Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1507.1 – Germline BRCA mutation testing in patients with locally advanced or metastatic HER2-negative breast cancer to determine eligibility for PBS-listed olaparib treatment

Applicant: **AstraZeneca Pty Ltd**

Date of MSAC consideration: **1–2 August 2024**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website.

1. Purpose of application

The streamlined codependent application requested:

- Medicare Benefits Schedule (MBS) listing of germline *BReast CAncer* (g*BRCA*) gene 1 and 2 variant testing in patients with human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (mBC) who have received prior (neo)adjuvant chemotherapy to determine eligibility for PBS-listed olaparib treatment; and
- Pharmaceutical Benefits Scheme (PBS) General Schedule Authority Required listing of olaparib for the treatment of HER2-negative mBC in patients with a confirmed *BRCA1* or *BRCA2* mutation.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the amendment of existing Medicare Benefits Schedule (MBS) item 73295 for the detection of germline *Breast Cancer gene 1 and 2* (g*BRCA*) pathogenic or likely pathogenic gene variants to determine access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS), in patients with metastatic breast cancer.

MSAC noted the applicant's proposed amendment was for *gBRCA* testing to determine access for olaparib, a poly-ADP ribose polymerase (PARP) inhibitor, under the PBS, in patients with metastatic breast cancer. MSAC recalled that it had previously considered g*BRCA* testing safe and effective in patients with early breast cancer and noted that the genetic testing is already well established in Australia. MSAC noted that Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of olaparib for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer and a confirmed *BRCA1/2* pathogenic variant at its July 2024 meeting.

MSAC considered timely access to testing and treatment to be important for patients and recognised the need to future-proof item 73295 to facilitate access to new relevant treatments where applicable. Therefore, MSAC supported broadening the eligible testing population beyond the criteria proposed by the applicant to include patients with "breast cancer", regardless of the type of breast cancer. MSAC also supported amending the MBS item for a broader purpose than

proposed by the applicant, such that it supports testing for "access to a relevant treatment on the PBS", rather than a "PARP inhibitor".

Table 1 Amended MBS item descriptor 73295 supported by MSAC

	Category 6 – Pathology Services **Group P7 – Genetics**
MBS item 73295 Detection of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants, requested by a specialist or consultant physician, to determine access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS), in a patient with: a) advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible; or b) breast cancer. Applicable once per lifetime. **Fee**: $1,200.00 **Benefit**: 75% = $900.00 85% = $1,101.30* (See para PN.0.23 of explanatory notes to this Category)	
Explanatory note PN.0.23 - Informed consent and genetic counselling for genetic tests Items 73297, 73300, 73305, 73334, 73339, 73340, 73393, 73394, 73417, 73418, 73440, 73441, 73442, 73443, and 73444 Prior to ordering these tests the ordering practitioner should ensure the patient (or approximate proxy) has given written informed consent. Testing should only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results. Items 73295, 73296, 73304, 73333, 73392, 73395, 73416 and 73419 Note should be taken of any relevant personal or family history that might indicate a cancer predisposition syndrome and influence the scope of germline testing that is requested. Patients who are found to have any form of affected allele 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 a clinical geneticist on referral.	

BRCA = *BReast CAncer* gene; FIGO = International Federation of Gynaecology and Obstetrics; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.
* 85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Consumer summary

This was a codependent application from AstraZeneca Pty Ltd to the Medical Services Advisory Committee (MSAC) and the Pharmaceutical Benefits Advisory Committee (PBAC). The application requested Medicare Benefits Schedule (MBS) funding for genetic testing in patients with human epidermal growth factor 2 (HER2)-negative breast cancer which has spread beyond the origin tumour. The purpose of the test is to determine if the patient has a type of breast cancer (germline *BRCA*-mutated) in order to access treatment with an oral medicine (olaparib) on the Pharmaceutical Benefits Scheme (PBS).

Breast cancer is the most commonly diagnosed cancer for females in Australia. Some patients with breast cancer have inherited (germline) *BRCA1* and *BRCA2* gene disease causing (pathogenic or likely pathogenic) variants, which can be identified by genetic testing.

Genetic testing (a type of medical test) looks at a person's deoxyribonucleic acid (DNA) for differences in genes (called genetic variants) that could explain why a person has a certain condition. A genetic variant is a permanent difference in a gene's DNA sequence. It can be

Consumer summary

inherited (called a germline variant) if it is present in a person's eggs or sperms and becomes incorporated into the DNA of cells throughout the body of the children. Or a genetic variant (called a somatic variant) can develop during the person's lifetime in the cells of the body but does not pass on DNA to children. If a variant has the potential to cause disease, it is called a pathogenic variant (if germline), or a variant of clinical significance (if somatic). Cancers are mostly caused by somatic variants. Less commonly, germline variants which predispose individuals to a higher lifetime risk of developing cancer, may be identified. If germline variants are identified in an individual, other members of their family may need to be offered testing to assess their cancer risk.

Olaparib comes from a family of medications called PARP inhibitors. Some medicines are more likely to work better if the person has certain genetic variants. In this case, drugs called PARP inhibitors, such as olaparib, work for people with disease causing variants in their *BRCA1* or *BRCA2* genes.

MBS item 73295 already supports *BRCA1* and *BRCA2* testing in patients with ovarian cancer, and from 1 July 2024 also supports testing in patients with certain subtypes of early breast cancer (triple negative breast cancer, or hormone receptor positive, HER2-negative breast cancer with high-risk characteristics). The applicant requested expanding the testing population to include patients with more advanced breast cancer (locally advanced or metastatic, HER-2 negative).

MSAC recalled that it had previously accepted germline *BRCA* genetic testing to be safe, effective and represents value for money. MSAC noted the great need for patients with advanced disease to access testing as soon as possible so that a relevant treatment (e.g., olaparib) can be started without unnecessary delay. MSAC therefore supported the expansion of the testing population to include all patients with breast cancer, rather than limiting testing to patients with certain subtypes of breast cancer.

MSAC advised that family members of patients found to have *BRCA1/2* pathogenic or likely pathogenic variants through this testing should also consider having *BRCA* testing. This is because having these pathogenic variants would mean having an increased chance of developing certain types of cancer.

MSAC supported the amendment of the MBS item description to 'determine access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS)' rather than specifying a drug or drug class, to minimise potential future delay in patients accessing new treatments. MSAC also supported modifying the descriptors for MBS items 73296 and 73927 to refer to 'one or more other relevant genes', to future proof both items from future gene list changes and avoid unnecessary treatment delay for patients.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported the amendment of existing MBS item 73295 to allow germline (inherited) *BRCA* testing to determine eligibility for a relevant treatment on the PBS, in patients with metastatic breast cancer. MSAC considered the testing to be safe, effective and good value for money, and important for people to have timely access to an appropriate treatment.

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

MSAC noted that this was a streamlined codependent application from AstraZeneca Pty Ltd seeking:

(a) MBS funding to identify germline *BRCA1* or *BRCA2* variants in patients with HER2-negative mBC who have received prior (neo)adjuvant chemotherapy to determine eligibility for access to treatment with olaparib under the PBS; and

(b) PBS funding for treatment with olaparib in patients with HER2-negative mBC and a confirmed *BRCA1* or *BRCA2* pathogenic/likely pathogenic variant.

MSAC noted that PBAC recommended the proposed PBS listing of olaparib at its July 2024 meeting. MSAC recalled it had recently supported the amendment of existing MBS item 73295 to detect *gBRCA* pathogenic or likely pathogenic variants to determine eligibility for access to PBS-subsidised olaparib in patients with hormone receptor positive, HER2-negative high-risk early breast cancer or triple negative early breast cancer (November 2023 MSAC meeting). MSAC noted the amendment was effective from 1 July 2024. MSAC noted that MBS item 73295 also supports germline *BRCA1* and *BRCA2* variant testing to determine eligibility for treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor under the PBS, in patients with ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible.

MSAC noted that the Medical Oncology Group of Australia provided positive feedback on the application citing benefits outweighed the risks associated with the testing. MSAC also noted that Medex Consulting provided input on this application as part of the consultation on the codependent PBAC submission.

MSAC noted the annual incidence of new patients with breast cancer in Australia and the various estimates used to determine the eligible patients with metastatic breast cancer. Furthermore, MSAC noted the median overall survival of patients with metastatic breast cancer. MSAC considered despite the availability of various treatment options, metastatic breast cancer remains an incurable condition.

MSAC noted that the main subtypes of breast cancer, classified by receptor status, was critical for guiding treatment decisions. MSAC noted that *BRCA 1* and *2* genes are important in DNA repairs and the presence of pathogenic or likely pathogenic variants in these genes resulted in higher risk of developing breast as well as ovarian, prostate and pancreatic cancers. MSAC noted that cancer cells with *BRCA1/2* variants are more sensitive to PARP inhibitors which exploit defects in DNA repair caused by the variants. Therefore, MSAC considered *BRCA* testing was important to identify patients at high risk of developing these cancers to allow monitoring and prophylactic treatment decision making such as determining eligibility for access to relevant therapies. MSAC noted that *BRCA* testing is also useful in determining sensitivity to carboplatin chemotherapy.

MSAC noted that g*BRCA* genetic testing was already well established in Australia. MSAC noted that safety and effectiveness had been addressed in previous g*BRCA* testing submissions and that MSAC considered g*BRCA* testing to be safe and effective.

