) using 16 samples.

The resubmission presented an inter-laboratory concordance study was conducted to compare two NGS tests in prostate cancer tissue samples:

- F1CDx assay used in PROfound, by Foundation Medicine Inc (FMI)
- QIASeq Targeted DNA Panel (DHS-102Z) sequencing kit offered by PMCC.

A cohort of 21 prostate tissue samples previously tested with known variants (including 3 *BRCA1*, 12 *BRCA2* and 6 *BRCA* wildtype samples) were supplied by an independent laboratory, the Kathleen Cunningham Foundation Consortium for research into Familial Breast Cancer (kConFab). The samples were supplied as 20 sectioned serial sections on uncharged slides that were split between PMCC and FMI, and the reference result for sample biomarker status was defined in the kConFab database. The resubmission did not specify if these prostate samples were obtained at initial diagnosis or at diagnosis of metastatic disease, or if they were from metastatic biopsies.

Of the 21 prostate tissue samples, one was unsuitable and failed with both labs due to the level of degradation.

Concordance results between QIASeq and F1CDx tests were reported for 16 samples. Four other samples were analysed by PMCC, but not by FMI (two samples had insufficient tumour content and results were not reported for the other two).

**Table 5: Concordance between QIASeq Targeted DNA panel and F1CDx NGS tests**

F1CDx	QIASeq Targeted DNA panel (DHS-102Z)		
	<i>BRCA1/2</i>	<i>BRCAwt</i>	Total
<i>BRCA1/2</i>	10	0	10
<i>BRCAwt</i>	0	6	6
Total	10	6	16
<b>Agreement</b>	PPA = 100%, NPA = 100%, Concordance = 100%		

Source: Table 29, p110 of the resubmission

*BRCA1/2*=breast cancer gene 1 and 2; *BRCAwt*=Breast cancer gene wild type; F1CDx=FoundationOne®CDx, NPA=negative predictive agreement, PMCC=Peter MacCallum Cancer Centre; PPA=positive predictive agreement.

**Table 6: Concordance between QIASeq Targeted DNA panel and the kConFab reference laboratory**

	QIASeq Targeted DNA panel (DHS-102Z)		
kConFab (reference laboratory)	<i>BRCA1/2</i>	<i>BRCAwt</i>	Total
<i>BRCA1/2</i>	14	0	14
<i>BRCAwt</i>	0	6	6
Total	14	6	20
<b>Agreement</b>	PPA = 100%, NPA = 100%, Concordance = 100%		

Source: Table 30, p111 of the resubmission.

*BRCA1/2*=breast cancer gene 1 and 2; *BRCAwt*=Breast cancer gene wild type; F1CDx=FoundationOne@CDx, kConFab=Kathleen Cunningham Foundation Consortium for research into Familial Breast Cancer, NPA=negative predictive agreement, PMCC=Peter MacCallum Cancer Centre; PPA=positive predictive agreement

Results showed 100% concordance between the QIASeq test and both the F1CDx (the clinical utility standard) and the kConFab reference laboratory.

### *Test failure rate*

Test failure was not addressed in the resubmission. However, the resubmission provided a poster by de Bono (2019) reporting data from the PROfound trial. The proportion of test failures and reasons for this were also reported. The failure rate in PROfound was 31%, of which 42.5% was due to failure in DNA extraction from FFPE samples (Figure 2).

Furthermore, the EMA assessment report for olaparib (p66) reported that in addition to patients who failed testing (as seen in Figure 2), 315 patients were initially reported as failed by the CLIA HRR CTA test but subsequently had another tissue sample tested which was successful. The reasons for reported failure of the first test were as follows:

- 100 (31.7%) out of these 315 patients failed due to not meeting pathology review criteria
- 119 (37.8%) patients failed DNA extraction failure criteria
- 81 (25.7%) patients failed post DNA extraction criteria
- 15 (4.8%) patients failed for more than one of the categories above.

In addition, the minor overview noted the prevalence of HRR gene alterations was higher in metastatic tumour samples than in primary tumour samples (31.8% vs. 27.2%, respectively), which suggests that some pathogenic variants detected in metastatic tissue may not be present at earlier disease stages.

