



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### **Application No. 1618 – Testing of tumour prostate tissue to detect BRCA1/2 pathogenic gene variants in men with metastatic castration-resistant prostate cancer to help determine eligibility for PBS olaparib**

**Applicant:** AstraZeneca Pty Ltd

**Date of MSAC consideration:** MSAC 81<sup>st</sup> Meeting, 31 March – 1 April 2021

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

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

The integrated codependent submission 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 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.

#### **Consumer summary**

This application was from AstraZeneca Pty Ltd. The application was for listing genetic testing for *BRCA1/2* 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

## Consumer summary

(PBS). Olaparib has been shown to improve survival in people with *BRCA1/2* variants in their prostate cancer.

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 *BRCA1/2* testing. If the tumour is positive for a *BRCA1/2* 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 *BRCA1/2* variant, their immediate family members could also be tested to see if they carry the same variant (this is called cascade testing).

MSAC considered that testing people with this type of prostate cancer would accurately identify *BRCA1/2* variants and thus help determine eligibility for olaparib. MSAC will quickly reconsider this application if the Pharmaceutical Benefits Advisory Committee (PBAC) recommends 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, but it did not yet make a decision about listing it on the MBS. MSAC noted that it would quickly reconsider this application if the PBAC recommends funding olaparib on the PBS for this group of people.

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

MSAC noted that this was an integrated codependent submission for the Medicare Benefits Schedule (MBS) listing of genetic testing for *BRCA1/2* pathogenic gene variants to help determine eligibility for treatment with olaparib of patients with metastatic castration-resistant prostate cancer (mCRPC). MSAC noted the original application as considered by its PICO Advisory Sub-Committee had also included testing the *ATM* gene, but this request was not included in the applicant developed assessment report (ADAR). MSAC noted that the March 2021 Pharmaceutical Benefits Advisory Committee (PBAC) meeting did not recommend listing olaparib on the Pharmaceutical Benefits Scheme (PBS) for the treatment of mCRPC in patients with pathogenic or likely pathogenic *BRCA1/2* gene variants. MSAC also noted the PBAC's request for MSAC advice on the likely prevalence in the Australian population with metastatic castration resistant prostate cancer of having a *BRCA1/2* pathogenic gene variant.

MSAC noted that olaparib is currently PBS-listed for platinum-sensitive patients with high-grade serous ovarian, fallopian tube or primary peritoneal cancer, who also have a *BRCA1/2* pathogenic gene variant.

MSAC noted the relevant randomised trials of olaparib (PROfound, TOPARP-B) enrolled patients with mCRPC who had pathogenic gene variants in prespecified lists of genes. The prespecified lists were of genes which had a direct or indirect role in the homologous recombination repair (HRR) pathway. The prespecified genes differed slightly between the two trials. MSAC noted that the PROfound trial was based on the assumption that all gene variants were equally predictive of tumour HRR deficiency. MSAC did not consider this assumption to be plausible given that the trial did not include functional assays for HRR deficiency and further that each gene variant is not predictive of HRR deficiency with the

same level of confidence. PROfound established two cohorts, the first based on alterations in *BRCA1*, *BRCA2* or *ATM* (regardless of other co-occurring gene variants) and a second cohort with alterations in 12 other genes. The submission requested funding for patients reflecting only a subgroup of those enrolled in the PROfound trial (ie only those with *BRCA1/2* variants) rather than reflecting the entire cohort of patients enrolled in the trial.

MSAC accepted the clinical utility of *BRCA1/2* testing to determine PBS eligibility for olaparib. MSAC noted the improved health outcomes in patients with *BRCA1/2* variants treated with olaparib, and considered the best evidence was for *BRCA2*. MSAC noted there were only 13 patients with *BRCA1* variants in the PROfound trial and the results showed it only weakly predicted improved health outcomes with olaparib treatment. For reasons outlined above, MSAC considered it unlikely that olaparib would be equally effective against all gene variants included in the PROfound study and further MSAC noted the very limited evidence available in relation to genes other than *BRCA1/2*. MSAC excluded *ATM* pathogenic gene variants despite the fact that the National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2021, 17 February 2021) recommend *ATM* testing in this context.

In accepting this evidence of clinical utility, MSAC also considered that the PROfound trial did not directly show that treatment effect size with olaparib was better for *BRCA1/2* positive patients than for *BRCA1/2* negative patients as the trial excluded HRR-negative patients. Despite this trial limitation, MSAC considered that this aspect of the claim could be indirectly inferred as being biologically plausible.

MSAC noted the high requested fee for the genetic test with some providers offering *BRCA1/2* testing at a lower fee. MSAC considered that a large number of *BRCA1/2* tests would be required to identify a small number of patients who would be able to access olaparib. MSAC therefore considered the \$1,200 fee resulted in a high cost to the MBS as this new purpose would result in a high-volume test. However, MSAC also noted that the lower fee from some providers may be the result of laboratory cross-subsidisation between various tests. In relation to next generation sequencing, the costs for library preparation remain high and, given the size of the *BRCA1/2* genes, the analysis takes considerable time.

MSAC considered that germline testing might be necessary after inconclusive tumour testing. MSAC therefore 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. 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.

MSAC considered that the economic model had inappropriately included testing costs for patients assumed to switch to olaparib in the comparator arm and noted that the pre-MSAC response had agreed this should be removed.

MSAC noted that the PBAC considered the economic evaluation to be highly uncertain, partly due to uncertainty regarding the proportion of tested patients who would qualify to access olaparib. MSAC noted the published prevalence rates for *BRCA*-positive patients with metastatic prostate cancer: 7% (calculated from TOPARP-B, Mateo 2020), and 9.7% (application based on PROfound). The NCCN guidelines (Version 2.2021, 17 February 2021) estimate 5.3% have *BRCA2* and 0.9% have *BRCA1* (total 6.2% *BRCA1/2*). MSAC therefore

advised that PBAC should rely on 7%–10% as the range of prevalence estimates of patients with mCRPC being *BRCA1/2* positive.

MSAC noted that the PBAC considered the economic evaluation to also be uncertain due to uncertainty regarding the number of cascade tests that would be required. MSAC noted that 50% of patients with *BRCA1/2* positive tumour tests will also be germline positive, and thus have relatives at risk. This would necessitate additional germline and cascade testing, which was not part of the economic evaluation. MSAC acknowledged the scope of the application was for access to olaparib, but considered that, although the cost of this additional germline and cascade testing would be relatively low in the context of the requested test and medicine listings, the applicant should include such cost consequences in both the economic evaluation and the financial analysis. However, the applicant would not have to include the health outcomes of germline and cascade testing in its economic evaluation. On balance, MSAC foreshadowed that it would support these other relatively small consequential costs of testing in the context of the overall application.

MSAC noted the submission's estimates that 4,613 patients would be tested for *BRCA1/2* variants to determine eligibility for olaparib in year 1, increasing to 6,623 in year 6 – resulting in 447 eligible patients for olaparib in year 1. MSAC noted that the net MBS costs were almost as large as the net PBS costs because a large number of patients would be undergoing testing to identify the small proportion of patients (less than 10%) eligible for olaparib treatment.

#### **4. Background**

Germline *BRCA1* or *BRCA2* testing to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed high-grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSOC) was listed on the MBS (item 73295) alongside PBS listings for olaparib (items 11034R and 11050N) on 1 February 2017.

In August 2020, MBS item 73301 was introduced for testing of the tumour tissue (somatic testing) to detect *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants, in a patient with advanced HGSOC. Additionally, item 73302 was introduced to determine whether the presence of somatic *BRCA* markers detected by item 73301 are the result of a pathogenic or likely pathogenic *BRCA1* or *BRCA2* gene variant. In its consideration of somatic *BRCA* testing in the aforementioned population, MSAC accepted that women first identified with a somatic *BRCA* pathogenic gene variant should be followed up with germline testing, and that predictive (cascade) testing should still be offered only to family members of women with confirmed germline *BRCA* pathogenic gene variant (MBS item 73297, [MSAC Application 1554 PSD](#), p4).

Germline gene testing, including *BRCA1* and *BRCA2* testing (item 73296), for patients with breast or ovarian cancer in patients at >10% risk of having a pathogenic gene variant, became available on the MBS from November 2017. Item 73296 requires characterisation of *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11*, *PTEN*, *CDH1*, *PALB2*, or *TP53*. Item 73297 is the corresponding MBS item for biological relatives. Item 73297 does not refer to a tumour type. Consistent with item 73296, item 73297 is for the characterisation of germline gene variants including copy number variation in *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11*, *PTEN*, *CDH1*, *PALB2*, or *TP53*.

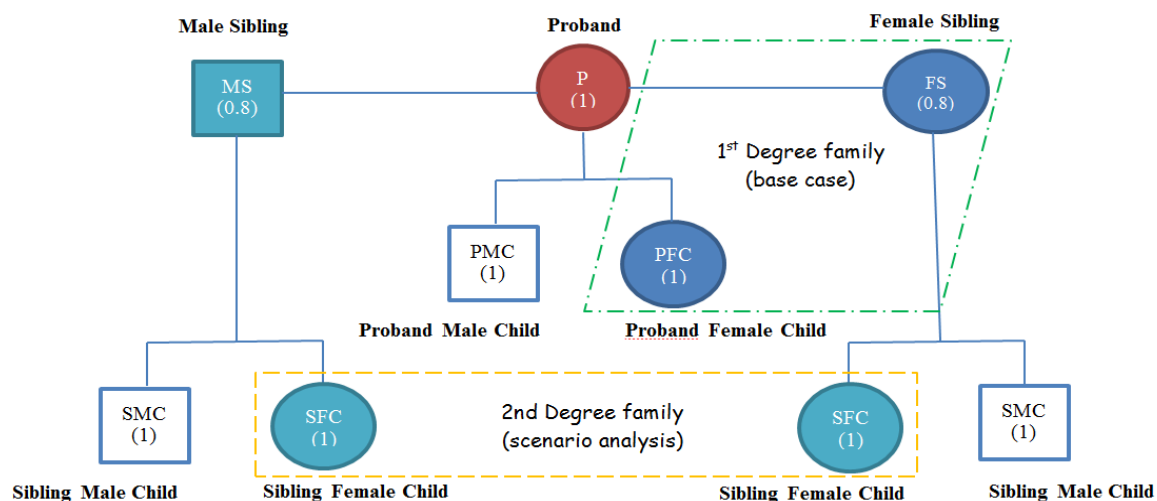
MSAC supported MBS listing of testing of the defined set of breast cancer/ovarian cancer group of genes in high risk affected individuals and for the specific gene mutation [variant] identified in their family members at its March 2016 consideration of [Application 1411.1](#).

In determining the appropriateness of utilising an integrated economic model for the resubmission, MSAC noted that the Predisposition Genetic Testing Economics Working Group (PGTEWG) considered the concept of ‘joint production’. The working group proposed that performing genetic tests in affected individuals not only impacts their own utility or disutility values, but also those of their family members. In this regard, the cost of testing the affected individuals is incurred for the production of utility and/or disutility values relevant to both the affected individuals and their family members. The working group extended its rationale to note that, if utilities are joint-produced by genetic tests, the cost-utility analysis must also be reframed to include the associated outcomes (whether or not testing of family members is eventually supported in addition to testing affected individuals or not). In turn, MSAC accepted that there was a strong conceptual case to support the use of an integrated model which included the costs and effects of initially testing affected individuals and then also testing their family members according to the results of the tests for the affected individuals ([MSAC Application 1411.1 PSD](#), p2-3).