MSAC agreed with the department's proposed changes to the item descriptor of MBS 73295 (Table 1). MSAC also supported the suggested change to Explanatory Note PN.0.23, to include 'Note should be taken of any relevant personal or family history that might indicate a cancer predisposition syndrome and influence the scope of germline testing that is requested'. MSAC noted the intent of the addition of the sentence was to remind clinicians that the most appropriate testing requested should be based on both the clinical scenario and the family history.

MSAC noted that expanding the restriction to include all breast cancers would encompass the populations proposed under the current application (mBC) and application 1716.1 (early BC considered in November 2023). This would uphold MSAC's previous advice under application 1716.1 that it was appropriate for the MBS test restriction to remain broader than the PBS treatment restriction, noting that aligning the MBS testing population and the PBS drug treatment population might lead to delay in commencement of treatment. MSAC considered timely access

to testing and treatment to be important for patients and recognised the need to future-proof item.

MSAC also noted that the proposed changes would future proof the item and ensure all breast cancer patients can access testing and treatment regardless of the subtype or stage of cancer. This approach would align with other *BRCA* testing items on the MBS, including MBS item 73296, which is open to patients with "breast cancer". It also meant that MBS item 73295 would not be restricted to patients who have received chemotherapy or to patients with "early" triple-negative breast cancer (TNBC).

MSAC agreed to amend wording for the item for a broader purpose than proposed by the applicant, such that it supported testing for 'access to a relevant treatment on the PBS', rather than a drug class, i.e., PARP inhibitor. MSAC noted this supported wording was consistent with the descriptor supported by MSAC in April 2024, under MSAC Application 1765 for the amendment of MBS items 73303 and 73304 (*BRCA1/2* variant testing in metastatic castration-resistant prostate cancer patients) to determine access to talazoparib, another PARP inhibitor.

To address the concerns raised during consultation, MSAC agreed to the department's proposed amendments to MBS items 73296 and 73297 to remove the gene lists from the item descriptors and include 'one or more other relevant genes' (Table 2). MSAC noted that this would future proof both items in the event of future gene list changed.

Table 2 Amended item descriptors for MBS 73296 and 73297 supported by MSAC

Category 6 – Pathology Services **Group P7 – Genetics**
MBS item 73296 Characterisation of germline gene variants, including copy number variation where appropriate, requested by a specialist or consultant physician: a) in genes associated with breast, ovarian, fallopian tube or primary peritoneal cancer, which must include at least: i. BRCA1 and BRCA 2 genes; and ii. one or more ~~STK11, PTEN, CDH1, PALB2 and TP53~~ other relevant genes; and b) in a patient: i. with breast, ovarian, fallopian tube or primary peritoneal cancer; and ii. for whom clinical and family history criteria place the patient at greater than 10% risk of having a pathogenic or likely pathogenic gene associated with breast, ovarian, fallopian tube or primary peritoneal cancer Once per cancer diagnosis **Fee**: $1,200.00 **Benefit**: 75% = $900.00 85% = $1,101.30* (See para PN.0.23 of explanatory notes to this Category)

MBS item 73297

Characterisation of germline gene variants, including copy number variation where appropriate, requested by a specialist or consultant physician:

a) in genes associated with breast, ovarian, fallopian tube or primary peritoneal cancer, which may include the following genes:
   i. BRCA1 or BRCA2;
   ii. ~~STK11, PTEN, CDH1, PALB2 and TP53~~ one or more other relevant genes; and
b) in a patient:
   i. who has a biological relative who has had a pathogenic or likely pathogenic gene variant identified in one or more of the genes mentioned in paragraph (a); or
   ii. who has not previously received a service to which item 73295, 73296 or 73302 applies

Once per variant

Fee: $400.00 **Benefit:** 75% = $300.00 85% = $340.00

(See para PN.0.23 of explanatory notes to this Category)

BRCA 1/2 = *BReast Cancer 1/2* gene; MBS = Medicare Benefits Schedule;
MSAC's supported changes included using green font text and strikethrough
* 85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

MSAC noted that the department's proposed changes would mitigate the need for future codependent MSAC applications, in the event of future changes to the PBS restrictions for relevant treatments. It would also address the delay for patients between PBS listings and MBS listings.

MSAC noted that the costs associated with testing presented in the submission ($10 million to < $20 million in Year 1 to $20 million to < $30 million in Year 6) were underestimated as the submission did not consider the costs of cascade testing. MSAC noted that the revised estimates by the department to include cascade testing were ($10 million to < $20 million in Year 1 and increasing to $20 million to < $30 million in Year 6 (Section 14, Table 18). MSAC considered that expanding item 73295 beyond the applicant's proposal, such that it includes all patients with "breast cancer", may lead to a marginal increase in claims; however, MSAC noted that the utilisation was low relative to items 73296 and 73297 and that the likely financial impact would also be low.

4. Background

MSAC has not previously considered g*BRCA* testing in patients with locally advanced or metastatic HER2-negative breast cancer to determine eligibility for PBS-listed olaparib treatment. MSAC's PICO Advisory Sub-committee (PASC) first considered the original application (MSAC 1507[2]) in December 2017, with the subsequent ratification of a PICO Confirmation[1] in January 2018. However, the applicant did not submit any assessment report and the application did not progress further.

MSAC however, had previously considered germline *BRCA1/2* testing to determine eligibility for access to PBS-subsidised adjuvant olaparib in patients with HER2-negative early breast cancer (eBC) (Application 1716[1]) in March and November 2023. MSAC considered the genetic testing safe, effective and good value for money and supported the expansion of MBS item 73295 to

[1] MSAC application 1507 PICO confirmation available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/D7C6D4F0118A502BCA2581AA0019BD60/$File/1507_PICOConfirmation-FINAL.pdf

include patients with people with early TNBC) or hormone receptor (HR)-positive, HER2-negative eBC with high-risk characteristics of high-grade tumour, to determine if they can access olaparib on the PBS (p3, 1716[1] PSD November 2023 MSAC meeting). The recommended amendment was implemented on 1 July 2024 (Table 3).

MSAC also considered and supported tumour *BRCA1/2* testing (and germline testing where tumour testing is not feasible) to determine eligibility for olaparib for the treatment of ovarian cancer (Applications 1380[3] and 1554[4]). MSAC recognised that g*BRCA* testing would not identify all women who could benefit from olaparib therapy. However, the lack of evidence on the performance of somatic *BRCA* testing, the incompleteness of the Study 19 *BRCA* testing data (the results of both germline and somatic *BRCA* testing were known for only 157/265 (59%) of the study participants), and the inadequate evidence for improved olaparib outcomes for women with an identified somatic *BRCA* variants only, argued against support for funding somatic *BRCA* testing at that stage. Subsequently, MSAC supported funding of somatic *BRCA* testing (Application 1554 PSD July 2020 MSAC meeting) as MSAC considered that it was biologically plausible that women with a somatic or germline *BRCA* pathogenic variant would each have an improved response to olaparib over women without any *BRCA* pathogenic variant, that is, clinical utility was expected regardless of where the *BRCA* pathogenic variant originated.

The Department of Health and Aged Care also received an application requesting MBS funding for *gBRCA* testing to determine eligibility for talazoparib, also a PARP inhibitor, treatment in patients with locally advanced or metastatic HER2-negative breast cancer (MSAC application 1568[2]) but the application did not progress further.

5. Prerequisites to implementation of any funding advice

Test

The submission stated that g*BRCA* testing is well established in Australia for patients with breast, ovarian and prostate cancers and reimbursed under MBS item 73296. It is anticipated that increasingly, patients with recurrent mBC will already know their *BRCA* status following testing in the early setting due to the positive recommendation for olaparib in high-risk eBC.

There is no single provider of *BRCA* gene variant testing in Australia. There are several different Australian molecular pathology service providers that offer g*BRCA* testing and more recently, tumour *BRCA* testing on a commercial basis. Germline *BRCA* testing is available to patients in all States and Territories of Australia via multiple labs located in Queensland, New South Wales, Victoria, South Australia and Western Australia as part of existing ovarian or breast cancer panels. Consequently, more patients will be detected by testing, leading to more equitable access to olaparib for patients with HER2-negative mBC.

BRCA testing is well established in a number of laboratories in Australia with external quality assurance available through the European Molecular Genetics Quality Network (1716 PSD November 2023 MSAC meeting[1]).

[2] MSAC Application 1568 available at MSAC http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1568-public

The TGA-approved Product Information for olaparib states that:

> Companion diagnostic (CDx) testing using an in vitro diagnostic (IVD), including notified assays performed by a NATA accredited laboratory, is essential for the use of olaparib to be safe and effective in indications that are BRCA and/or HRD specific. Where specified in the indication, confirmation of the relevant BRCA mutation (BRCAm) or HRD status must be obtained prior to initiating treatment (p2, Olaparib PI, February 2024).

In the pivotal OlympiAD trial (NCT02000622), germline *BRCA* mutation was detected by central testing with BRCAAnalysis (Myriad Genetics) in 297 patients and by local testing in 167 patients (with confirmation by central testing with BRCAAnalysis in all but 5 of those patients.[3]

Codependent drug

Olaparib is TGA-registered (Olaparib Product Information[4]) as monotherapy in breast cancer for:

- adjuvant treatment of adult patients who have HER2-negative, high-risk early breast cancer with a deleterious or suspected deleterious germline *BRCA* mutation (g*BRCA*m), for which they have previously been treated with neoadjuvant or adjuvant chemotherapy.
- treatment of adult patients who have HER2-negative mBC with a deleterious or suspected deleterious germline *BRCA* variant (g*BRCA*m), for which they have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

Olaparib is also registered as monotherapy or as part of combination therapy in indications for ovarian cancer, adenocarcinoma of the pancreas and prostate cancer.