### **Figure 2: Patient flow in PROfound and test failure (removed due to copyright restrictions).**

Source: de Bono ESMO 2019 poster, attachment A1.6 of the resubmission. The poster can be accessed at <https://register.event-works.com/elsevier/esmo2019/ps/pb/> using the search term 'de Bono'.

\*Patients could have more than one tissue sample tested and samples may have failed at different stages of the NGS testing process

†Sample does not meet pathology requirements for the test if there is ≤20% tumour content or <5–7.5 mm<sup>2</sup> viable nucleated tissue

### *Prevalence*

At its March 2021 meeting, MSAC advised that PBAC should rely on 7%–10% as the range of prevalence estimates of patients with mCRPC being *BRCA1/2* positive.

The minor overview highlighted that the resubmission provided a poster by de Bono (2019) to support its claim that the prevalence of *BRCA1/2* pathogenic variants is 9.7% in the proposed population. de Bono (2019) reported that 8.7% (242/2,792) and 1.0% (27/2,792) of the screened population had pathogenic variants of *BRCA2* only or *BRCA1* only, respectively. However, the minor overview highlighted that a further 38 patients (1.4% of 2,792 screened participants) had a pathogenic variant of *BRCA1/2* and another HRR gene. This suggests the prevalence of *BRCA1/2* pathogenic variants is 11.0% (307/2,792).

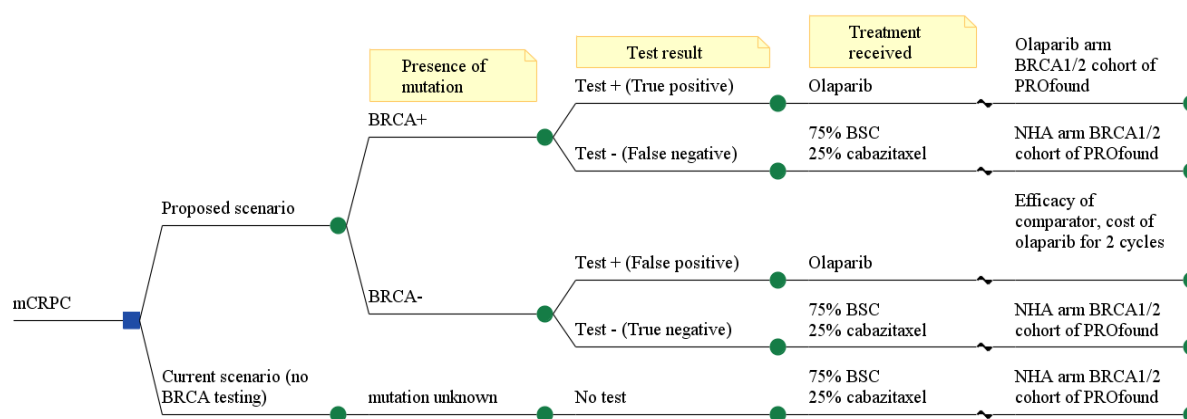
### Clinical claim

The resubmission claimed that for patients diagnosed with mCRPC who have failed first- or second-line NHA treatment and have a pathogenic or likely pathogenic *BRCA1/2* gene variant in tumour tissue or the germline, olaparib is superior in efficacy to BSC, but inferior in safety. Olaparib is superior in efficacy to cabazitaxel and non-inferior in safety.

## 12. Economic evaluation

The resubmission to PBAC presented a new stepped economic evaluation based on the PROfound trial. This included a cost utility model comparing the proposed scenario (testing for *BRCA1/2* pathogenic variants with eligible patients receive olaparib, other patients receive SOC) and current scenario (no testing, all patients receive SOC). The model had a time horizon of 7.5 years in the base case. The treatment comparison in the model was updated to be SOC: 25% cabazitaxel and 75% best supportive care, with new evidence and extrapolations presented to support the comparison.