Key model inputs included:

- The model used age-specific incidence of both breast and ovarian cancers. A pathogenic *BRCA* variant is likely to increase the risk of breast and ovarian cancers at an earlier age compared to the general population ([Application 1411.1 Economic Evaluation Report](#), p3).
- 15% of affected individuals will test positive for a *BRCA1* or *BRCA2* mutation [variant] ([Application 1411.1 Economic Evaluation Report](#), p4). Instead of adopting the cancer risk from a *BRCA1* mutation [variant] only, the model considered the lower risk with a *BRCA2* mutation [variant] and used the weighted average risk based on 54% and 46% prevalences for *BRCA1* and *BRCA2*, respectively ([Application 1411.1 Economic Evaluation Report](#), p3).
- The scenario analysis of first-degree relatives considered first degree female family members (children and siblings) of probands ([Application 1411.1 Economic Evaluation Report](#), p3). Mothers of affected individuals were excluded since at an age of >65 years on average, there is little utility of genetic testing to prevent future cancer ([Application 1411.1 Economic Evaluation Report](#), p4).
- In the scenario analysis, the second degree family members (female children of siblings who test positive) were also considered. Male siblings were not included in the model, but the cost of testing them was included to inform the need to test their children ([Application 1411.1 Economic Evaluation Report](#), p5).

MSAC noted that the impact of genetic testing compared to no testing for affected individuals and their first-degree family members (female siblings and female children of identified probands) was considered as the base case analysis, with their second-degree family members (female children of positively tested male and female siblings of identified probands) considered in a scenario analysis (refer to Figure 1; [MSAC Application 1411.1 PSD](#), p3).



**Figure 1** Proband's family members included in the Application 1411.1 economic model

Source: Figure 4.2, p5 of the [Application 1411.1 Economic Evaluation Report](#)

Square = male; Circle = female.

\*Male siblings will not be included in the model but the cost of testing them will be included in the scenario analysis to inform the need to test their children.

Table 1 summarises the results of the economic evaluation when various cohorts were included in the model. MSAC noted that the base case ICER generated was less than the ICERs calculated in the previous analysis, with a cost of \$18,283 per QALY gained. MSAC also considered that the scenario analyses, incorporating different assumptions about the extent to which family members are tested, did not have a large effect on the ICERs: for affected individuals only (\$21,303/QALY), for affected individuals plus identified probands' female siblings only (\$18,241/QALY), for affected individuals plus identified probands' female children only (\$20,987/QALY), and for affected individuals plus identified probands' first and second-degree family members (\$18,752/QALY, [MSAC Application 1411.1 PSD, p3](#)).

MSAC also explored the impact of limiting the revised model to genetic testing for the identification of *BRCA1* mutations [variants] alone and *BRCA2* mutations [variants] alone on the ICERs generated. When the model was limited to *BRCA2* testing, this led to a reduced QALY increment of 0.13 and a less favourable ICER of \$31,562 per QALY. In turn, MSAC noted that the addition of *BRCA2* testing in the primary analysis made the ICER less favourable, while *BRCA1* testing, given its association with the detection of early disease and consequent improvements in life expectancy, represented the main driver behind the ICER presented for the base case ([MSAC Application 1411.1 PSD, p4](#)).

MSAC also noted that the revised model in the current application did not capture the testing of parents or male children in scenario analyses and that these should be conducted, if relevant to diseases presented in future applications ([MSAC Application 1411.1 PSD, p7](#)).

**Table 1 Incremental costs and effects for testing various cohorts in Application 1411.1**

	Cost	QALY	Incremental cost	Incremental effect	ICER/QALY
Affected individuals only	\$6,012	17.42	\$2,614	0.12	\$21,783
Affected individuals + proband's female siblings	\$7,230	19.50	\$3,150	0.17	\$18,241
Affected individuals + proband's female siblings + proband's female children	\$7,788	22.45	\$3,470	0.19	\$18,283
Affected individuals + proband's siblings (male and female) <sup>a</sup> + proband's female children + female children of siblings who test positive	\$8,324	24.81	\$3,815	0.20	\$18,752

Source: Table 6-6.6, p12-13 of Application [1411.1 Economic evaluation report](#)

QALY = Quality-adjusted life-year; ICER = incremental cost-effectiveness ratio

<sup>a</sup> Proband's male siblings will not be included in the model but the cost of testing them will be included to inform the need to test their children.

## 5. Prerequisites to implementation of any funding advice

### *Test*

The submission focused on tumour testing for *BRCA1/2* pathogenic gene variant using NGS-based methods, but did not specify which particular NGS-based diagnostic method was the proposed test.

The Commentary considered that the submission did not provide adequate information on the regulatory status of *BRCA1/2* pathogenic gene variant testing. The submission also did not discuss the regulatory status of the *BRCA1/2* testing in prostate tumour tissue to determine eligibility for olaparib.

Pathology laboratories must participate in an external quality assurance programme (QAP) to obtain National Association of Testing Authorities (NATA) accreditation to offer medical genetic testing services in Australia. The submission stated that the following laboratories have NGS capabilities and have NATA accreditation: Peter MacCallum Cancer Centre (PMCC) in Melbourne VIC, Pathology North in Newcastle NSW, Sonic Genetics in Sydney NSW, Genomic Diagnostics in Melbourne VIC, and Genomics for Life in Brisbane QLD. The submission stated the PMCC has completed validation and TGA notification of its NGS testing for both *BRCA1/2* and other pathogenic gene variants in prostate cancer, but no TGA documentation was provided during the evaluation.

The submission provided no information regarding which of these laboratories would be testing in prostate cancer, and instead it was just stated that some would perform testing in prostate cancer.

The submission reiterated that *BRCA1/2* testing is not expected to be a barrier to treatment and will be conducted in a timely and appropriate manner. The submission did not discuss issues associated with access to genetic counselling and testing in Australia, nor provide any discussion on how the time gap between the test and availability of results (at least 4-6 weeks) would be managed regarding ongoing treatment.

The National Pathology Accreditation Advisory Council advised that testing for *BRCA1/2* is already established in a number of laboratories in Australia. An External Quality Assurance Program is available through Royal College of Pathologists of Australasia Quality Assurance Programs P/L. The addition of *ATM* testing (as originally proposed) was not considered to be complex.



## Medicine

An application to the TGA to extend the registration of olaparib to include patients with mCRPC and a detected pathogenic gene variant was made on 29 February 2020. The requested indication was:

*Treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair (HRR) gene mutation [variants] (germline and/or somatic) who have progressed following a prior new [novel] hormonal agent. HRR gene mutation [variant] status should be determined by an experienced laboratory using a validated test method.*

Based on the same PROfound trial, regulators in other countries approved olaparib for different biomarker-defined populations. The FDA approved olaparib on 19 May 2020 for treatment of adult patients with germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. In Canada, olaparib was approved in August 2020 for treatment of adults with deleterious or suspected deleterious germline and or somatic *BRCA* or *ATM* mutated mCRPC who have progressed following prior treatment with a non-hormonal agent. The European Medicines Agency (EMA) granted marketing authorisation in November 2020 for the use of olaparib for treatment of adult patients with mCRPC and *BRCA1/2* pathogenic gene variants (germline or somatic) who have progressed following prior therapy that includes a new hormonal agent.

The TGA Delegate's overview (dated 4 January 2021) was received during the evaluation, and the Delegate's recommendation was to approve the registration of olaparib, with a limitation of the indication to patients with *BRCA1* or *BRCA2* pathogenic gene variants. The TGA Delegate explained that exploratory analyses of PFS and OS in the *ATM* and *CDK12* subgroups within PROfound do not support a conclusion of meaningful efficacy in these groups, over the comparator. The TGA Delegate concluded that the presence of a non-*BRCA* HRR pathogenic gene variant is not considered a biomarker that sufficiently predicts for response on a population level to justify exposing this population to the additional toxicity that is conferred by treatment with olaparib compared to a "novel hormonal agent" (NHA; abiraterone or enzalutamide). Efficacy in the *BRCA1/2* group was mainly driven by results in patients with *BRCA2*; however, the delegate felt grouping of *BRCA1* and *BRCA2* was reasonable given the breadth and strength of pre-clinical and clinical evidence of sensitivity of PARP inhibitors in *BRCA1* and *BRCA2* pathogenic gene variants. It was noted, that like other rarer genetic variants, the relative low rate of *BRCA1* pathogenic gene variants in prostate cancer makes it difficult to assess responses in *BRCA1* population independent of *BRCA2*.



## 6. Proposal for public funding

**Table 2 Proposed MBS listing**

Category 6 – PATHOLOGY SERVICES	
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 eligibility relating to BRCA 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
Detection of germline BRCA1 or BRCA2 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 1-7, p44 of the submission.

The wording of the proposed MBS item descriptors was similar to that in the ratified PICO ([Application 1618 Ratified PICO Confirmation](#), p18-20), with modification to remove *ATM* testing. The submission stated that *BRCA1/2* and *ATM* are well characterised pathogenic gene variants in prostate cancer and were included in Cohort A of the PROfound trial (the ITT population), but analysis of the Cohort A subgroups suggested that olaparib was not effective in patients with the *ATM* gene variant (Hussain et al 2020).

The Commentary noted that Hussain et al 2020 reported a larger improvement in overall survival (OS) for olaparib versus NHA in the *BRCA1/2* subgroup versus the ITT population of Cohort A, with hazard ratios (95% CIs) being 0.63 (0.42, 0.95) and 0.69 (0.50, 0.97), respectively<sup>1</sup>, but there was no improvement in OS in the *ATM* subgroup, HR 0.93 (95% CI: 0.53, 1.75), despite a reasonable sample size<sup>2</sup>. The Commentary considered that it was unclear whether these hazard ratios for the subgroups could be accepted as different from each other and from the ITT hazard ratio. The Commentary highlighted that another small cohort study of 23 patients with mCRPC treated with olaparib also found that patients with *ATM* alterations may not respond to olaparib as well as those with *BRCA1/2* pathogenic gene variants (Marshall et al 2019<sup>3</sup>). In this study, OS was longer in patients with *BRCA1/2* pathogenic gene variants than in those with *ATM* alterations (29.8 vs 4.1 months; hazard ratio (95% CI) of 0.14 (0.02, 0.88). The data from Marshall et al 2019 were not presented in the submission.

The submission added the Committee for Medicinal Products for Human Use (CHMP) had recommended to the European Medicines Agency (EMA) that olaparib should only be approved in the *BRCA1/2* gene variant population, and it was likely that the TGA indication

<sup>1</sup> The ITT HR was reported in the submission.

<sup>2</sup> Hussain et al 2020 supplementary appendix.