6. Proposal for public funding

Table 3 presents the current item descriptor for MBS 73295 (including newly implemented changes from 1 July 2024) and the proposed amendments. Table 4 presents the proposed amendment in the submission, based on item descriptor prior to 1 July 2024.

[3] Robson M, et al. (2017) Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med*. Aug 10;377(6):523-533. doi: 10.1056/NEJMoa1706450. Epub 2017 Jun 4. Erratum in: *N Engl J Med*. 2017 Oct 26;377(17):1700. doi: 10.1056/NEJMx170012. PMID: 28578601.

[4] https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01771-1&d=20240703172310101

Table 3 MBS 73295 - current item descriptor (w.e.f. 1 July 2024), the applicant's proposed amendment (underlined) and the department's proposed amendment (red texts)

Category 6 – Pathology Services	
MBS item 73295	**Group P7 – Genetics**
Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, requested by a specialist or consultant physician, to determine eligibility for treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor under the Pharmaceutical Benefits Scheme (PBS), in a patient with: a) advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible; or b) triple negative early breast cancer; or c) hormone receptor positive, HER2-negative, early breast cancer with one or more high-risk characteristics; or d) HER2-negative metastatic breast cancer who has received prior (neo)adjuvant chemotherapy; or e) de novo metastatic HER2-negative breast cancer. Applicable once per lifetime. Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,101.30* (See para PN.0.23 of explanatory notes to this Category)	

Source: MBS online (accessed 9 July 2024).
Underline indicates text proposed by the submission
MBS = Medicare Benefits Schedule; w.e.f. = with effect from.
* 85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Table 4 Proposed amendment (red texts) of MBS item 73295 in the submission, based on item descriptor prior to 1 July 2024

Category 6 – Pathology Services	
MBS item 73295	**Group P7 – Genetics**

Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with:
• advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible; or
• HER2-negative metastatic breast cancer who have received prior (neo)adjuvant chemotherapy
• triple negative early breast cancer; or
• hormone receptor positive, HER2-negative, early breast cancer with at least one of the following high-risk characteristics:
  ○ tumour histological grading of at least 3; or
  ○ tumour size of greater than 2 cm; or
  ○ one or more axillary lymph node metastases
requested by a specialist or consultant physician, to determine eligibility for treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor under the Pharmaceutical Benefits Scheme (PBS)
Maximum of one test per patient's lifetime.	

Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,101.30*	
Explanatory note PN.0.27 Patients who are found to have any form of affected allele 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 a clinical geneticist.	

Red font text indicates proposed amendment in the submission.
Source: Table ES 3, page iv of OlympiAD Executive Summary FINAL.
MBS = Medicare Benefits Schedule.
* 85% benefit reflects the 1 November 2023 Greatest Permissible Gap (GPG) of $98.70. All out-of-hospital Medicare services that have an MBS fee of $658.35 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Underlined text indicates proposed amendment; red font indicates text added during evaluation

The submission proposed an amendment of MBS item 73295 to include patients with HER2-negative mBC who has received prior (neo)adjuvant chemotherapy for g*BRCA* testing to determine eligibility for a PARP inhibitor under the PBS.

The commentary noted that the proposed amendment of item descriptor did not specifically include patients with HER2-negative *de novo* mBC, which appeared to be an error, since the *de novo* population would also require access to the *BRCA* test if olaparib is recommended for PBS listing for these patients and these patients would not have received prior (neo)adjuvant chemotherapy. Therefore, the department proposed amendments to the descriptor to include *de novo* metastatic HER2-negative breast cancer (Table 3).

The proposed MBS item descriptor indicated that only patients with HER2-negative mBC and have received prior (neo)adjuvant chemotherapy would be eligible for the MBS item, i.e. the patient would require a HER2-negative test result to be eligible for the proposed g*BRCA* test. The MSAC 1507 PICO Confirmation indicated that testing for HER2 status was a prior test.

The submission proposed a test cost of $1,200, which was consistent with the test cost proposed in the 1716 PSD March 2023 MSAC meeting[1] for *BRCA* testing in eBC. The proposed MBS listing would likely increase the number of people eligible for *BRCA1/2* testing on the MBS, but the submission assumed that many patients (ranging from redacted% to redacted% in Years 1 to 6 of listing) would already know their *BRCA* status prior to the metastatic setting (Table 17).

The 1716 PSD March 2023 MSAC meeting[1] noted that an increase in volume of testing using next generation sequencing (NGS) method may result in reduction in the average cost of testing due to a lower sequencing cost achieved when samples are run at maximum flow cell capacity. However, MSAC noted that MBS item 73295 still had a fee of $1,200, and that the department was investigating whether a fee of $1,000 or $1,200 would be more appropriate. MSAC acknowledged that *BRCA1/2* are large genes and the cost of testing could be higher than smaller genes. MSAC noted stakeholder feedback that a fee of $1,200 was more appropriate and better reflected the costs involved in undertaking the assay and necessary reporting requirements. MSAC also acknowledged that supporting an insufficient fee could result in out-of-pocket costs to consumers. MSAC considered that if a fee of $1,200 were accepted for this application that the fee for item 73304 might need to be reconsidered to align the two.

The submission stated that g*BRCA* testing informed patients of familial risk and facilitated cascade testing for unaffected family members. The commentary noted that the submission did not include consideration of cascade testing.

7. Population

The submission's proposed test population was patients with HER2-negative disease with mBC who have received prior (neo)adjuvant chemotherapy.

Clarification from the sponsor received during the PBAC evaluation stated that the requested population included two populations:

- Population 1 (no prior chemotherapy for mBC) includes patients who received chemotherapy (anthracycline/taxane) in an early disease setting (neoadjuvant or adjuvant) prior to progressing to the metastatic disease setting. These patients may receive 1L olaparib treatment, thus keeping in line with the TGA approved indication for olaparib treatment; and
- Population 2 (*de novo* mBC) includes patients who have metastatic disease at the time of first diagnosis. This population still require some form of chemotherapy (anthracycline/taxane) prior to receiving olaparib treatment in order to remain in line with the TGA indication. As such, the submission proposed that these patients will be required to receive chemotherapy

(anthracycline/taxane) as 1L treatment for mBC and subsequently should receive 2L olaparib treatment. The submission claimed that clinicians would appreciate the flexibility to initiate treatment with olaparib in *de novo* patients without the need to first prescribe chemotherapy *The Pharmaceutical Benefits Advisory Committee (PBAC) Economics Sub Committee (ESC) did not consider it appropriate to initiate olaparib treatment in patients who had not received prior chemotherapy, a use not supported by the current evidence (para. 1.5, Olaparib ESC ADV 07-2024).*

MSAC application 1507[1] was considered at the 8 December 2017 PICO Advisory Sub-Committee (PASC) meeting, however the MSAC application was not previously considered by MSAC ESC or MSAC. The requested population in the current submission specified that patients must have received no prior chemotherapy in the metastatic setting. Whereas the population in the ratified MSAC 1507 PICO Confirmation required that patients had received chemotherapy (taxane or anthracycline) in the neoadjuvant, adjuvant or metastatic setting (consistent with the TGA indication).

The MSAC 1507 PICO Confirmation[1] included the clinical management algorithm presented in Figure 1.