The testing component used a decision tree analysis (reproduced in Figure 3), where patients in the proposed scenario are allocated to olaparib following a positive test result (true positive, TP; false positive, FP) or receive SOC with a negative test (true negative, TN; false negative, FN). The minor overview noted the testing model did not include uptake rate for testing. Patients in the proposed scenario were assumed to receive one test for *BRCA1/2* pathogenic variants and no time delay was assumed as a result of testing. In PROfound, somatic testing failed in 31.0% of cases using archival tissue, and therefore the minor overview considered that patients may require a germline test preceded by genetic counselling, all of which will result in delays to treatment. There is a predicted delay of 4-6 weeks alone with somatic testing ([Ratified PICO, Application 1618](#), p9). Given the population of interest has metastatic disease, the minor overview considered that some patients may progress or die prior to receiving their test results. The minor overview considered that this was an inappropriate omission.



**Figure 3: Structure of the decision tree model**

Source: Worksheet 'Model Summary' of the Excel workbook 'olaparib\_mCRPC\_CEA\_AstraZeneca.xlsx'

BRCA+=*BRCA1/2* pathogenic variant; BRCA-=*BRCA1/2* wild type; BSC=best supportive care; mCRPC=metastatic castrate-resistant prostate cancer; NHA= novel hormonal agent

The minor overview highlighted that the costs for cascade testing to identify family members of *BRCA1/2* pathogenic variant positive patients were also not included in the model, which was not appropriate given MSAC had requested such costs be considered in the modelled economic evaluation (p4, 1618 PSD, March 2021).

In the base case, the sensitivity and specificity of the *BRCA1/2* testing were both assumed to be 100%. As such, all patients in the proposed scenario arm were identified correctly and no

unintentional consequences were modelled as a result of incorrect test results. When sensitivity was assumed to be <100% FN patients were modelled identically to TN patients. When specificity was assumed to be <100% FP patients were assumed to have same clinical outcomes as TN patients, adverse events were modelled as in TP and costs of olaparib were applied for 2 cycles. The minor overview highlighted that no justification was given for why patients would cease the use of olaparib after 2 cycles.

Table 7 presents the results of the economic evaluation and sensitivity analyses.

**Table 7: Results of the economic evaluation and sensitivity analyses**

Sensitivity analyses	Incremental cost	Incremental QALY	ICER	% Δ ICER
<b>Base case</b>	\$redacted	0.09	\$redacted <sup>1</sup>	-
Time horizon (base case 7.5 years)				
Time horizon 5 years	\$redacted	0.08	\$redacted <sup>1</sup>	+1.5%
Test accuracy (base case sens 100%, spec 100%)				
Sens 76% spec 100% (31.0% failed somatic test, 59.4% somatic <i>BRCA1/2</i> and 8.1% germline only, somatic test sens 100%)	\$redacted	0.06	\$redacted <sup>1</sup>	+7.4%
Sens 100% spec 95% (FP receive OLA for 2 months)	\$redacted	0.09	\$redacted <sup>1</sup>	+13.1%
No testing (OLA allocated at random to 50% patients)	\$redacted	0.04	\$redacted <sup>2</sup>	+242.6%
No testing (OLA allocated at random to 9.7% patients: 9.7% sens, 90.3% spec)	\$redacted	0.01	\$redacted <sup>2</sup>	+242.6%
Uptake rate of <i>BRCA1/2</i> test (base case 100%)				
80%	\$redacted	0.07	\$redacted <sup>1</sup>	+5.9%
80% and sens 76%	\$redacted	0.05	\$redacted <sup>1</sup>	+15.1%
Cost of diagnostic testing (no cascade testing, \$1,200 per pt)				
Test cost \$0	\$redacted	0.09	\$redacted <sup>3</sup>	-23.4%
Additional cost of archival tissue retrieval (\$85 per patient)	\$redacted	0.09	\$redacted <sup>1</sup>	+1.7%
Cascade testing (proband+3 rels=\$1,280 per somatic <i>BRCA1/2</i> pt = \$124 per pt)	\$redacted	0.09	\$redacted <sup>1</sup>	+1.7%
Cascade testing (proband+6 relatives)	\$redacted	0.09	\$redacted <sup>1</sup>	+2.6%
<b>Multivariate analysis</b>				
Sensitivity 76% (incl. test failure), cascade testing	\$redacted	0.06	\$redacted <sup>1</sup>	+11.3%