<sup>3</sup> Marshall CH, Sokolova AO, McNatty AL, Cheng HH, Eisenberger MA, Bryce AH, et al. Differential response to olaparib treatment among men with metastatic castration-resistant prostate cancer harboring *BRCA1* or *BRCA2* versus *ATM* mutations. *Eur Urol* 2019;76(4):452-8.

would be similar. Thus, listing was only requested for the *BRCA1/2* subgroup. Given the TGA delegate has since recommended olaparib only for the *BRCA1/2* pathogenic gene variant subgroup, the Commentary considered the exclusion of patients with the *ATM* pathogenic gene variant from the requested PBS/MSB listings was reasonable, however considered that this left open the question of whether to accept any variation in the extent of benefit from the estimate for the ITT population of Cohort A.

The proposed wording was similar to existing MBS items 73301/73295 in HGSOc and addressed the eligibility criteria for olaparib in mCRPC. The submission considered there would be an increase in utilisation of MBS item 73301 for tissue sample retrieval as consequence of the requested testing.

The submission also stated that existing MBS items 73302 and 73297 for germline testing in patients and cascade testing of unaffected family members in the context of identified *BRCA1/2* pathogenic gene variants would not require amendment as they are tumour agnostic. These MBS item descriptors are provided in Table 3 for reference.

**Table 3 Existing MBS items for germline/cascade testing**

Category 6 – Pathology Services	
MBS item 73302 (no change required)	Group P7 - Genetics
Characterisation of germline gene variants including copy number variants, in BRCA1 or BRCA2 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	
MBS item 73297 (no change required)	
Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in BRCA1 and BRCA2 genes and one or more of the following genes STK11, PTEN, CDH1, PALB2, or TP53 in a patient who is a biological relative of a patient who has had a pathogenic mutation identified in one or more of the genes specified above, and has not previously received a service under item 73296.	
Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00	

Source: Table 1-7, p44 of the submission.

PASC advised that related MBS items would need to be developed or amended for the associated consequential germline and cascade testing (p21, [Ratified PICO](#)) when the proposed test included *ATM* gene variants. MBS items 73302 and 73297 are not specific to a tumour site. MBS item 73297 for cascade testing was intended for biological relatives of patients with breast, ovarian, fallopian tube or primary peritoneal cancer with pathogenic variants in the following genes: *BRCA1/2*, *STK11*, *PTEN*, *CDH1*, *PALB2* or *TP53*. The item descriptor requires testing of *BRCA1/2* and at least one of the aforementioned genes which may not be appropriate for the proposed population. As the submission did not consider the health outcome or cost consequences of the proposed testing in prostate cancer to these MBS services or the new patients who would access them, MSAC should advise whether these two MBS item descriptors need to be modified to prevent these unknown flow-on consequences. For example, there is no evidentiary basis provided to even judge how the likelihood of a patient having inherited the variant or of a family member having the variant might vary depending on whether the trigger for this flow-on testing comes from a patient with prostate cancer or with ovarian cancer.

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

Four targeted consultation responses were received; one from a pathology professional organisation, one from a pathology provider, and two from consumer groups. The consultation feedback was generally supportive. The following feedback points were identified in the public consultation:

- 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 variants have been rarely reported and these would only be present in metastatic disease.
- The feedback from the pathology provider and professional organisation highlighted the importance of cascade testing and appropriate genetic counselling.

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

### Description of proposed intervention

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.

### 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 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 current and proposed clinical management algorithms are presented in Figure 2 and Figure 3, respectively.

The submission proposed testing of tumour tissue in a patient with mCRPC to detect *BRCA1/2* pathogenic gene variants would be performed at diagnosis of mCRPC. The turnaround time of the test of 4-6 weeks is due to retrieval of archived samples, which may take 1-2 weeks, and preparation, DNA extraction and interpretation. The Commentary considered that this was appropriate, but noted this contradicted statements elsewhere in the submission (see below).

The submission recommended the treating clinician should order a germline test when the tumour test was unsuccessful or not feasible, and re-biopsy was not practicable. However, the Commentary considered germline testing alone may not adequately identify patients with somatic-only *BRCA1/2* pathogenic gene variants. The Commentary highlighted that studies suggest approximately half to more than half of detected *BRCA1/2* pathogenic gene variants in prostate cancer are somatic only<sup>4,5</sup> and thus would not be detected via germline testing alone. Clinical guidelines advocate for both germline and somatic testing in patients with

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<sup>4</sup> Abida W et al. Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol.* 2017 Jul;2017:PO.17.00029.

<sup>5</sup> Lang SH, Swift SL, White H, Misso K, Kleijnen J, Quek RGW. A systematic review of the prevalence of DNA damage response gene mutations in prostate cancer. *Int J Oncol.* 2019;55(3):597-616. doi:10.3892/ijo.2019.4842.

metastatic prostate cancer<sup>6</sup>. Pathogenic germline variants (PGVs) may also be missed by tumour testing alone. In one report, 2023 patients with cancer unselected for family history received germline testing and previously had tumour DNA sequencing, 8.1 percent of the PGVs were found to have been missed by tumour sequencing alone<sup>7</sup>.

The Commentary highlighted that the disparity between germline and somatic testing has been highlighted in the Public Summary Document (PSD) of Application No. 1554 ([PSD Application No. 1554](#)) for olaparib treatment for high-grade epithelial ovarian, fallopian tube and primary peritoneal cancer (HGEOC). In Table 6 (p13) of the PSD, the overall concordance between tumour and germline NGS *BRCA1/2* test results ranged from 90%–96%, and the positive and negative concordance ranged from 54.4%–85.7% and 85.7%–94.7%, respectively. The Commentary considered that these values were explained by somatic variants that could not be detected by a germline test, when the patients with somatic variants were removed from the analysis, the concordance between the somatic and germline NGS *BRCA1/2* tests was 100% for detection of germline *BRCA1/2* pathogenic gene variants.

Furthermore, given guidelines increasingly recommend germline testing for patients with metastatic prostate cancer,<sup>8,9</sup> the Commentary considered that it may be more practical to consider germline results prior to tumour testing. The Commentary noted that some mCRPC patients may already know their *BRCA* status through cascade testing of germline pathogenic gene variants associated with other familial cancers (e.g., breast and ovarian), and would require no further somatic testing to ascertain eligibility for olaparib.

The submission also noted that patients with pathogenic gene variants on tumour testing should be referred to clinical genetics services for genetic counselling and germline testing to determine if the variant is heritable, followed by cascade testing after counselling testing if a germline *BRCA1/2* pathogenic gene variant was identified as there may be implications for other family members. These steps were included in the proposed cascade testing algorithm (Figure 4), but were not explored further in the submission in either the clinical evaluation or the economic model.

The submission indicated a separate biopsy was not required as most patients would have undergone a biopsy of tumour tissue at diagnosis or at another timepoint during their treatment. The submission explained that archived samples collected and prepared at initial diagnosis or subsequent biopsy can be used for somatic testing. The Commentary considered that this contradicts the submission's statement above, as archived samples at initial diagnosis of prostate cancer or at another time point may not be suitable, and re-biopsy at mCRPC diagnosis would be required. As noted by PASC from the public consultation, somatic alterations may be acquired only when in the metastatic setting.

The ratified PICO ([1618 Ratified PICO Confirmation, p9](#)) stated that 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 maybe required. Moreover, the Ratified PICO included re-biopsy rates as a test-related outcome ([1618 Ratified PICO Confirmation, p15](#)).

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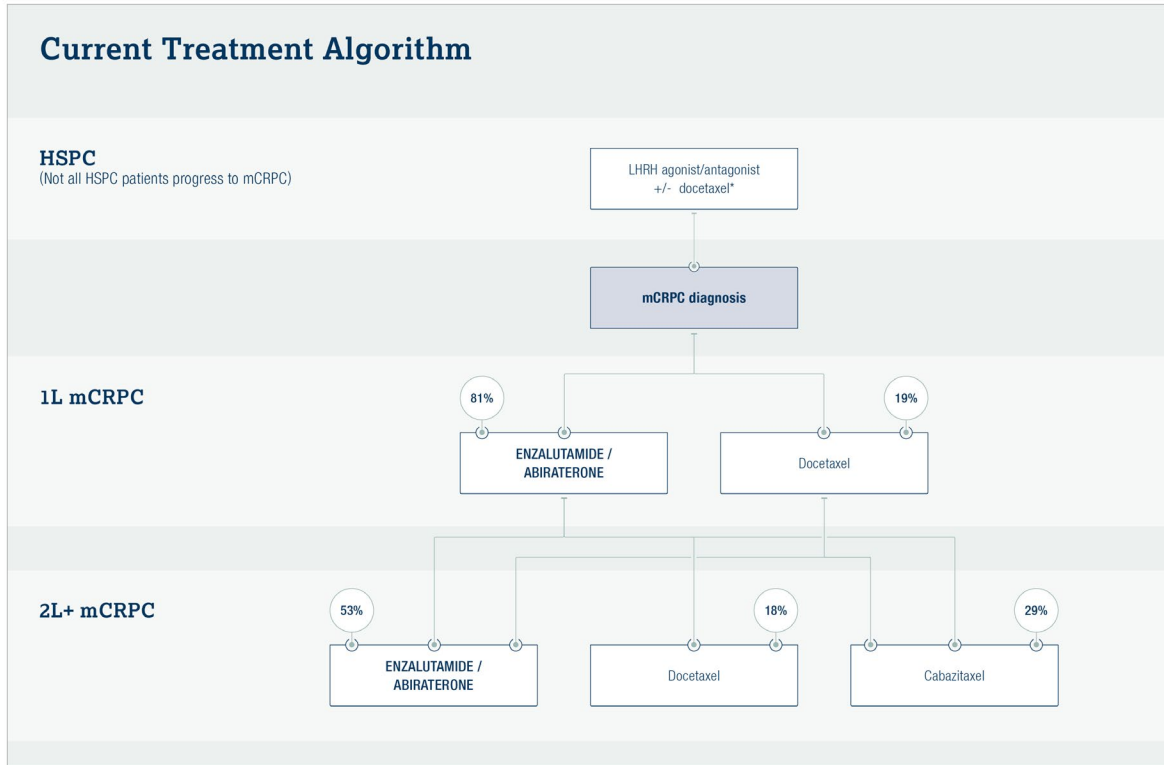
<sup>6</sup> NCCN Guidelines, Prostate Cancer, V3 2020.

<sup>7</sup> Lincoln SE, Nussbaum RL, Kurian AW, Nielsen SM, Das K, Michalski S, Yang S, Ngo N, Blanco A, Esplin ED. Yield and Utility of Germline Testing Following Tumor Sequencing in Patients With Cancer. *JAMA Netw Open*. 2020 Oct 1;3(10):e2019452. doi: 10.1001/jamanetworkopen.2020.19452.

<sup>8</sup> NCCN Guidelines, Prostate Cancer, V3 2020.

<sup>9</sup> Giri VN, Knudsen KE, Kelly WK et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol* 2-2-:JCO2000046.