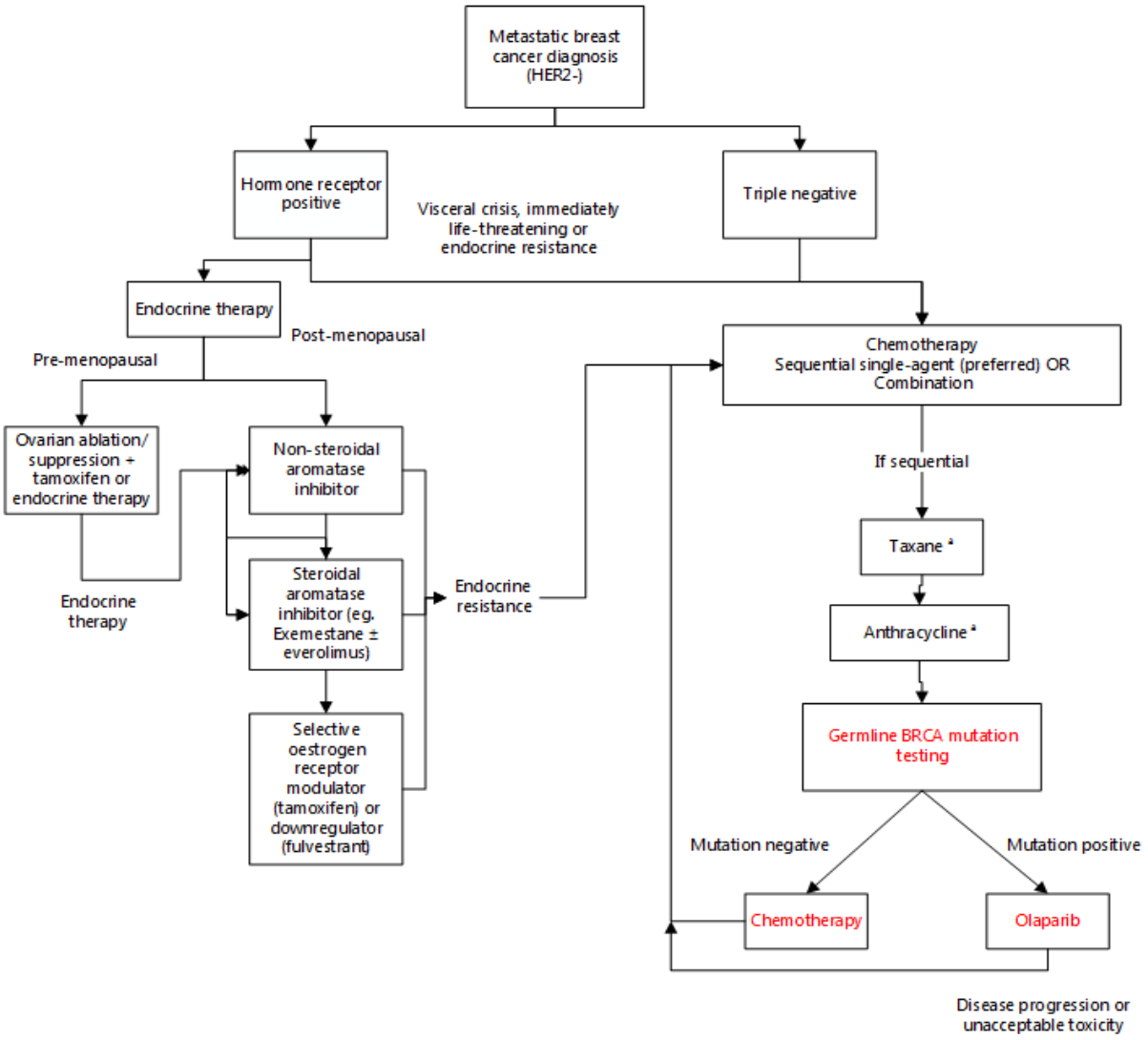

Figure 1 Proposed clinical treatment algorithm in the MSAC 1507 PICO Confirmation

Source: Figure 2, p15 of 1507 PICO confirmation.

However, the commentary noted that treatment had evolved since 2017, with the advent of CDK4/6 inhibitors for hormone receptor positive (HR+) disease and of targeted therapies such as pembrolizumab plus chemotherapy and sacituzumab govitecan in TNBC. The submission presented the following proposed clinical management algorithms, but they only represent management for patients after they have tested positive for *BRCA 1/2* variants. This is further discussed in the comparator section below.

Figure 2 presents the submission's proposed treatment algorithm for HER2-negative g*BRCA*m mBC patients with no prior chemotherapy in the metastatic setting (but who have previously had (neo)adjuvant chemotherapy). The submission stated the algorithm aligns with the European Society of Medical Oncology (ESMO) treatment guidelines (ESMO Living Guidelines May 2023) prepared by Curgliano 2023[5] and ASCO guidelines (Al Sukhun 2024)[6] , for this patient group. The commentary noted this was not entirely accurate. In HR+ patients, except in the case of risk of organ failure, chemotherapy is not recommended as a second line option, which was inconsistent with both the nominated comparator and the comparator in the pivotal OlympiAD trial.

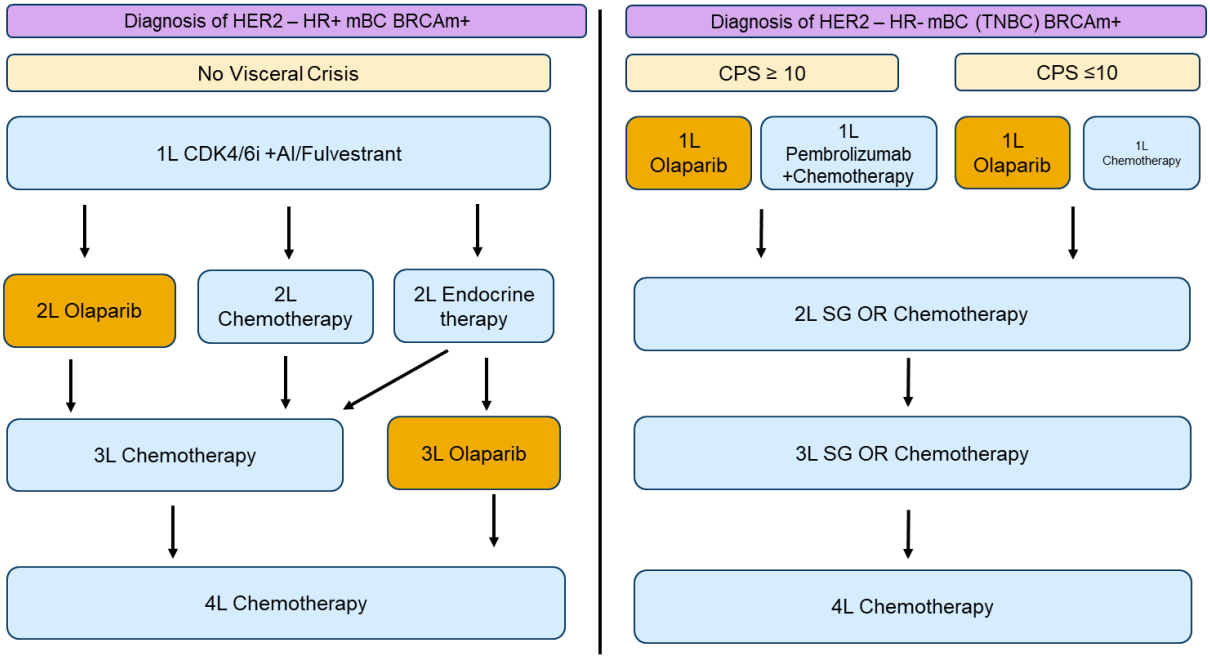

Figure 2 Submission's proposed treatment algorithm for HER2- g*BRCAm* mBC in patients with no prior chemo in mBC

Source: Figure 1.3, p28 of the submission.
1L = 1st Line; 2L = 2nd Line; 3L = 3rd Line; 4L = 4th Line; AI = Aromatase inhibitor; BRCAm+ = BReast Cancer gene mutated; CDK4/6i = CDK4/6 inhibitors; CPS = combined positive score; Fulv = Fulvestrant; HER2- = human epidermal growth factor 2; HR+ = hormone receptor positive ;; HR- = hormone receptor negative; mBC = metastatic breast cancer; SG = Sacituzumab Govitecan; TNBC = triple negative breast cancer.

Figure 3 presents the proposed treatment algorithm for patients with *de novo* mBC with a g*BRCA*m in the submission.

[5] Curigliano et al (2023). ESMO Metastatic Breast Cancer Living Guidelines, v1.1 May 2023, https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline.
[6] Al Sukhun S, et al (2024). Systemic Treatment of Patients With Metastatic Breast Cancer: ASCO Resource-Stratified Guideline. *JCO Glob Oncol*. Jan;10:e2300285

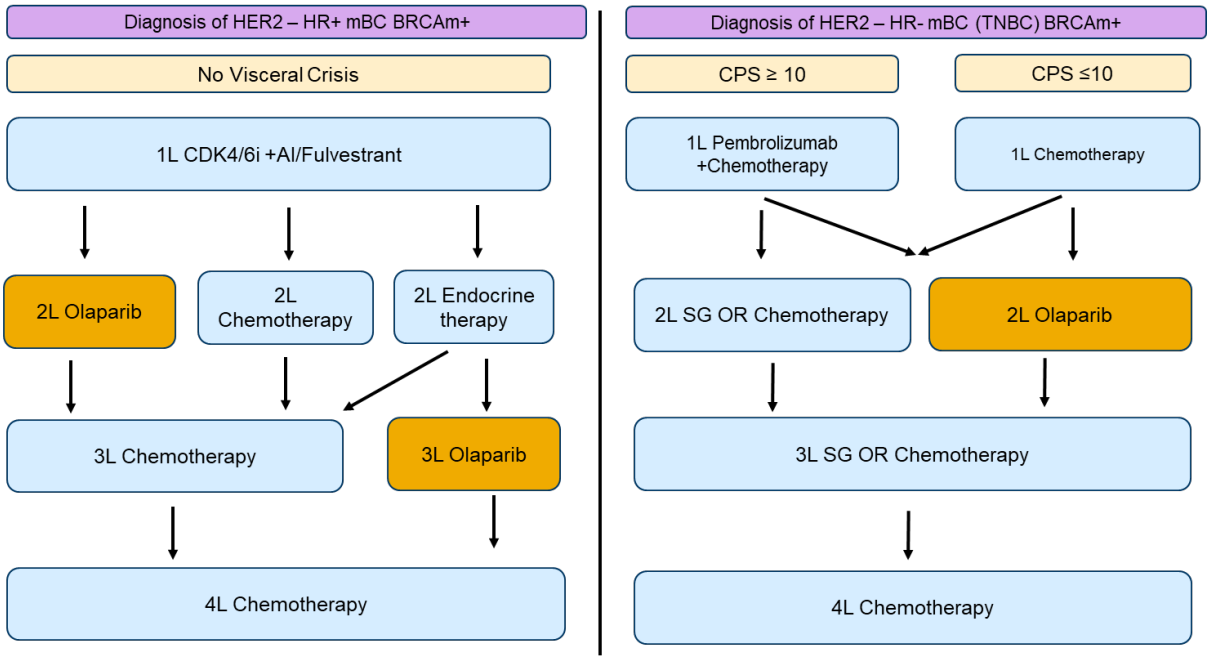

Figure 3 Proposed treatment algorithm for patients with *de novo* metastatic breast cancer with g*BRCA*m in the submission

Source: Figure 1.4, p28 of the submission.
1L = 1st Line; 2L = 2nd Line; 3L = 3rd Line; 4L = 4th Line; AI = Aromatase inhibitor; BRCAm+ = BReast Cancer gene mutated; CDK4/6i = CDK4/6 inhibitors; CPS = combined positive score; HR+ = hormone receptor positive; HR- = hormone receptor negative; mBC = metastatic breast cancer; SG = Sacituzumab Govitecan; TNBC = triple negative breast cancer.