Source: Table 155, p380-381 of the resubmission to PBAC and Table 3.9.1, p137 of the olaparib commentary to PBAC

Δ=change, *BRCA1/2*=*BRCA1/2* pathogenic variant, BSC=best supportive care, FP=false positive for *BRCA1/2* pathogenic variant, ICER=incremental cost-effectiveness ratio, OLA=olaparib pt=patient, QALY=quality adjusted life year, rels=relatives, sens=sensitivity, spec=specificity

The redacted values correspond to the following ranges

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$155,000 to < \$255,000

<sup>3</sup> \$45,000 to < \$55,000

The minor overview noted the model was sensitive to the inclusion of *BRCA1/2* testing, with the ICER increasing to \$155,000 to < \$255,000/QALY if allocated at random to otherwise eligible patients without reference to the results of this testing. The minor overview noted that if everyone in the proposed scenario received olaparib, the ICER increased to \$255,000 to < \$355,000/QALY.

The PBAC requested the resubmission present an ICER of less than \$55,000 to < \$75,000 per QALY. The ICER increased from \$55,000 to < \$75,000 to \$55,000 to < \$75,000 in the multivariate sensitivity analysis where the test sensitivity was reduced to 76% to account for failed somatic testing and cascade testing costs were included.

### 13. Financial/budgetary impacts

The resubmission provided new predicted use and financial implications associated with testing and treating for olaparib. The main changes and impact of those changes from the March 2021 submission are summarised in the table below.

**Table 8: Changes and impact of those changes from the March 2021 submission**

Change in resubmission	Comment	Impact on predicted use/financial implications compared to March 2021 submission
Incident rather than prevalent approach to project annual patient numbers	DUSC recommended a combined incident and prevalent approach	Fewer estimated patients, lower total net cost.
Inclusion of cascade testing costs	This was appropriate	Higher estimated net MBS cost.
Removal of subsequent germline testing for patients in whom tumour testing was not feasible or not successful	While MSAC indicated that subsequent testing arising from failed tests should not accrue an additional cost, these tests do have consequences for the accuracy of the testing strategy, and in practice, clinicians may prefer to re-biopsy patients than have them undertake germline testing.	Lower estimated net MBS cost.

Source: Table 4.1, p142 of the minor overview to PBAC. *Italics* indicates changes most influential to the financial estimates.

The resubmission adopted an epidemiological approach using NHA initiation data to estimate the financial implication of the proposed olaparib listing. The minor overview considered the resubmission's approach was not consistent with the recommendation in the minor overview (of the previously submission) to use a combined incident/prevalent approach. A prevalent pool of patients who would initiate treatment in Year 1 (in addition to incident patients) were not identified and their continued use was not captured in the forward estimates. This is likely to underestimate utilisation and cost for both testing and olaparib.

The resubmission considered that *BRCAl/2* testing would occur at diagnosis of metastatic disease, with uptake increasing from redacted% in Year 1 to redacted% in Year 2.



**Table 9: Estimated utilisation**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use of BRCA1/2 test</b>						
Total patients tested for <i>BRCA1/2</i>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>
<i>Total patients tested for BRCA1/2</i>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>
Patients likely to receive a positive test result	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
<i>Patients likely to receive a positive test result</i>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
<b>Estimated MBS service use</b>						
MBS 72860 archival tumour sample retrieval	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>
<i>MBS 72860 archival tumour sample retrieval</i>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>
MBS services <i>BRCA1/2</i> somatic testing	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>
<i>MBS services BRCA1/2 somatic testing</i>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>	Redacted <sup>2</sup>
MBS services <i>BRCA1/2</i> germline testing <sup>a</sup>	0	0	0	0	0	0
<i>MBS services BRCA1/2 germline testing</i>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>	Redacted <sup>1</sup>
MBS 73302 germline characterisation	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
<i>MBS 73302 germline characterisation</i>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
MBS 73297 cascade testing (3 relatives)	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
<i>MBS 73297 cascade testing</i>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
MBS services (chemo admin avoided)	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>	Redacted <sup>3</sup>
<i>MBS services (chemo admin avoided)</i>	0	0	0	0	0	0

Text in italics represents estimates from the March 2021 submission.  
*BRCA1/2=BRCA1/2* pathogenic variant, MBS=Medicare Benefits Schedule

<sup>a</sup> Tumour and germline testing were combined for the resubmission.