**Figure 2 Current clinical management algorithm**

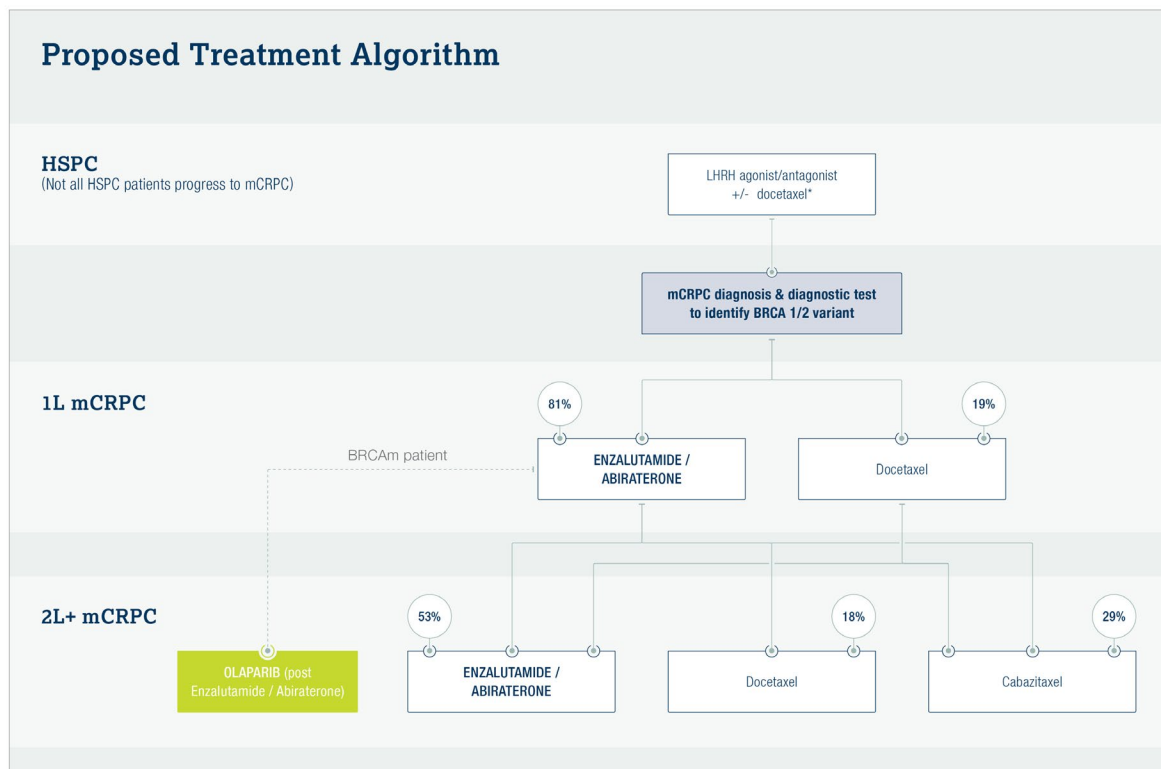


\*Docetaxel use in mHSPC setting (docetaxel initiated within 4 months of LHRH) increasing in recent years since CHAARTED clinical study data read out.  
 NOTES: Treatment flow with frequency of <5% removed. 2L+ treatments combined due to heterogeneity of treatment sequencing & diminishing patient numbers.  
 SOURCE: 2019 PBS data 10% sample, Model Solutions Tableau Online.

Source: Figure 1-4, p45 of the submission

HSPC=hormone sensitive prostate cancer; mCRPC=metastatic castration resistant prostate cancer

Figure 3 Proposed clinical management algorithm

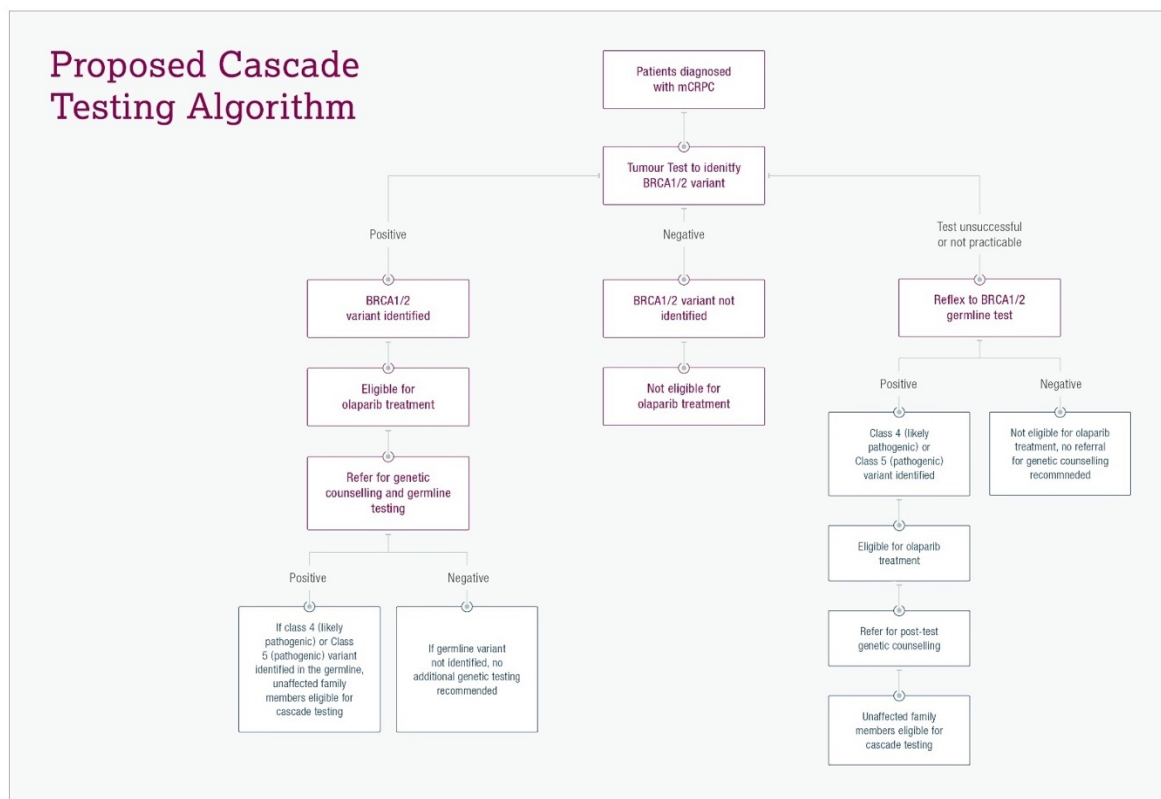


\*Docetaxel use in mHSPC setting (docetaxel initiated within 4 months of LHRH) increasing in recent years since CHAARTED clinical study data read out.  
 NOTES: Treatment flow with frequency of <5% removed. 2L+ treatments combined due to heterogeneity of treatment sequencing & diminishing patient numbers.  
 SOURCE: 2019 PBS data 10% sample, Model Solutions Tableau Online.

WL127078738, September 2020

Source: Figure 1-5, p46 of the submission  
 BRCA1/2=breast cancer genes 1 and 2; HSPC=hormone sensitive prostate cancer; mCRPC=metastatic castration resistant prostate cancer

Figure 4 Germline and cascade testing – flow on consequences



Source: Figure 1-3, p43 of the submission  
 BRCA1/2=breast cancer genes 1 and 2; mCRPC=metastatic castration resistant prostate cancer

## 9. Comparator

The main comparator for testing of *BRCA1/2* pathogenic gene variants in patients with mCRPC was no genetic testing. This was confirmed by PASC as appropriate ([Ratified PICO](#), p13).

## 10. Comparative safety

The approach taken in the submission was to present a linked evidence approach to support its contention that olaparib will improve survival in patients with mCRPC when targeted to those patients with *BRCA1/2* pathogenic gene variants in their tumours.

The ratified PICO ([1618 Ratified PICO Confirmation, p9](#)) stated that the evidence for the codependency submission should include the proposed test and a comparison to alternative options available in Australia, including information on the assay (panel) used, the type of tumour tissue, and the processing of the tissue.

The PROfound CSR stated that all patients must have had a qualifying HRR mutation [variant] assessed via the Foundation Medicine Inc. Clinical Trial Improvement Amendments (CLIA) HRR clinical trial assay (CTA). The submission did not provide any further information on this evidentiary standard test (i.e., the test option used in the generation of evidence of clinical utility), and only presented data on the proposed test, FoundationOne<sup>®</sup>CDx (F1CDx), which was used in a subset of trial patients (n=376). Nevertheless, the TGA delegate stated that exploratory efficacy analyses indicated consistent results for the confirmed Foundation Medicine Inc. F1CDx subgroup and the ITT population, and stated that F1CDx was an appropriate companion diagnostic for this indication.

The submission presented two NGS-based tests but did not compare them to each other:

- FoundationOne<sup>®</sup>CDx (F1CDx) is an NGS-based gene panel that uses the Illumina<sup>®</sup> HiSeq 4000 sequencing platform for detection of pathologic HRR gene alterations (including *BRCA1/2* gene variants) in DNA isolated from formalin-fixed, paraffin embedded (FFPE) prostate tissue. This was the test used in the PROfound trial (i.e. the evidentiary standard).
- QIAseq targeted DNA extended panel is another NGS-based gene panel that uses the Illumina MiSeq<sup>®</sup> v2 sequencing platform to detect pathologic HRR gene alterations in DNA samples from FFPE tumour tissue. This test was validated by the Peter MacCallum Cancer Centre (PMCC) and presented in the submission.



**Table 4 Summary of the linked evidence approach**

Study type	Type of evidence supplied	Extent of evidence supplied
Accuracy and performance of the test (analytical validity)	The submission did not conduct a search for studies of diagnostic performance. The following data was included for: <u>F1CDx</u> : the summary of two concordance analyses included in the FDA label comparing F1CDx with evNGS and F1LTD. <u>QIAseq</u> : A validation report conducted by the PMCC comparing QIAseq to two in-house NGS assays: CCP and the FRCP.	<input type="checkbox"/> k=0
Prognostic evidence	Comparison of outcomes in patients receiving usual care conditioned on the presence or absence of biomarker positive status.	<input checked="" type="checkbox"/> k=2 n=13,369
Clinical utility of the test Predictive effect (treatment effect variation)	The submission did not compare outcomes in patients with and without <i>BRCA1/2</i> pathogenic gene variants who received olaparib or NHA. Even though this information is available from the PROfound trial, with patients without <i>BRCA1/2</i> pathogenic gene variants forming the complement.	<input type="checkbox"/> k=0
Change in patient management	No evidence was provided to show that biomarker determination guides decisions about treatment with the medicine.	<input type="checkbox"/> k=0
Treatment effectiveness	PROfound trial: open label, randomised, phase 3 study of olaparib vs enzalutamide or abiraterone in mCRPC with HRR alterations and a subpopulation with <i>BRCA1/2m</i> .	<input checked="" type="checkbox"/> k=1 n=245

Source: Constructed during the evaluation

*BRCA1/2m* = *BRCA1* or *BRCA2* pathogenic gene variant; CCP=Comprehensive Cancer Capture Panel, evNGS= externally validated NGS assay, F1CDx=FoundationOne@CDx, F1LTD=FoundationOne laboratory developed test, FRCP= Familial Risk Cancer Panel, HRR=homologous recombination repair, k=number of studies, mCRPC=metastatic castration resistant prostate cancer, n=number of patients, NGS=next generation sequencing, NHA= novel hormonal agent.

A summary of data availability to inform comparisons is presented in the table below.