8. Comparator

Test

The comparator nominated by the submission was no test. *This was appropriate*.

In the context of eBC, (Application 1716) the MSAC Executive noted that g*BRCA* testing under the MBS item 73296 is available for patients only when somatic testing is unavailable (based on MBS items 73295 and 73304) and "for whom clinical and family history criteria (as assessed, by the specialist or consultant physician who requests the service, using a quantitative algorithm) place the patient [with breast cancer] at greater than 10% risk of having a pathogenic or likely pathogenic gene variation". In Australia, many Genetic/Familial Cancer Centres use the criteria outlined in the eviQ Guidelines (eviQ Guidelines for genetic testing for heritable variants in the *BRCA1* and *BRCA2* genes, 2020), to identify suitable candidates for g*BRCA* pathogenic or likely pathogenic variant testing for the purpose of familial cancer risk assessment. The eviQ guidelines currently recommend *BRCA* pathogenic or likely pathogenic variant testing for the purpose of familial cancer risk assessment in individuals with a greater than 10% probability of carrying a pathogenic or likely pathogenic variant, based on their personal or family history of cancer. Therefore, the MSAC Executive advised that for the proposed population of patients with "triple negative early breast cancer or hormone receptor positive, HER2-negative, early breast cancer with high risk characteristics", no *BRCA1/2* testing would be a comparator. MSAC noted that germline and somatic *BRCA1* and *BRCA2* testing is used in routine clinical practice for patients with a number of cancers, including breast, ovarian and prostate and sequencing is already funded under the MBS items 73295, 73296, 73304 and single variant testing under MBS items 73297 (cascade) and 73302 (somatic positive) (1716 PSD November 2023 MSAC meeting).

Codependent drug

The comparator nominated for olaparib in the submission and the ratified PICO both considered standard of care as the comparator, but the ratified PICO specified that 'capecitabine, vinorelbine and eribulin are commonly used agents'.

The commentary considered that standard of care was a reasonable comparator, but chemotherapy may not be the most representative treatment for standard of care in the proposed populations. Newer treatment options have become standard of care for certain subgroups of mBC patients, as discussed below.

The submission proposed the place in therapy for olaparib as follows:

- In patients who may have received chemotherapy (anthracycline/taxane) in an early disease setting (neoadjuvant or adjuvant) prior to progressing to metastatic disease setting, olaparib will be used as first line (1L) prior to treatment with chemotherapy; and
- In *de novo* mBC patients who have metastatic disease at time of first diagnosis, these patients are required to receive chemotherapy (anthracycline/taxane) as 1L treatment for mBC and subsequently should receive (second line) 2L olaparib treatment.

The submission claimed that currently in the HR+ population, treatment with CDK 4/6 inhibitors (e.g. abemaciclib, palbociclib, ribociclib) in combination with endocrine therapy is the standard of care. Upon progression, treatment moves to chemotherapy, or, less commonly in Australia, on to everolimus with exemestane, or fulvestrant in the second line, and olaparib would be an option in this line of therapy. The commentary considered that this was not consistent with the European Society of Medical Oncologists (ESMO) guidelines (Curgliano 2023, p1481) which recommend at least two lines of endocrine therapy before initiating chemotherapy, and do not recommend chemotherapy directly after first line CDK 4/6 inhibitors for patients not at risk of imminent organ failure. The American Society of Clinical Oncologists (ASCO) guideline recommendations (Al Sukhun 2024) are generally consistent with those from ESMO. As such, chemotherapy may not be the standard of care after progression with first line CDK 4/6 inhibitors unless the patient was at risk of imminent organ failure. Instead, a second line of endocrine therapy was the standard of care and would be the comparator for olaparib in these patients.

After endocrine therapy has failed, single agent chemotherapies are then used sequentially, and olaparib would also be an option in this line of therapy.

The submission also noted that a small contingent of HR+ patients may receive first line chemotherapy, if they are in visceral crisis, however, the submission did not include this in the algorithm as the requested population in the submission was limited to patients who have not previously received treatment with chemotherapy in the metastatic setting.

For patients with TNBC, pembrolizumab plus chemotherapy is used in patients with a combined positive score (CPS; a marker of PD-L1 status) of 10 or above, otherwise single agent chemotherapy is given in the first line. The submission proposed that olaparib may be an option in this line of therapy. As such, the commentary considered that pembrolizumab plus chemotherapy would be the most relevant comparator in patients with TNBC, CPS ≥10 and *BRCA*m.

The submission stated that there does not seem to be any correlation between *BRCA* status and PD-L1 status (Sobral Leite 2018[7], Turulijic 2017[8]), and considered it likely that there will be patients with both biomarkers. The submission stated that international guidelines recommend pembrolizumab plus chemotherapy for PD-L1 positive patients and olaparib for *BRCA*m patients; however current guidelines do not make a recommendation of one over the other when both alterations occur. Specifically, the ASCO guidelines do not explicitly make a recommendation in this case. The commentary noted, however, that the ESMO guidelines only recommend PARP inhibitors in g*BRCA*m PD-L1 negative patients, which may suggest that pembrolizumab would be preferred in all CPS >10 patients.

In TNBC, the submission considered that the first line of therapy currently reimbursed is chemotherapy for the majority of patients where the current chemotherapy regimens are usually a taxane (e.g., paclitaxel or nab-paclitaxel or docetaxel) or carboplatin or doxorubicin as monotherapy or combinations of carboplatin + gemcitabine, doxorubicin + cyclophosphamide, or epirubicin + cyclophosphamide. The commentary observed that these chemotherapies differed to those used in the pivotal OlympiAD trial (capecitabine, vinorelbine and eribulin) and may represent an applicability issue.

In patients with *de novo* mBC, at least one line of chemotherapy must be used before patients can be eligible for olaparib based on the requested restriction and TGA approved indication. In this case, olaparib will become a 2L therapy. Notably, in patients with *de novo* TNBC who have failed 1L chemotherapy (with or without pembrolizumab, depending on CPS), sacituzumab govitecan may be used. Eligibility for sacituzumab govitecan requires at least one line of prior systemic therapy in the metastatic setting and can therefore be used in the second or third line setting. The commentary therefore concluded they both would be a valid comparator for olaparib in both lines of treatment.

Following treatment with sacituzumab govitecan, chemotherapy remains the mainstay of treatment for triple negative patients. The commentary supposed that it is plausible that olaparib may be used in this line of therapy (i.e. after pembrolizumab plus chemotherapy and sacituzumab govitecan, as third line therapy) in which case, chemotherapy may be the relevant comparator.

Overall, given the evolution of treatment options in recent years, the commentary considered that the proposal to use chemotherapy as the proxy for standard of care for all patients eligible for olaparib under the proposed PBS listing was likely unreasonable. For a proportion of patients, a second line endocrine therapy (after CDK 4/6 inhibitors and endocrine therapy), pembrolizumab plus chemotherapy (TNBC with CPS ≥10) or sacituzumab govitecan (as second or third line therapy in *de novo* patients with TNBC) were also comparators which should have been considered based on the proposed population. *The PBAC ESC noted multiple issues with the nominated comparator of chemotherapy.*

9. Summary of public consultation input

Consultation input to the application was received from one (1) professional organisation, the Medical Oncology Group of Australia (MOGA), who was supportive of Application 1507.1.

[7] Sobral-Leite M, et al (2018). Assessment of PD-L1 expression across breast cancer molecular subtypes, in relation to mutation rate, BRCA1-like status, tumor-infiltrating immune cells and survival. *Oncoimmunology*. Sep 11;7(12):e1509820

[8] Turajlic S, et al (2017). Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis. *Lancet Oncol*. Aug;18(8):1009-1021.

Medex Consulting provided feedback on the proposed amendment to MBS Item 73295 to allow germline *BRCA1/2* testing to determine eligibility for a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor in metastatic breast cancer.

Benefits

- Knowing the germline *BRCA1/2* P/LP variant status of a patient diagnosed with breast cancer is essential to determining whether they might benefit from olaparib.
- Olaparib has been shown to be more efficacious and to result in better quality of life than standard of care chemotherapy in patients with metastatic breast cancer in the setting of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic germline variant (OlympiaD trial).
- Testing will result in more breast and ovarian cancers prevented (through surgical interventions/preventative medications) or detected early in family members of patients.

Disadvantages

- Psychological harm from germline genetic testing
- Increased difficulty obtaining some types of insurance
- Negative impact on family members and relationships

Additional comments

MOGA believes the benefits of funded germline genetic testing for *BRCA1* and *BRCA2* in the setting of access to funded adjuvant olaparib substantially outweigh the disadvantages, and commented that patients will receive pre-test counselling from their oncologist or genetics service which will enable them to make informed decisions about whether testing is right for them personally.

In relation to the proposed population, MOGA noted inconsistencies between the application's title on MSAC website (includes locally advanced breast cancer) and the application (which includes metastatic breast cancer only). MOGA considered that the population for the proposed medical service should include patients with metastatic disease and those with locally advanced disease.