The redacted values correspond to the following ranges

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> < 500

Table 10 presents the net cost to the MBS.

**Table 10: Net costs to the MBS**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated cost to MBS</b>						
Cost to MBS of increased services less copayments	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>
Cost to MBS of decreased services less copayments	\$redacted <sup>2</sup>	\$redacted <sup>2</sup>	\$redacted <sup>2</sup>	\$redacted <sup>2</sup>	\$redacted <sup>2</sup>	\$redacted <sup>2</sup>
<b>Net cost to MBS</b>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>
<i>Net cost to MBS</i>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>
Net cost to MBS with 6 relatives	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>
<b>Net cost of olaparib to PBS/RPBS</b>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>
<i>Net cost olaparib to PBS/RPBS</i>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>	\$redacted <sup>1</sup>
<b>Net change to government budget</b>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>4</sup>
<i>Net change to government budget</i>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>

Text in italics represents estimates from the March 2021 submission, these were extracted from the last commentary during the evaluation.

Source: Tables 192-196 p412-413, Table 198 p414, and Table 4.2.1 of the commentary for PBAC.

MBS=Medicare Benefits Schedule

The redacted values correspond to the following ranges

<sup>1</sup> \$0 to < \$10 million

<sup>2</sup> Net cost saving

<sup>3</sup> \$10 million to < \$20 million

<sup>4</sup> \$20 million to < \$30 million

The net cost to the government was approximately \$100 million to < \$200 million (previous submission \$90 million to < \$100 million) over the first six years of listing, with the net cost to the MBS approximately \$20 million to < \$30 million (previously \$40 million to < \$50 million). The minor overview considered the financial estimates to the MBS may be uncertain due to:

- An underestimate of NHA use based on 2020 data, which is likely lower due to the COVID-19 pandemic. The minor overview presented a scenario analysis where incidence is extrapolated from 2019 data, which results in total net cost to government of approximately \$100 million to < \$200 million (net cost to MBS of approximately \$20 million to < \$30 million). Furthermore, while the PBAC recommended (paragraph 6.44, olaparib PSD, March 2021) the inclusion of both incident and prevalent data in the first year, only incident data have been used, potentially underestimating the use of olaparib in at least year 1.
- An underestimate of the proportion of patients progressing from NHA. In current practice there are limited treatment options for mCRPC patients, as such NHA use may be more protracted than if other treatment options were available.
- No cost for potential re-biopsy was included. While this is in line with the resubmission's suggestion that patients who fail somatic testing should go on to germline testing, this is a scenario that could require >30% of patients to receive genetic counselling (not currently available on MBS) in order to receive a germline *BRCA1/2* test. Furthermore, >50% of *BRCA1/2* pathogenic variants are somatic only (i.e., they will be missed by a germline test alone). Therefore, re-biopsy may be preferable in clinical practice.
- Some patients may know their germline status prior to mCRPC (e.g., previously identified through cascade testing of a relative with a *BRCA1/2* pathogenic variant) and therefore will not need to undergo testing. However, even when germline status has been identified in all patients prior to mCRPC, approximately 95% of patients will still need to undergo somatic testing (as at least 50% of *BRCA1/2* pathogenic variants in mCRPC are expected to be somatic only).

On balance, the minor overview considered that it is likely the net costs are underestimated.

#### **14. Other significant factors**

Nil.

#### **15. Applicant comments on MSAC's Public Summary Document**

The applicant did not provide a comment.

#### **16. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC websites](#)