**Table 5 Data availability to inform comparisons**

Proposed test vs no test	No evidence presented	
Proposed test vs alternative test	No evidence presented	
Test + medicine	<b>Olaparib</b>	<b>Nominated comparators: abiraterone or enzalutamide</b>
Biomarker test positive	PROfound	PROfound
Biomarker test negative	No evidence presented	No evidence presented

Source: Table MSAC.6, p16 of the Commentary

The Commentary considered that the diagnostic evidence was poorly presented in the submission and there were significant gaps in the evidence presented to support the test performance:

- There was no direct evidence presented comparing testing with no testing (and no olaparib).
- Considering evidence needed for a linked evidence approach:
  - There was no evidence presented in the submission for an appropriate reference standard to compare with the proposed testing.
  - The submission did not present any evidence to inform a comparison of diagnostic accuracy in mCRPC, and no search to identify diagnostic accuracy studies was conducted.
  - The submission did not present any evidence supporting the clinical utility of testing mCRPC patients for *BRCA1/2* germline and somatic pathogenic gene variants. This was despite information being available from the PROfound trial

suggesting benefit of olaparib for patients with *BRCA1/2* pathogenic gene variants but not in those without *BRCA1/2* pathogenic gene variants. This information was sourced during the evaluation and is presented in Table 6, but no comparative statistics were reported comparing outcomes between the subgroups and/or the ITT population. However, all patients in the PROfound trial had HRR pathogenic gene variants, and so the subgroup of patients without *BRCA1/2* pathogenic gene variants presented may not be fully representative of the wider population of mCRPC patients without *BRCA1/2* pathogenic gene variants who may not necessarily carry HRR alterations.

- The submission presented insufficient evidence to support the analytical validity of the F1CDx test to detect *BRCA1/2* pathogenic gene variants in mCRPC. While the submission had referred to the FDA label document to support the diagnostic performance of F1CDx NGS in DNA derived from FFPE tissue samples from a variety of tumours, there were no diagnostic performance data specific to mCRPC. Also, the particular pathogenic gene variants identified by the test were not reported. This document was also not included with the submission and was instead sourced during the evaluation.
- The submission did not compare the analytical performance of alternative options available in Australia to that of the evidentiary standard test.
- The submission presented an external validation and concordance report developed by the PMCC in Australia using the QIASeq NGS, but the FFPE samples in the report were from a variety of tumour samples and did not include mCRPC tumour tissue. In the clinical validation sample (Table 9, p8-9 of the validation report), *BRCA1/2* pathogenic gene variants were only identified in breast and ovarian cancer tissue, while *ATM* and *CHEK* were detected in prostate tissue. Therefore, the performance of the test to identify *BRCA1/2* pathogenic gene variants in the population of interest remains uncertain. No further details, including TGA documentation were provided.
- The submission did not compare the performance of the FoundationOne®CDx (F1CDx) test in archival FFPE samples to fresh mCRPC tissue samples.
- The flow-on consequences of germline/cascade testing were also inappropriately not included in the submission.

#### *Adverse events from testing*

The submission did not discuss the safety of testing for *BRCA1/2* pathogenic gene variants. The Commentary considered that this was not appropriate. The submission did not discuss potential psychological harms associated with *BRCA1/2* testing or the need for re-biopsy. Given that some patients would only have somatic variants (see above), the need for re-biopsy may need to be considered.

The Commentary noted that the FDA label for the test used in the PROfound trial, FoundationOne®CDx (F1CDx), indicates that failure to extract DNA from FFPE prostate tissue has occurred in 20% of samples. The Commentary therefore concluded that additional biopsies would be needed from patients with inadequate tumour samples suitable for DNA extraction, with associated harms. Generally, while a biopsy is a safe procedure, there is a risk of complications. The most common complications arising from biopsies include bleeding, infection and accidental injury to adjacent structures.

### *Adverse events from changes in clinical management*

The submission did not discuss the consequences of change in management as a result of *BRCA1/2* testing beyond the requested change in clinical management by initiating olaparib in *BRCA1/2*-positive patients.

No evidence was presented to compare response to olaparib in mCRPC patients with and without *BRCA1/2* pathogenic gene variants. The submission did not present any data regarding the proportions of false positive and false negative mCRPC patients. The Commentary considered that the effects on overall survival for false positive patients (receiving olaparib) and false negative patients (not receiving olaparib) were unknown.

## **11. Comparative effectiveness**

### *Prognostic evidence*

The submission did not present a systematic search of prognostic evidence in the population of patients with mCRPC. The submission only mentioned four studies in its prognostic section, but the Commentary considered only two of those were relevant prognostic studies in this population. Other studies were mentioned in other sections in the submission, which did not provide additional information.

The two relevant prognostic studies included were a cohort study (Nyberg 2020) and a systematic review (Oh 2019) that evaluated the prognostic effect of *BRCA1/2* pathogenic gene variants in patients with any stage of prostate cancer.

Nyberg 2020 reported prognostic outcomes in patients with prostate cancer and *BRCA1/2* pathogenic gene variant carriers compared to the general population. In the meta-analysis by Oh 2019, eleven studies were included to calculate the hazard ratio of patients with prostate cancer carrying *BRCA1/2* pathogenic gene variants compared to non-carriers for the outcomes of prostate cancer mortality and overall mortality.

Nyberg 2020 reported a significantly higher standardised mortality ratio for *BRCA2* carriers compared to prostate cancer-specific mortality rates in the UK. Similar results were shown in the Oh 2019 meta-analysis for the outcome of prostate cancer specific mortality in *BRCA2* carriers compared to non-carriers. In both studies, cancer-specific mortality in *BRCA1* carriers was not significantly different to non-carriers.

### *Predictive evidence*

Evidence supporting the effectiveness of olaparib maintenance therapy vs. use of alternate NHA (abiraterone or enzalutamide) in mCRPC patients with *BRCA1/2* pathogenic gene variants (PROfound trial) was presented in the submission. The key outcomes from PROfound for olaparib versus NHA are summarised in the table below.

**Table 6 Summary of rPFS and OS reported in PROfound**

	Number of events/total number of patients (%)		HR (95% CI)	Median month (95% CI)	
	Olaparib	NHA	HR	Olaparib	NHA
<b>Radiological progression-free survival (rPFS) – BICR assessed (data cut off: 4 June 2019)</b>					
Cohort A (ITT) <sup>a</sup> (BRCA1/2, ATM)	106/162 (65.4)	68/83 (81.9)	<b>0.34 (0.25, 0.47)</b>	7.39 (6.24, 9.33)	3.55 (1.91, 3.71)
Cohort A+B	180/256 (70.3)	99/131 (75.6)	<b>0.49 (0.38, 0.63)</b>	5.82 (5.52, 7.36)	3.52 (2.20, 3.65)
Cohort A + B (BRCA1/2)	62/102 (60.8)	51/58 (87.9)	<b>0.22 (0.15, 0.32)</b>	9.79 (7.62, 11.30 <sup>e</sup> )	2.96 (1.81, 3.55)
Cohort A + B (BRCA1/2, ATM) <sup>b</sup>	108/165 (65.5)	69/84 (82.1)	<b>0.38 (0.28, 0.52)</b>	7.39 (6.87, 9.33)	3.52 (1.87, 3.65)
Cohort B genes <sup>c</sup>	30/39 (76.9)	16/24 (66.7)	1.00 (0.55, 1.88)	3.91 (2.00, 7.20)	3.71 (1.87, 5.75)
Any single HRR gene <sup>d</sup>	169/239 (70.7)	91/120 (75.8)	<b>0.53 (0.41, 0.69)</b>	6.08 (5.52, 7.36)	3.52 (1.97, 3.71)
BRCA1 <sup>d</sup>	7/8 (87.5)	5/5 (100)	0.41 (0.13, 1.39)	2.07 (1.38, 5.52)	1.84 (1.71, 3.71)
BRCA2 <sup>d</sup>	47/81 (58.0)	40/47 (85.1)	<b>0.21 (0.13, 0.32)</b>	10.84 (9.17, 13.08)	3.48 (1.74, 3.65)
ATM <sup>d</sup>	46/62 (74.2)	17/24 (70.8)	1.04 (0.61, 1.87)	5.36 (3.61, 6.21)	4.70 (1.84, 7.26)
CDK12 <sup>d</sup>	47/61 (77.0)	18/28 (64.3)	0.74 (0.44, 1.31)	5.09 (3.61, 5.52)	2.20 (1.71, 4.83)
<b>Overall survival (OS) (final analysis, data cut off 20 March 2020)</b>					
Cohort A (ITT) <sup>a</sup> (BRCA1/2, ATM)	91/162 (56.2)	57/83 (68.7)	<b>0.69 (0.50, 0.97)</b>	19.09 (17.35, 23.43)	14.69 (11.93, 18.79)
-Adjusted <sup>f</sup> for 67% crossed over			<b>0.42 (0.19, 0.91)</b>		11.73 (NR, NR)
Cohort A+B	160/256 (62.5)	88/131 (67.2)	0.79 (0.61, 1.03)	17.31 (15.47, 18.63)	14.00 (11.47, 17.08)
Cohort A + B (BRCA1/2)	53/102 (52.0) <sup>e</sup>	41/58 (70.7) <sup>e</sup>	<b>0.63 (0.42, 0.95)</b>	20.11 (17.35, 26.81)	14.44 (10.71, 18.89)
Cohort A + B (BRCA1/2, ATM) <sup>b</sup>	93/165 (56.4)	58/84 (69.0)	<b>0.70 (0.51, 0.98)</b>	19.09 (17.35, 23.43)	14.62 (11.93, 18.79)
Non-BRCA pathogenic variants	107/154 (69.5)	47/73 (64.4)	0.95 (0.68, 1.34)	15.80 (13.86, 17.31)	13.34 (11.17, 17.74)
Cohort B genes <sup>c</sup>	69/94 (73.4)	31/48 (64.6)	0.96 (0.63, 1.49)	14.1 (11.1, 15.9)	11.5 (8.2, 17.1)
-Adjusted <sup>f</sup> for 63% crossed over			0.83 (0.11, 5.98)		
Any single HRR gene	NR	NR	NR	NR	NR
BRCA1 <sup>d</sup>	5/8 (62.5)	5/5 (100)	0.42 (0.12, 1.53)	11.70 (1.38, NC)	9.40 (5.45, 14.62)
BRCA2 <sup>d</sup>	39/81 (48.1)	32/47 (68.1)	<b>0.59 (0.37, 0.95)</b>	24.84 (17.35, NC)	15.15 (10.71, 19.75)
ATM <sup>d</sup>	39/62 (62.9)	15/24 (62.5)	0.93 (0.53, 1.75)	18 (14.42, 23.43)	15.57 (12.12, 22.01)
-Adjusted <sup>f</sup> for 63% crossed over			0.84 (0.19, 3.75)		
CDK12 <sup>d</sup>	47/61 (77.0)	18/28 (64.3)	0.97 (0.57, 1.71)	14.06 (11.14, 15.87)	11.47 (7.82, 17.74)

Source: TGA delegate overview (Table 5), PROfound CSR sections tables listings figures.pdf (Table 14.2.1.4.1, 14.2.5.1). Hussain et al 2020 publication and supplement. Table 2-13, p85; Table 2-30, p94; Section 2.2.D.7, p113-125 of the submission.