Medex Consulting responded to proposed amendments to the current MBS item 73295 to expand the population eligible for germline *BRCA1/2* testing to include patients with metastatic HER2-negative breast cancer (who have received prior (neo)adjuvant chemotherapy) to allow access to a PARP inhibitor in the metastatic setting. The proposed amendments were:

- Remove the requirement to have received prior chemotherapy – to allow for earlier testing, to reduce delay of timely access to a PARP inhibitor (current delays in accessing already constrained genetic testing services in Australia or appointment for genetic testing);
- Remove the word "early" from "triple negative early breast cancer" – to make any patient with triple-negative breast cancer eligible for genetic testing regardless of their disease stage at diagnosis.
- Include in the explanatory note that "Note should be taken of any relevant personal or family history that might indicate a cancer predisposition syndrome and influence the scope of germline testing that is requested." The rationale was to avoid duplication of testing or the patient missing out on the broader testing for the ovarian and/or breast cancer predisposition genes that MBS Item 73296 allows following an uninformative testing of *BRCA1* and *BRCA2* genes per MBS Item 73295.

Medex Consulting also proposed the following changes for MBS item 73296 under *a) in genes associated with breast, ovarian, fallopian tube or primary peritoneal cancer, which must include at least:*

(i) ***BRCA1 and BRCA 2 genes****; and*
(ii) one or more ***ATM, BARD1, BRIP1, CDH1, CHEK2, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D,*** *STK11,* ~~***PTEN, CDH1, PALB2***~~ *and TP53 genes.*

10. Characteristics of the evidence base

The submission was based on one trial, OlympiAD, an open label randomised controlled trial which compared olaparib (n=205) to chemotherapy (n=97). Patients had a confirmed deleterious or suspected deleterious g*BRCA* variant and HER2-negative mBC, and had received no more than two previous chemotherapy regimens for metastatic disease. Patients had been previously treated with chemotherapy (including anthracycline (unless contraindicated) and a taxane) in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone-receptor-positive breast cancer had received at least one endocrine therapy (adjuvant therapy or therapy for metastatic disease) and had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate.

The submission also focused on the subgroup of patients who had not received prior chemotherapy for mBC (n=87, of which 59 were randomised to olaparib and 28 were randomised to chemotherapy). The submission assumed that this subgroup was representative of the requested population for treatment.

The commentary considered that, based on the populations clarified by the sponsor, the subgroup of patients with no prior chemotherapy for mBC would only be applicable to Population 1. The requested restriction for Population 2 required patients to have received previous chemotherapy in the metastatic setting. The submission proposed that efficacy of olaparib from the no prior chemotherapy subgroup in the OlympiAD trial could be used to inform the treatment effect in the *de novo* subgroup in the economic model. It may have been more appropriate to apply the treatment effect from the whole trial population (up to two lines of prior chemotherapy in metastatic setting) or the prior chemotherapy subgroup.

Results from three data cut-offs (DCO) were reported: the Primary progression-free survival (PFS) DCO on 9 December 2016 (at around 230 PFS events, median follow-up 14.1-14.5 months), the final overall survival (OS) DCO on 25 September 2017 (at around 190 OS events, median follow-up 15.5-18.9 months) and the Extended OS DCO on 17 November 2019 (included longer follow-up of patients previously censored at final OS DCO, although median follow-up was unchanged at 15.5-18.9 months).

Results were presented for the full analysis set (FAS) (N=302) which included all patients who were randomised into the study, regardless of treatment actually received. The safety analysis set (N=296) included all patients who received at least one dose of randomised study drug.

The key features of the included evidence are summarised in Table 5.

Table 5 Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Olaparib versus SoC						
OlympiAD (ITT)	302	R, OL, 14-19 months[c]	*Low* [a]	*BRCA* mutation HER 2-, who received no more than two previous chemo regimens for metastatic disease	OS, PFS	OS, PFS1, PFS2
OlympiAD (no prior chemo subgroup)	87	R, OL	*High* [b]	*BRCA* mutation HER 2-, who received no prior chemo regimens for metastatic disease	OS, PFS	OS, PFS1, PFS2

Source: pp44-50 of the submission.
BRCA = *BReast CAncer gene;* HER2 – human epidermal growth factor receptor type 2; ITT = intention to treat; OL = open label; OS = overall survival; PFS1 = progression-free survival; PFS2 = time to second progression or death; R = randomised; SoC = standard of care.

[a] primary outcome of PFS was based on blinded review and secondary outcome of OS unlikely to be affected by open label status

[b] high risk of bias due to imbalances between baseline characteristics, small sample size and lack of statistical adjustment for subgroup analysis

[c] duration of follow-up for the no prior chemotherapy subgroup (Final OS analysis) was 22.1 months in the olaparib arm and 14.1 months in the chemotherapy arm

The submission claimed that reimbursement was sought for the subgroup of patients who derived the most benefit based on the OlympiAD trial (patients who have not received chemotherapy in the metastatic setting) and the subgroup of patients with the greatest unmet clinical need (i.e. *de novo* mBC patients). The commentary stated that it was unclear why the submission claimed *de novo* mBC patients had the greatest unmet clinical need. File 2022[9] reported that *de novo* mBC patients had longer median OS than recurrent mBC patients by nine months (median 36.4 vs 27.4 months, p<0.001). The submission claimed that the *de novo* metastatic and the patients with no prior chemotherapy in the metastatic setting are the least pretreated populations and could therefore be assumed to exhibit similar outcomes.

In the OlympiAD trial, 38 of 302 patients in the whole trial population had *de novo* mBC (12.6%). The submission claimed that it was not possible to separately model the *de novo* metastatic population due to limited data to input in the model. The commentary considered that, regardless of the statistical considerations, outcomes in the subgroup of *de novo* patients (particularly PFS and OS) would be useful for indicative purposes.

The commentary considered that given *de novo* patients and recurrent patients who have had no prior chemotherapies have different disease history (one being recurrent and the other not), it was unclear that both populations being the 'least pre-treated' was sufficient grounds to use the no prior chemotherapy subgroup as a proxy for the *de novo* population. Additionally, based on the proposed restriction and TGA indication, *de novo* patients must first be treated with chemotherapy in the metastatic setting to be eligible for olaparib treatment. Consequently, it was unclear if the no prior chemotherapy subgroup in OlympiAD was a useful proxy for *de novo* patients. Instead, the complement subgroup of patients who have received prior chemotherapy in the metastatic setting, or the whole trial population, may be more applicable to *de novo* mBC patients (Population 2).

The commentary noted that there were inconsistencies between the OlympiAD trial and available local registry information in estimates of proportion metastatic patients who were diagnosed with *de novo* disease, which may affect applicability as well as have implications for the utilisation and financial estimates. Of patients in the OlympiAD trial, 12.6% (38/302) included only mBC patients who were g*BRCA*m and diagnosed in the metastatic setting. While this was consistent

[9] File DM, et al (2022). Clinical subtype, treatment response, and survival in De Novo and recurrent metastatic breast cancer. *Breast Cancer Res Treat*. Nov;196(1):153-162

with the March 2023 olaparib for eBC submission which claimed that patients with *de novo* metastatic disease was roughly 5% to 15% of *BRCA*-positive patients in Australia (paragraph 2.7, olaparib PSD March 2023 PBAC meeting); this proportion differed to the registry data relied upon by the submission for the financial estimates, which used the average of:

- The Kisqali Access Registry for Metastatic Breast Cancer in Australia (KARMA) registry, which included patients who received first-line treatment with ribociclib and aromatase inhibitor for hormone receptor positive, HER2-negative metastatic breast cancer, included 26% (42/160) *de novo* patients; and
- The Advanced Hormone Receptor Positive Breast Cancer (ARORA) registry analysis included: patients diagnosed with metastatic, or inoperable histologically confirmed HR+, HER2- breast cancer (either *de novo* metastatic or relapsed), after 1st January 2020. The ARORA registry estimated 41% (173/424) of included patients to be *de novo*.

While chemotherapy use in the metastatic setting was one of several pre-planned subgroup analyses, the commentary considered it unclear whether stratification for this variable would be sufficient for the small sample sizes in each arm of the no prior chemotherapy subgroup. For example, differences in baseline Eastern Cooperative Oncology Group (ECOG) status and metastatic sites between arms were identified and potential issues with patient selection are indicated by differences in OS in the chemotherapy arms of the whole trial and subgroup populations (see Table 7 and Table 8).

The commentary noted that the subgroup analysis of no prior chemotherapy had not been included in OlympiAD's sequential hypothesis testing plan; therefore, statistical significance cannot be claimed in the subgroups.

Additionally, the commentary noted the following applicability issues when comparing the OlympiAD trial to the Australian population:

- The mean age of patients in the trial (45.3 years) was almost 20 years younger than in the expected Australian population (64 years). In addition to creating uncertainty as to whether age may be a treatment effect modifier, it would be expected that background mortality (due to age) would be higher in the Australian population and any OS gains may be reduced in a more elderly population;
- The proportion of patients with an ECOG status of 0 was much greater in OlympiAD (80%) than in the requested population (61%). This would likely impact the applicability of the OS estimates; and
- The chemotherapies used in OlympiAD may not be reflective of the chemotherapy regimens used in Australia, particularly for 1L TNBC.

PBAC ESC considered the no prior chemotherapy subgroup in OlympiAD was not a reasonable proxy for de novo *patients (para. 6.10, Olaparib ESC ADV 07-2024).*

11. Comparative safety

Test

The submission did not make an explicit clinical claim with respective to comparative safety.

The commentary noted that in previous considerations of the test, adverse events resulting from the testing procedure were unlikely and that due to the high performance of testing it was unlikely to have downstream safety concerns resulting from false positive or false negative test results (p15, 1716 PSD March 2023 MSAC meeting).