*Italics=results extracted/corrected during the evaluation* **Bold**=statistically significant

BICR=blinded independent central review; BRCA=breast cancer gene; CI=confidence interval; HR=hazard ratio; NHA=novel hormonal agent (abiraterone, enzalutamide); NR=not reported; NC=not calculable, OS=overall survival; rPFS=radiological progression-free survival;

<sup>a</sup> primary end point

<sup>a</sup> this was incorrectly reported in the submission as 11.20.

<sup>b</sup> patients with single and co-variants.

<sup>c</sup> includes patients from PROfound with variants in the following genes: *BARD1* &/or *BRIP1* &/or *CHEK1* &/or *CHEK2* &/or *PALB2* &/or *PPP2R2A* &/or *RAD51B* &/or *RAD51D*.

<sup>d</sup> gene subgroup analysis is based on patients with a single HRR variant (results presented for genes with >10 patients in each arm in the trial)

<sup>e</sup> the number and proportion of deaths in the *BRCA1/2* subgroup was not provided by the submission, but was available in Table 14.2.4.5 of the CSR addendum supplementary tables provided with the submission.

<sup>f</sup> rank preserving structural failure time model (RPSFTM) used to adjust for patient who crossed over from NHA to olaparib treatment.

While the submission mentioned two trials, TOPARP-A (Mateo 2015)<sup>10</sup> and TOPARP-B (Mateo 2020)<sup>11</sup> to support the predictive claim of olaparib, the Commentary considered there was insufficient evidence in these trials to establish the predictive effect of the test. The submission also included a study by Abida 2020 in patients with mCRPC treated with rucaparib as supportive evidence of the predictive effect. However, the Commentary considered that the predictive effect of the test in this population was not applicable to that in patients treated with olaparib given that equivalence between these two PARP inhibitors has not been established.

<sup>10</sup> Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med.* 2015;373(18):1697-1708.

<sup>11</sup> Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2020;21(1):162-174.

No attempt was made by the submission to demonstrate the benefit of *BRCA1/2* testing by comparing outcomes of olaparib versus NHA for patients with and without *BRCA1/2* alterations. Data for patients with and without *BRCA1/2* pathogenic gene variants were available from PROfound (see Table 6), but comparative analysis of these two subgroups was not performed by the submission. As with all claims based on subgroup analyses, the Commentary considered clarity over prespecification of the subgroups, biological rationale for variation in effect, tests for interaction between results across the subgroups, and adjustment for multiple subgroup analyses would help to establish the clinical utility of the test in the *BRCA1/2* subgroup compared to the ITT population of Cohort A. Some of these points were addressed in the pre-ESCs response, primarily with reference to the secondary outcome of progression-free survival (PFS).

The TGA delegate's overview stated that the F1CDx has "clinical utility in this setting and ...[is] an appropriate companion diagnostic for this indication". The delegate's assessment appeared to be based on an exploratory analysis (not presented in the submission) showing consistent survival outcomes for patients whose HRR status were reconfirmed using FMI F1CDx computation rules compared to the Foundation Medicine Inc HRR Clinical Trial Assay (CTA) rules used at trial recruitment. This analysis, however, did not compare outcomes of olaparib treatment in patients with and without *BRCA1/2* pathogenic gene variants, and therefore the clinical utility of the F1CDx test could not be fully established. It is important to demonstrate that the population that would have been excluded from accessing the medicine by the test result should not experience harm or forgone benefit as a consequence of not receiving the medicine after a negative test result.

#### *Comparative analytical performance*

The submission did not present any studies on the diagnostic accuracy of the proposed tests compared to a reference standard in tissue samples from mCRPC patients. The reference standard for analytical validity stated in the ratified PICO was testing of high-quality DNA obtained from fresh tissue (p2, [Application 1618 Ratified PICO](#)). The PICO also recommended the evidentiary standard test should be defined, against which the likely alternative test options (available in Australia) should be compared (p13, [Application 1618 Ratified PICO](#)). The submission did not provide any evidence to support the comparison of FFPE-extracted DNA to DNA extracted from fresh tissue.

The Commentary noted that the submission did not identify an appropriate reference standard, rather the submission stated that analytical validity may be determined using commercially available reference standard cell lines. The Commentary noted that cell lines are used to validate specific testing methods, but these are not reference standard tests (such as Sanger sequencing). In previous submissions ([MSAC 1380](#), [MSAC 1554](#)), reference standard tests identified included: 1) Sanger sequencing plus MLPA of tumour tissue and 2) repeat NGS with confirmatory Sanger sequencing of all variants. In the absence of an accepted reference standard, the analytical validity of the proposed tests (i.e. a comparison of the results of different tests against those of an accepted reference standard) could not be established.

Instead, the submission presented analytical concordance of the proposed tests versus other NGS-based methods (i.e. a comparison of the results of different tests using the same target samples).

The submission mentioned the FDA label document (although this was not provided) to support the analytical validity of F1CDx. This document included a summary of concordance studies of F1CDx and other NGS-based methods in a variety of tissue samples to assess

various genetic variants. The concordance studies presented a range of HRR variants, but did not provide separate results for *BRCA1/2* pathogenic variants. There were no references to any published studies, and none of these summaries reported sensitivity or specificity of the test to accurately detect *BRCA1/2* pathogenic gene variants in prostate tissue.

The submission included a validation report developed by the PMCC in Melbourne of the commercial QIAseq targeted DNA extended panel<sup>12</sup> for NGS. However, the Commentary highlighted that the sensitivity and specificity of the QIAseq NGS to detect *BRCA1/2* pathogenic gene variants in prostate cancer was not reported.

The submission stated the validation was an extension of the currently used *BRCA1/2* QIAseq assay to include other genes and regions. The PMCC report referred to the validation report MP-VAL-MF03B for the validation of this previous QIAseq assay, but this was not provided in the submission.

The PMCC validation report in the submission included 16 clinical and research DNA samples, with 80 known variants detected across 7 different genes. All variants were detected by the QIAseq-Illumina MiSeq® technology, with no false positives or false negatives. However, these results were not restricted to *BRCA1/2* pathogenic gene variants. Two prostate tissue samples were included, but the variant detected in these samples was ATM. *BRCA1/2* were only detected in breast and ovarian tissue (Table 9 of the validation report).

Based on this data, the submission stated that analytical sensitivity was the lower limit of detection, which was 5%. This value was later converted into a diagnostic sensitivity of 95% in the economic model. The Commentary considered that this was not appropriate. The limit of detection in chemistry is not equivalent to analytical sensitivity of the test; the higher the analytical sensitivity, the lower the detection limit but diagnostic sensitivity cannot be directly inferred from the lower limit of detection of the technology.

Further concordance analyses between QIAseq and the Familial Risk Cancer Panel (FRCP) assay (germline testing) were conducted using DNA from HapMap cell line NA12878; and between QIAseq and Comprehensive Cancer Capture (CPC) Panel (tumour testing) using the OncoSpan cell line. The submission reported 100% concordance with the 80 variants analysed.

The Commentary considered that it was also unclear whether the performance of F1CDx (the evidentiary test) would be comparable to that of QIAseq panel or the other in-house assays from PMCC, as they were not directly compared. The submission stated the PMCC has completed validation and TGA notification of its NGS testing for both *BRCA1/2* and other pathogenic gene variants in prostate cancer, but no TGA documentation was provided during the evaluation. It was also unclear which NGS test the submission referred to when stating “their NGS testing”, as the PMCC report compared the QIAseq commercial panel to two other in-house gene panels.

The Commentary noted that the analytical performance of these tests was also not evaluated in samples from patients with mCRPC. Comparison of NGS-based methods in the target tissue is important, as manufacturers use different DNA extraction and library preparation methods, which may lead to variations in quality and quantity of DNA extracted<sup>13</sup>.

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<sup>12</sup> Commercially available from QIAseq at: <https://www.qiagen.com/au/products/discovery-and-translational-research/next-generation-sequencing/dna-sequencing/somatic-panels/qiaseq-targeted-dna-extended-panels/#orderinginformation>

<sup>13</sup> McDonough SJ, Bhagwate A, Sun Z, et al. Use of FFPE-derived DNA in next generation sequencing: DNA extraction methods. Plos one. 2019;14(4):e0211400. DOI: 10.1371/journal.pone.0211400.

In summary, the Commentary highlighted that the submission:

- did not provide sufficient information on the proposed tests' sensitivity and specificity to detect *BRCA1/2* pathogenic gene variants in mCRPC tissue samples
- did not discuss the place of germline testing in the proposed algorithm, or cascade testing for family members
- did not discuss the need for additional biopsies or retesting of tumour tissue, even though results presented in F1CDx FDA label suggested lower DNA extraction pass rate and higher test failure rate for prostate compared to other tissues.

### *Prevalence*

The submission did not present any direct evidence on the prevalence of *BRCA1/2* pathogenic gene variant in Australians with prostate cancer.

The submission presented two tables with estimates of *BRCA1/2*m prevalence from several studies. These studies however were not formally assessed nor described. From these, while the submission estimated weighted average prevalence values for *BRCA1/2* pathogenic gene variants of 5.4% and 12%, these values are not used in the modelled economic evaluation, which used a prevalence of 9.7% derived from PROfound in mCRPC patients.

### *Change in management in practice*

The submission did not provide any evidence regarding other changes in clinical management associated with *BRCA1/2* pathogenic gene variant testing.

Given that around 50% of HRR gene variants detectable in tumour tissues constitute germline variants, the Commentary considered any increase in somatic testing of prostate tumour tissue would also increase: i) genetic counselling and germline testing in a patient with a positive tumour test (existing MBS item: 73302), and ii) cascade testing of family members of those shown to have a germline variant (existing MBS item: 73297). While these flow on consequences of somatic testing for *BRCA 1/2* pathogenic gene variants were noted in the submission and in the Ratified PICO 1618, the submission did not present an assessment of either the clinical utility or the cost-effectiveness of these flow-on effects.

### *Claim of codependence*

The submission claimed that identification of *BRCA* gene variants in patients with mCRPC could optimise treatment in these patients, through access to a targeted therapy and by prolonging survival in this population. The Commentary considered that the submission did not provide adequate evidence to support this claim, as all patients in PROfound (the main trial supporting the submission) had pathogenic gene variants, and no comparisons were provided against patients without the biomarker.

The Commentary noted the economic model also did not include a test and treatment structure, and costs and outcomes associated with testing were not properly incorporated into the model. Therefore, the cost-effectiveness of *BRCA1/2* testing and olaparib as codependent technologies could not be fully established.

## **12. Economic evaluation**

The submission presented a stepped economic evaluation, based on the PROfound trial, comparing olaparib and NHA (abiraterone/enzalutamide), in a population of mCRPC patients with *BRCA1/2* pathogenic gene variants who have failed previous treatment with NHA. The modelled economic evaluation was a cost-utility analysis using a partitioned survival model with three health states: progression free survival (PFS), progressed disease (PD), and death.



The modelled economic evaluation over a period of 10 years estimated an incremental cost/QALY of **\$redacted**. The Commentary considered this value did not accurately represent the ICER of olaparib in mCRPC patients with *BRCA1/2* pathogenic gene variants, for the following reasons:

- The comparator for olaparib in the model, NHA treatment, corresponded to the comparator in PROfound (olaparib versus NHA in patients who had progressed on previous NHA treatment) and was not representative of treatment in Australia as patients cannot receive a second NHA on the PBS if they have progressed on an NHA. As such, the comparison in the model does not represent a treatment sequence that will occur in Australian clinical practice. Use of data from the trial likely favoured olaparib since subsequent NHA is less likely to be effective due to cross resistance.
- Along with the key comparator issue, the lack of information provided regarding the *BRCA1/2* subgroup OS data and rPFS data used in the model does not allow for adequate consideration of the evidence. For rPFS, the submission applied values based on the *BRCA1/2* subgroup of PROfound. While this population was representative of the proposed PBS population, the submission did not provide any information on the baseline demographic and disease characteristics of this subgroup, nor did the submission provide results for analysis of the complement subgroup. Thus, the subgroup analyses were not strongly supported.
- For OS, the submission indicated that the model would be based on the *BRCA1/2* subgroup of PROfound, and that OS data would be adjusted for treatment switching. However, except for the point estimate and 95% CI for the treatment-switching adjusted analysis of OS for the *BRCA1/2* subgroup, the adjustment method used (rank preserving structural failure time model or RPSFTM), and the type of extrapolation applied, the submission provided no information on the subgroup analysis for OS that was used in the model (ie median OS, test of interaction results, subgroup complement results). In addition, the use of RPSFTM to adjust for treatment switching was not the appropriate methodology to use. The change in point estimate with adjustment for switching (HR changed from 0.63 to **redacted**<sup>14</sup>) was considerable and could not be validated. Sensitivity analysis showed the model was sensitive to use of adjustment for treatment switching, with the ICER increasing from **\$redacted**/QALY to **\$redacted**/QALY when unadjusted OS data was used.
- Costs applied in the model were not likely to be accurate. Testing costs were inappropriately applied to 67% of patients in the NHA arm to account for patients who switched to olaparib treatment in the PROfound trial. In addition, the submission did not consider germline testing in patients with a positive *BRCA1/2* somatic test, or cascade testing of family members.
- While the utility values were trial-based, they appeared high for mCRPC patients (0.7532 for progression-free survival and 0.7034 for progressed disease). The submission also applied the same utility values to olaparib and NHS-treated patients, which may not be reasonable given more AEs are expected with olaparib treatment compared to NHA. Finally, a ‘time to death’ disutility was applied (for death within 1 year, value depended on proximity to death) although the ICER was not sensitive to this variable, its use, which was not explained or justified by the submission.
- The model applied an exponential distribution to time on treatment from PROfound. The time on treatment extrapolated was sourced from the combined Cohort A and Cohort B populations, which were not representative of the claimed model population, ie patients with *BRCA1/2* pathogenic gene variants. Further, the submission’s extrapolation of time on treatment, which used an exponential distribution (no

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<sup>14</sup> Adjusted OS hazard ratio: manuscript submitted to *European Urology* for publication

justification was provided for the chosen method of extrapolation), resulted in patients being available for treatment for years longer than they were predicted to be alive by the model (2.7 years longer for olaparib-treated patients and 2.6 years longer for NHA-treated patients). While treatment costs were obviously not applied once patients were no longer alive, the extrapolation used did not seem to accurately estimate treatment duration. Further, the time on treatment that was extrapolated by the submission was based on the June 2019 data cut for PROfound, but the OS results used in the model were based on the March 2020 data cut. The submission did not justify why treatment duration from an earlier data cut was used.

- While there was an overall survival advantage for olaparib-treated patients in the PROfound trial, which was claimed to increase for the proposed *BRCA1/2* subgroup and when treatment switching was adjusted for, the estimated ICER cannot be considered accurate, given the points noted above.
- Consideration of various *BRCA1/2* and olaparib funding scenarios (test funded by MBS and treatment funded by PBS, respectively) was not possible given the submission did not provide a test and treatment model, and also given that the model assumed all patients truly had a *BRCA1/2* pathogenic gene variant.

**Table 7 ICERs and considerations of various *BRCA* testing and olaparib funding scenarios**

	<b>Proposed PBS funded olaparib in mCRPC patients who failed NHA</b>
Submission base case	Sponsor estimated ICER: \$redacted/QALY <sup>1</sup> (or \$redacted/LY) <sup>2</sup>
No MBS funded test	Not modelled. The submission assumed every patient in the model was <i>BRCA1/2</i> positive and no scenario analyses were possible.
MBS funded test: restricted to germline testing	Not modelled. The submission did not differentiate tumour and germline testing in the model.
MBS funded test: restricted to tumour testing	Not modelled. The submission did not differentiate tumour and germline testing in the model.

Source: Table 3.29, p196-197 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$35,000 to < \$45,000

### 13. Financial/budgetary impacts

While the submission stated that patient population estimates in the ratified PICO for Application 1618 were based on an incident prostate cancer population, the submission based its estimates of use on a prevalent population.

The submission stated that the literature supports the assertion that the prevalent population is the main source of patients for the requested listing because patients with prostate cancer typically progress to mCRPC over a number of years. The Commentary considered the use of a combined incident/prevalent approach to determine patient numbers may have provided more accurate estimates. The pre-MSAC response presented revised financial estimates with increased olaparib treatment duration and reduced compliance. No reasons were given for the revised estimates of net costs to the MBS.

**Table 8 Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use of BRCA1/2 testing</b>						
Number of patients tested	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>2</sup>	redacted <sup>2</sup>	redacted <sup>2</sup>	redacted <sup>2</sup>
Number of tumour tests	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>2</sup>	redacted <sup>2</sup>	redacted <sup>2</sup>
Number of germline tests	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>1</sup>	redacted <sup>1</sup>
Number of patients with a positive test result	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>Estimated financial implications of BRCA1/2 testing to the MBS</b>						
Tumour testing cost	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>
Germline testing cost	\$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 item 72860 (sample retrieval)	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>
Cost to the MBS	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>
Cost to the MBS (pre-MSAC response)	\$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 financial implications of BRCA1/2 germline and cascade testing for family members following a positive tumour test</b>						
MBS item 73302	\$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 item 73297	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>
Cost to the MBS	\$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>Net financial implications</b>						
Net cost to MBS (base case)	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>
Net cost to MBS (including germline and cascade testing)	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>	\$redacted <sup>3</sup>

Source: Table 4.2.5, p213; Table 4.2.6, p214; Table 4.5.4, p220 of the submission; worksheet '7. Net changes – MBS' of the Excel workbook 'Olaparib in mCRPC\_Section\_4\_Workbook\_Final'.

\* Added during the evaluation. The submission did not include cascade testing costs in the total MBS costs.

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> \$0 to < \$10 million

The submission's estimated net cost to Government, together with the flow-on costs to the MBS of germline and cascade testing, was \$redacted over the first 6 years of listing, and this was evenly split between PBS/RPBS costs (\$redacted) and MBS costs (\$redacted). The Commentary considered that the basis of the submission's estimate was uncertain, for the following reasons:

- Patient numbers were not likely to be accurate, given use of a prevalent population that has not been accurately defined, likely overestimation of the CRPC population, and likely overestimation of the proportion of patients who have progressed or failed on NHA treatment.
- Given the above, script numbers are also not likely to be accurate, and the accuracy of these was further impacted by the assumption that treatment will last for 227 days, which was sourced from the Cohort A + B population and therefore, potentially not representative of treatment duration in BRCA1/2 patients. The submission also assumed 95% compliance with treatment, but no source was provided for this compliance level. Further, the submission provided no explanation as to why a strategy of dose reduction was used (5% of patients had a dose reduction for the entire

treatment period), when the economic model applied a dose intensity of 91.51%. This was revised in the pre-MSAC response.

- Estimated costs for testing were based on patient numbers, which as noted above are not likely to be accurate. Further, the submission appeared to not include the test cost for the 9% of patients who do not have a tissue sample available. This would underestimate the cost.

Furthermore, the Commentary highlighted that the submission did not acknowledge the differential distribution of germline and somatic *BRCA1/2* pathogenic gene variants in mCRPC, and the potential for germline testing alone to miss out patients with somatic variants. Therefore, the need for re-biopsy and somatic testing in some patients with inadequate tissue samples may be considered. In addition, some patients might already know their *BRCA1/2* status through germline testing and may not require further testing.

As discussed in Section 6 above, the Commentary considered it may be more appropriate to consider germline *BRCA* results prior to tumour testing given germline testing is increasingly been recommended in guidelines for metastatic prostate cancer. Some patients may already know their *BRCA* status through cascade testing of germline pathogenic gene variants associated with other familial cancers and thus would require no further testing for olaparib eligibility.

The submission indicated that there will be three MBS items that will be impacted: i) a new item for tumour testing to detect pathogenic or likely pathogenic *BRCA1/2* gene variants, or an amendment to MBS item 73301; ii) a new MBS item for germline testing when tumour testing is not feasible or successful, or an amendment to MBS item 73295; and iii) a sample retrieval fee (MBS item 72860).

Although the submission conducted a sensitivity analysis to account for cascade germline testing in patients with a positive tumour test (MBS item 73302) and family members (MBS item 73297), cascade testing costs were not added to the total MBS costs (included in Table 8 during the evaluation).

The submission's estimates for MBS item 73297 imply that two family members of a patient with a positive germline test will receive testing. The submission provided no discussion around why it was assumed that only two family members will be tested, and the limitation of testing to only two family members may underestimate costs. In the PSD of MSAC Application 1411 (p8), two scenarios were assumed where genetic counselling in family members of patients with breast and/or ovarian cancer occurred at a ratio of 1 proband to 6 family members (1:6) and 1 proband to 3 family members (1:3).

The Commentary considered the results should be interpreted with caution given the likely inaccuracy of the estimated patient and test numbers.

## 14. Key issues from ESCs for MSAC

ESCs key issue	ESCs advice to MSAC
Clinical utility of <i>BRCA1/2</i> testing	The ESCs concluded that there was sufficient indirect evidence to support the clinical utility of <i>BRCA1/2</i> testing in the proposed population. The ESCs considered the PROfound trial reported a clinically meaningful improvement in overall survival for the <i>BRCA1/2</i> subgroup that was not seen for other pathogenic variants of other homologous recombination repair (HRR) genes. Additionally, the ESCs noted that the Phase II TOPARP-B trial of olaparib also showed a greater response in the <i>BRCA1/2</i> subgroup than other genetic variants. The ESCs noted that, although there was no direct evidence of clinical utility, the evidence suggested olaparib was not as effective in non- <i>BRCA</i> HRR genetic variants.
Implementation of <i>BRCA1/2</i> testing	The ESCs considered that pathology providers will be able to implement <i>BRCA1/2</i> testing as it is similar to somatic <i>BRCA1/2</i> testing already MBS-listed for high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.
Subsequent germline and cascade testing	Patients whose prostate tumour sample tests positive for a <i>BRCA1/2</i> pathogenic variant would be considered for germline testing. This could lead to consideration of cascade testing of biological relatives of patients who have a germline <i>BRCA1/2</i> pathogenic variant. Neither of these consequences were assessed in the submission. MBS item 73297 is tumour agnostic and funds cascade testing of biological relatives. The item was based on MSAC's assessment of application 1411.1 that assessed genomic testing of selected affected individuals with breast or ovarian cancer. MSAC may wish to consider whether its assessment in application 1411.1 is applicable to the current population, specifically, whether the proband's type of cancer (including difference in the prevalence of <i>BRCA1</i> and <i>BRCA2</i> pathogenic variants), age or sex might result in any difference in the likelihood of the biological relative testing positive for the identified variant and having the same predisposition risk. Additionally, MSAC may wish to consider what the health outcome and cost consequences are of adding male first-degree relatives to the cascade testing of female first-degree relatives.