Codependent drug

The comparative safety of treatment with olaparib will be considered by the PBAC. The submission described olaparib as non-inferior in terms of safety to chemotherapy. This was generally supported when compared to the three chemotherapy regimens included as comparators in the OlympiAD (capecitabine, eribulin and vinorelbine). However, in the Australian setting, it would be expected that a proportion of patients would be treated with second line endocrine therapy (for HR+ patients) as well as pembrolizumab plus chemotherapy for some TNBC patients and even sacituzumab govitecan in some cases. Consequently, it is unlikely that the comparator safety profile in OlympiAD reflects the average safety profile for the requested population.

12. Comparative effectiveness

Comparative analytical performance

The submission did not present any comparison of analytical performance for *BRCA* testing. In the context of the economic model (discussed below), the model implicitly assumed 100% diagnostic accuracy.

Progression free survival

The primary outcome of OlympiAD was PFS. At the time of the primary PFS analysis (9 December 2016), median PFS in the whole trial population was 2.8 months longer in the olaparib group than in the chemotherapy group and treatment with olaparib resulted in a 42% reduction in the risk of disease progression or death compared to chemotherapy in the whole trial population (median PFS 7.0 months vs 4.2 months; hazard ratio [HR] for disease progression or death 0.58; 95% confidence interval [CI] 0.43 to 0.80; p<0.001). The submission considered that this improvement in PFS was both statistically significant and clinically relevant.

The submission noted that in patients who received no prior chemotherapy for mBC, olaparib significantly extended PFS by 3.8 months and reduced the risk of disease progression or death by 44% compared to chemotherapy (median 7.7 vs 3.9 months; HR=0.56; 95% CI: 0.34, 0.98; p<0.05). The proportion of patients who had not progressed or died at DCO for the primary PFS analysis was 74.6% in the olaparib arm compared with 71.4% in the chemotherapy arm, respectively.

Table 6 presents the primary endpoint, PFS by blinded independent central review (BICR) at the primary PFS DCO in the whole trial population as well as the no prior chemotherapy subgroup and its complement.

Table 6 Progression-free survival, primary PFS DCO

	Whole trial population		No prior chemotherapy for mBC		Prior chemotherapy	
	Olaparib N=205	**Chemotherapy N=97**	**Olaparib N=59**	**Chemotherapy N=28**	**Olaparib N=146**	**Chemotherapy N=69**
Number (%) of patients who had not died or progressed [a]	163 (79.5)	71 (73.2)	44 (74.6)	20 (71.4)	119 (81.5)	51 (73.9)
HR (95% CI)[b]	**0.58 (0.43, 0.80)**		0.56 (0.34, 0.98)		0.65 (0.47, 0.91)	
p-value	0.0009		NR		NR	
Median PFS (95% CI), months [c]	7.03 (5.68, 8.31)	4.17 (2.79, 4.27)	7.66 (5.45, 8.51)	3.88 (1.41, 7.95)	7.03 (5.55, 8.31)	4.17 (2.76, 4.63)
Progression-free at 6 months, %	54.1	32.9	NR			
Progression-free at 12 months, %	25.9	15.0	NR			
Median time to censoring, months [d]	13.62	4.29	13.70	6.32	11.79	3.43

Source: Table 2.15, p67 of the submission and Table 2.32, p91 of the submission.
Abbreviations: CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NR = not reported; PFS = progression-free survival
Data in **bold** indicate statistically significant difference. Statistical significance could not be claimed in subgroups as not part of sequential hypothesis testing.
a Based on independent central review of radiological scans. Patients who had not progressed or died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline).
b A hazard ratio <1 favours olaparib 300 mg bd. The CI was calculated using a profile likelihood approach.
c Calculated using the Kaplan-Meier technique
d Censored patients only

Overall survival

OS results from the final OS DCO and extended OS DCO for the whole trial population of OlympiAD, the no prior chemotherapy subgroup and its complement are presented in Table 7 and Table 8, respectively.

As of the final OS DCO, the OS whole trial data had reached 64% maturity, with 192 events (130 patients had died in the olaparib arm, and 62 in the chemotherapy arm).

As of the DCO for the extended OS analysis, OS data had reached 76.8% maturity, with a further 40 events (total 159 deaths in the olaparib arm and 73 deaths in the chemotherapy arm).

In the whole trial population, no significant difference in the median OS was observed between the olaparib and the chemotherapy arms at either DCO. The commentary noted that the clinical study report (CSR) had stated that all efficacy analyses in the extended OS analysis were exploratory, and all p-values were nominal.

In the final OS analysis for the no prior chemotherapy subgroup, the submission considered that the OS benefit was numerically greater than in the olaparib arm, where median OS was increased by 7.9 months and the risk of death reduced by 49% compared to chemotherapy (median 22.6 vs 14.7 months; HR = 0.51; 95%CI: 0.29, 0.90). In the extended OS analysis for the no prior chemotherapy subgroup, the submission considered that the OS benefit remained numerically greater in the olaparib arm, with the difference in median OS remaining at 7.9 months and the risk of death reduced by 45% compared to chemotherapy (median 22.6 vs 14.7 months; HR=0.55; 95% CI: 0.33, 0.95; for extended DCO data cut). The submission argued this was clinically relevant given the recommended minimal clinically relevant difference (MCID) of 4.5 to

6 months derived by consensus of working groups convened by the Cancer Research Committee of the American Society of Clinical Oncology (Ellis 2014). In this subgroup, 40.8% of patients in the olaparib arm were alive at 3 years compared with 12.8% of patients in the chemotherapy arm.

Table 7 Median OS and log-rank test, final OS DCO (full analysis set)

	Whole trial population		No prior chemotherapy for mBC		Prior chemotherapy	
	Olaparib N=205	**Chemotherapy N=97**	**Olaparib N=59**	**Chemotherapy N=28**	**Olaparib N=146**	**Chemotherapy N=69**
Total number of deaths, n (%)	130 (63.4)	62 (63.9)	30 (50.8)	21 (75.0)	100 (68.5)	41 (59.4)
Median OS (95% CI), months	19.25 (17.15, 21.55)	17.12 (13.86, 21.85)	22.6 (17.8, NC)	14.7 (11.0, 21.3)	18.8 (16.3, 20.4)	17.2 (13.5, 27.2)
HR (95% CI)	0.90 (0.66, 1.23)		0.51 (0.29, 0.90)		1.13 (0.79, 1.64)	
p-value (2-sided)	0.5131		0.0218		*0.5156* [b]	
Survival at 6 months, %	93.1	85.8	93.2	88.5	93.1	84.9
Survival at 12 months, %	72.7	69.2	76.0	65.4	71.4	70.8
Survival at 18 months, %	54.1	48.0	62.1	46.2	50.8	48.8
Survival at 24 months, %	NR	NR	48.0	26.9	35.0	44.1
Median follow-up for OS in all patients, months	18.92	15.54	22.05	14.14	17.40	16.76
Median follow-up for OS in censored patients, months	25.30	26.25	25.53	26.91	25.17	25.95

Source: Table 2.19, p72 and Table 2.30, p88 of the submission.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; NC = not calculable; OS = overall survival
Note: Each subgroup analysis was performed using a single Cox proportional hazards model containing the treatment term, the subgroup covariate of interest and the treatment by subgroup interaction. A hazard ratio <1 favours Olaparib 300 mg bd. The CI was calculated using a profile likelihood approach. P-values were calculated from likelihood ratio statistics, using a contrast statement for each subgroup level.
b reported as 0.05156 in submission, corrected during evaluation

Table 8 Median OS and log-rank test, no prior chemotherapy for mBC, extended OS DCO (full analysis set)

	Whole Trial Population		No prior chemotherapy for mBC		Prior chemotherapy	
	Olaparib N=205	Chemotherapy N=97	Olaparib N=59	Chemotherapy N=28	Olaparib N=146	Chemotherapy N=69
Total number of deaths, n (%)[a]	159 (77.6)	73 (75.3)	42 (71.2)	22 (78.6)	117 (80.1)	51 (73.9)
Median OS (95% CI), months [b]	19.25 (17.15, 21.55)	17.12 (13.86, 21.85)	22.6 (17.8, 36.7)	14.7 (11.0, 21.3)	18.8 (16.3, 20.4)	17.2 (13.5, 27.2)
HR (95% CI)	0.89 (0.67, 1.18)		0.55 (0.33, 0.95)		1.05 (0.76, 1.47)	
p-value (2-sided)	0.4167		NR		NR	
Survival at 6 months, %	93.1	85.8	93.2	88.5	93.1	84.9
Survival at 12 months, %	72.7	69.2	76.0	65.4	71.4	70.8
Survival at 18 months, %	54.1	48.0	62.1	46.2	50.8	48.8
Survival at 24 months, %	39.0	39.1	48.1	26.9	35.0	44.1
Survival at 36 months, %	30.8	25.6	40.8	12.8	22.4	24.7
Survival at 48 months, %	27.9	21.2	27.8	12.8	16.1	15.8
Survival at 60 months, %	23.8	18.1	18.6	NC	12.3	15.8
Median follow-up for OS in all patients, months	19.6	14.8	22.05	14.14	17.40	16.76
Median follow-up for OS in censored patients, months	16.9	14.8	49.81	28.11	48.00	31.72

Source: Table 2.20, p74 and Table 2.31, p90 of the submission.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; mBC= metastatic breast cancer; NC = not calculable; NR = not reported; OS = overall survival
a Overall survival is defined as the time from the date of randomisation until death due to any cause. Patients not known to have died at the time of analysis are censored at the last recorded date on which the patient was known to be alive.
b Calculated using the Kaplan-Meier technique.