### ESCs discussion

The ESCs noted that, consistent with the existing items for testing in high-grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSOC, MBS items 73301 and 73295), the two proposed MBS items were for testing prostate tumour tissue for somatic pathogenic variants of the *BRCA1/2* gene and germline testing where tumour testing was not feasible. The ESCs favoured adding new items for the mCRPC population rather than modifying these existing items. The ESCs noted that, also consistent with these items, the proposed somatic testing item was limited to once per primary tumour diagnosis. However, the ESCs queried if this was appropriate given that tumour testing can be affected by the purity of the tissue sample. The ESCs noted that, also consistent with these items, the proposed fee for both items was \$1,200. However, the ESCs queried if this was relatively large for testing of only two genes, and noted that some pathology providers charge considerably less for this service.<sup>15</sup>

The ESCs noted that *BRCA1/2* are the source of the most prevalent homologous recombination repair (HRR) pathogenic genetic variants in prostate cancer.

The ESCs noted that the United States (US) National Comprehensive Cancer Network (NCCN) and eviQ guidelines supported germline *BRCA1/2* testing after positive somatic results in prostate cancer.

<sup>15</sup> Hereditary breast and ovarian cancer (germline). Sonic Genetics website. Accessed February 9, 2021. <https://www.sonicgenetics.com.au/our-tests/all-tests/hereditary-breast-and-ovarian-cancer-germline>

The ESCs noted that the ADAR identified several laboratories that conduct *BRCA1/2* testing. The ESCs considered the proposed NGS-based testing of prostate tissue for somatic *BRCA1/2* variants was similar to existing testing of somatic *BRCA1/2* testing of ovarian cancer. The ESCs noted the National Pathology Accreditation Advisory Council (NPAAC) advice that *BRCA1/2* testing is established in a number of laboratories in Australia and that an external quality assurance is available. The ESCs concluded that pathology laboratories are in a position to offer the proposed service.

The ESCs noted that the proposed comparator for *BRCA* testing was no testing.

The ESCs noted the TGA Delegate's recommendation was to largely approve the registration of olaparib as requested, but with a limitation of the indication to patients with *BRCA1* or *BRCA2* pathogenic variants. Efficacy in the *BRCA1/2* group was mainly driven by results in patients with *BRCA2* variants; however, the delegate considered grouping of *BRCA1* and *BRCA2* was reasonable given the breadth and strength of pre-clinical and clinical evidence of sensitivity of PARP inhibitors in *BRCA1* and *BRCA2* pathogenic variants. The delegate considered that, like other rarer pathogenic variants, the relative low rate of *BRCA1* pathogenic variants in prostate cancer makes it difficult to assess responses in *BRCA1* independent of *BRCA2*.

The ESCs noted that there was a PFS benefit for Cohort A (*BRCA1*, *BRCA2* or *ATM*). The ESCs noted there was a clinically meaningful improvement in overall survival (OS) in Cohort A, but not for Cohort B (other HRR genetic variants). The ESCs noted that the gene-level analyses are complex and the comparisons may be confounded by factors such as sample size and treatment history. Additionally, the PROfound trial was not designed to test the OS benefit of olaparib at the individual gene level. However, the ESCs agreed with the pre-ESCs response that the exploratory analyses suggested that patients with *BRCA1/2* pathogenic variants derived the most benefit from olaparib. The ESCs highlighted that in the PROfound trial, a clear clinical benefit was not seen for other pathogenic HRR gene variants. The ESCs noted the pre-ESCs response reported that a test for interaction was conducted for Cohort A which supported that *BRCA1/2* status is a positive treatment effect modifier whereas *ATM* status is a negative treatment effect modifier (p-value of <0.0001), which the pre-ESCs response claimed indicated there are significant differences between the subgroups. Additionally, the ESCs noted that the Phase II TOPARP-B trial showed a greater response in the *BRCA1/2* subgroup than in patients with other genetic variants. The ESCs noted that although there was no direct evidence of clinical utility over patients with no variants, the evidence suggested olaparib was not as effective in non-*BRCA* HRR genetic variants. Therefore, the ESCs concluded that there was some indirect evidence to support the clinical utility of somatic *BRCA1/2* testing in the proposed population.

The ESCs noted that the Commentary raised the issue of discordance between germline and somatic variant status. The Commentary had noted that, when tumour testing is not possible, germline testing alone may not adequately identify all patients with *BRCA1/2* pathogenic variants. Studies suggest approximately half to more than half of detected *BRCA1/2* pathogenic variants in prostate cancer are somatic only<sup>16 17</sup> and thus would not be detected via germline testing alone. Pathogenic germline variants may also be missed by tumour testing alone. In one report, 2023 patients with cancer unselected for family history received

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<sup>16</sup> Abida W et al. Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol.* 2017 Jul;2017:PO.17.00029.

<sup>17</sup> Lang SH, Swift SL, White H, Misso K, Kleijnen J, Quek RGW. A systematic review of the prevalence of DNA damage response gene mutations in prostate cancer. *Int J Oncol.* 2019;55(3):597-616. doi:10.3892/ijo.2019.4842

germline testing and previously had tumour DNA sequencing, 8.1 percent of the pathogenic gene variants were found to have been missed by tumour sequencing alone<sup>18</sup>.

The ESCs noted that no consultation feedback was received at the time of the meeting. The ESCs noted that, with the exception of health-related quality of life, no other patient reported outcomes or patient experience outcomes were reported. The ESCs noted there may be equity of access issue for patients outside major cities.

The ESCs noted that the economic model focussed on patients with a pathogenic *BRCA1/2* variant. The ESCs noted that, although costs of testing in the olaparib arm were included based on the number needed to be tested for each olaparib-eligible patient, this approach did not allow the consideration of different testing and treatment scenarios. The ESCs noted that the economic model included testing costs for 67% patients in the comparator arm based on the proportion of patients who subsequently switched to olaparib in the PROfound trial. The ESCs considered that this was inappropriate and not addressed in the pre-ESCs response. The ESCs also noted that the model did not consider the analytical performance of *BRCA1/2* testing. The ESCs agreed with the pre-ESCs response that NGS results in few false positive or false negative results. Overall the ESCs considered that the inclusion of false positive and false negative results would not have a meaningful impact on the ICER. However, the ESCs considered that it may be worth considering whether the failure to consider repeat biopsies would have had an impact on the ICER.

The ESCs also considered that it was inappropriate that the economic model did not include germline *BRCA1/2* testing of patients with a positive somatic test.

The ESCs noted that the economic model also did not include cascade testing of biological relatives despite the known autosomal dominant inheritance pattern for germline *BRCA1/2* variants. As a result of this inheritance pattern, there may be an increased risk for any *BRCA1/2*-associated malignancy among first-degree male and female relatives of a proband. The ESCs noted that there are reasons for supporting and not supporting the inclusion of cascade testing in the assessment of this application. The ESCs noted that the pre-ESCs response argued that including the cost of cascade familial testing in the model is outside of the scope of the analysis and that the cost effectiveness of *BRCA1/2* cascade testing has been demonstrated previously. However, the ESCs recalled that MSAC supported cascade testing of *BRCA1/2* in biological relatives of probands with breast or ovarian cancer ([PSD Application No. 1411.1](#), p1). The ESCs recalled that in MSAC's consideration of Application 1411.1, the concept of 'joint production' was considered as performing genetic tests in affected individuals not only impacts their own utility or disutility values, but also those of their at-risk family members. MSAC accepted that there was a strong conceptual case to support the use of an integrated model which included the costs and effects of initially testing affected individuals and then also testing their family members according to the results of the tests for the affected individuals ([PSD Application No. 1411.1](#), p2-3). The ESCs noted that although cascade testing was not explicitly considered in the [current MSAC investigative guidelines \(Version 3.0, July 2017\)](#), the [CUC profoma](#) (p1) includes assessment of cascade testing for family members of individuals who test positive for a relevant pathogenic genetic variant, and only when this pathogenic variant is also associated with having clinical utility for the family members. The ESCs concluded that failing to extend the economic model to incorporate the question of cascade testing in the economic model was inappropriate and should be addressed with reference the Background section above.

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<sup>18</sup> Lincoln SE, Nussbaum RL, Kurian AW, Nielsen SM, Das K, Michalski S, Yang S, Ngo N, Blanco A, Esplin ED. Yield and Utility of Germline Testing Following Tumor Sequencing in Patients With Cancer. *JAMA Netw Open*. 2020 Oct 1;3(10):e2019452. doi: 10.1001/jamanetworkopen.2020.19452



The ESCs therefore considered that MSAC may wish to consider whether its assessment of *BRCA1/2* cascade testing in Application 1411.1 is applicable to the population in the current application. In its consideration of Application 1411.1, MSAC noted that the economic model did not capture the testing of parents or male children in scenario analyses and that these should be conducted, if relevant to diseases presented in future applications ([PSD Application No. 1411.1](#), p5). MSAC may wish to consider whether the proband’s histological cancer type (including difference in the prevalence of germline *BRCA1* and *BRCA2* variant, or parent of origin of the variant), age or sex result in any difference in the likelihood of the first-degree relative testing positive for the identified variant has a differential effect on their predisposition risk. Any differences observed may impact on the generalisability between cancer types of the previously modelled impact of cascade testing in breast/ovarian cancer. Additionally, MSAC may wish to consider what the health outcomes and cost consequences are of cascade testing male and female first-degree relatives separately. Table 10 outlines some of the key differences between the current application and the population considered in Application 1411.1. Further detail on the Application 1411.1 is presented in the Background section above.

**Table 10 Key differences in the population in the current application and Application 1411.1**

Characteristic	Application 1411.1	Application 1618
Proband characteristics		
Age	40 years	67 years
Sex	Female	Male
Cancer diagnosis	Breast or ovarian	Prostate
Prevalence of pathogenic variants		
<i>BRCA</i> pathogenic variant positive	15% (germline)	9.7% (tumour)
<i>BRCA1</i>	54%	10% <sup>a</sup>
<i>BRCA2</i>	46%	90% <sup>a</sup>

<sup>a</sup> The submission reported that 1.0% were *BRCA1* positive and 8.7% were *BRCA2* positive in the PROfound trial.

The ESCs noted that the pre-ESCs response reiterated that the use of a prevalence based approach was appropriate to estimate financial implications, but were not confident that the approach adopted in the submission accurately estimated the number of patients starting olaparib each year. The ESCs also considered that the financial estimates should include germline testing following a positive somatic test, and testing of biological relatives of patients with germline variants. The ESCs noted that when these flow-on costs were considered costs to the MBS accounted for 47.4% of overall financial costs to the MBS and PBS. However, the ESCs considered that these analyses did not include the complete financial impact of additional cascade testing, including the cost of preventative strategies.

## 15. Other significant factors

Nil.

## 16. Applicant comments on MSAC’s Public Summary Document

The applicant had no comment.

## 17. Further information on MSAC

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