The submission argued that the OS in the whole trial comparison may have been confounded by an imbalance between treatment arms in the use of subsequent therapies following progression. Specifically, more patients in the chemotherapy arm received PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy after disease progression on the assigned treatment, compared to the olaparib arm. Subsequent PARP inhibitor use post-discontinuation was reported for eight (8.2%) patients in the chemotherapy arm and two (1.0%) patients in the olaparib arm in the final OS analysis.

The commentary considered that this was not reasonable. The use of subsequent cancer treatments actually appeared to favour the olaparib arm in OlympiAD after accounting for continued use of study treatment after discontinuation, as 37 (18.1%) patients in the olaparib arm at the final PFS DCO 'continued study treatment' after a protocol defined discontinuation, such that these patients were effectively using subsequent PARP inhibitor but were not included as such. Nonetheless, the lack of difference in OS HRs between the final OS (0.90) and extended OS (0.89) analyses despite the claimed differences in subsequent PARP inhibitor use in between the final OS (8% in chemotherapy arm) and the extended OS (12% in chemotherapy arm) casts uncertainty as to the effect of subsequent PARP inhibitor on OS.

Further, acknowledging that the numerical differences in OS between the olaparib and chemotherapy arms in the subgroup of patients with no prior chemotherapy in the metastatic setting at the final OS data cut and the extended OS data cut appeared more favourable when compared to the whole trial population and the complement, the commentary stressed that these results are highly uncertain and should not be relied upon given:

- OS results in subgroups should not be considered statistically significant as they have not been formally tested in the trial (and not included in the trial's hierarchical hypothesis testing strategy). The subgroup with no prior chemotherapy had a relatively small sample size and correspondingly, wide confidence intervals. The CSR cautioned that all subgroup results should only be interpreted to be supportive of the primary PFS outcome;
- The larger median OS difference between treatment arms in the no prior chemotherapy subgroup was driven by both longer olaparib OS (22.6 months) and shorter chemotherapy OS (14.7 months) when compared to the complement subgroup (18.8 and 17.2 months for olaparib and chemotherapy respectively) and the whole trial population (19.25 and 17.12 months for olaparib and chemotherapy respectively). It was unclear why there would be a lower chemotherapy OS in patients with no prior chemotherapy compared to those who had 1-2 lines of prior chemotherapy (difference of 2.5 months, around 30% of the claimed OS benefit associated with olaparib in the no prior chemotherapy subgroup). Instead this suggests that there may be other inherent differences in patients in the no prior chemotherapy subgroup compared to the complement which may have led to the observed difference, and that the OS in the no prior chemotherapy subgroup may be underestimated in OlympiAD. For comparison, the median survival for vinorelbine (one of the chemotherapies used in the comparator arm) in advanced breast cancer (ABC) was 19.3 months in the 96 CA 201 study and 23.9 months in the 97 CA 206 study, which the submission noted included only patients who did not receive any prior chemotherapy for advanced or metastatic disease, though the *BRCA* status in these patients was unknown;
- In the FAS, 72% (148/205) of olaparib patients had ECOG 0 at baseline compared to 64% (62/97) in the chemotherapy arm. In the no prior chemotherapy subgroup, this difference between arms increased further, as 80% (47/59) had ECOG 0 in the olaparib arm versus 61% (17/28) in the chemotherapy arm at baseline. This imbalance likely favoured olaparib and contributed to the observed OS difference in the no prior chemotherapy subgroup;
- Similarly, the proportion of patients with ≥2 metastatic sites in the olaparib arm was lower in the no prior chemotherapy subgroup (40/59, 67.8%) than in the whole trial population (159/205, 77.6%). Conversely, the proportion of patients with≥2 metastatic sites in the chemotherapy arm was higher (22/29, 75.8%) in the subgroup than in the whole trial population (72/97, 74.2%). File 2022 reported an increased risk of death with a higher number of metastatic sites, with OS HR of 1.4 (95% CI 1.14-1.84) and 1.5 (95% CI 1.15-1.92) for having two and three metastatic sites, respectively, using one metastatic site as the baseline. As such, this imbalance also favoured olaparib and likely biased the OS results in favour of olaparib in the no prior chemotherapy subgroup; and
- There was little difference between the point estimate for the PFS HR in the no prior chemotherapy subgroup (PFS HR 0.56, 95% CI 0.34, 0.98) compared to the whole trial population (PFS HR 0.58, 95% CI 0.43, 0.80), or with the prior chemotherapy subgroup (PFS HR 0.65, 95% CI 0.47, 0.91), suggesting this was not a mechanism by which any additional OS benefit was derived. The submission has not proposed a biologically plausible argument as to why an OS benefit was observed only in the subgroup with no prior chemotherapy when the PFS benefit was of similar magnitude across the whole trial, no prior chemotherapy and prior chemotherapy subgroups.

Health-related quality of life

The submission discussed results of global health-related quality of life (HRQoL) evaluated based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module (EORTC QLQ C3). The CSR stated that this outcome was not formally tested and as such the p-values should be interpreted with caution. Additionally, the CSR cautioned that as this was an open-label study design with patients being aware of their

treatment arm allocation, the patient-reported outcome results are less robust and need to be interpreted with caution. The CSR also noted that after the first year (from Visit 24 onwards), EORTC QLQ-C30 compliance fell below 50% at some visits in both treatment arms and therefore the results should be considered more uncertain after this time point.

The mean score on the QLQ-C30 at baseline was 63.2 (SD=21.0) in the olaparib arm and 63.3 (SD=21.2) in the chemotherapy arm. The adjusted mean change from baseline across all time points was 3.9 (SE=1.2) in the olaparib arm (among the 191 patients who completed the questionnaire at baseline and at least once thereafter) and -3.6 (SE=2.2) in the chemotherapy arm (among 73 patients), corresponding to an estimated mean difference of 7.5 points (95% CI: 2.5, 12.4; p=0.004).

The submission claimed that the QLQ-C30 results showed a statistically and clinically significant improvement in QoL favouring olaparib treatment. Osoba 1998[10] reported a change of 5-10 points in the EORTC-QLQC30 as a small change, however statistical significance could not be concluded as QLQ-C30 was not part of the sequential hypothesis testing of OlympiAD.

In the olaparib arm, 69/205 (33.7%) patients compared with 13/97 (13.4%) patients in the chemotherapy arm showed improvement in the global health status/QoL score best overall QoL response (2 visit responses of 'improved' a minimum of 21 days apart without an intervening response of 'deterioration'). The proportion of patients with no change or deterioration (at least a 10-point decrease) was generally more favourable for the olaparib arm (41.5% no change; 11.7% deterioration) compared with the chemotherapy arm (25.8% no change; 19.6% deterioration).

The submission stated that the median time to a ≥10 point decrease in QLQ-C30 score was not reached in the olaparib arm and was 15.3 months in the chemotherapy arm (HR= 0.44; 95% CI: 0.25, 0.77; p=0.0043). The commentary noted, however, that neither arm reached 50% of patients with events. Consequently, the median time to ≥10 point decrease could not be verified during the evaluation. Additionally, as the comparison was based on available (under median) event data, it may be immature and uncertain.

The submission stated that this represented a nominally statistically significant delay in the time to HRQoL deterioration in the olaparib arm compared with chemotherapy. The EORTC-QLQC30 results from OlympiAD primary PFS DCO were used to inform the economic model.

Clinical claim

The submission made the following clinical claims regarding olaparib:

- In the whole trial population which included patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who had previously received up to two lines of chemotherapy for mBC, olaparib was superior in terms of effectiveness compared with chemotherapy based on PFS and non-inferior in terms of safety compared with chemotherapy.
- In the subgroup of patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who had not previously received chemotherapy for mBC, olaparib was superior in terms of OS and PFS compared with chemotherapy.

As the OlympiAD trial enrolled people with metastatic breast cancer who have germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2*, the submission did not present evidence on the treatment effect of olaparib for patients who were *BRCA1/2* positive versus

[10] Osoba D, et al (1998). Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. Jan;16(1):139-44.

patients who were not *BRCA1/2* positive. Thus, an estimate of the variation in this treatment effect due to *BRCA1/2* positivity could not be established from the evidence presented.

13. Economic evaluation

The submission presented a cost-utility analysis comparing olaparib with chemotherapy in patients with HER2-negative, *BRCA*m mBC who had not previously received chemotherapy in the metastatic setting based on the corresponding subgroup in the OlympiAD trial (hence referred to has the subgroup model). The submission has also presented an additional cost-utility analysis reflective of the whole trial population (hence referred to as the ITT model).

Table 9 presents a summary of the overview, key inputs and rationale of the submission's economic evaluation.

Table 9 Summary of model structure, key inputs and rationale

Component	Summary/ comment
Treatments	Olaparib versus chemotherapy
Perspective	Health system
Population	The submission base case was the subgroup of patients with HER2-negative mBC with a confirmed *BRCA1* or *BRCA2* mutation who had not previously received chemotherapy for mBC. The submission also included results reflective of all patients in the OlympiAD trial. (i.e. those who had received up to two lines of chemotherapy in the metastatic setting.)
Prior testing	Model assumes prior *BRCA* testing in the early breast cancer setting as well as testing in the metastatic setting
Time horizon	10 years based on median 18 months of follow-up in the Final OS analysis of OlympiAD.
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life years gained
Methods used to generate results	Partitioned survival model
Health states	PFS1, PFS2, progressive disease (PD), death
Cycle length	1 month
Allocation to health states	PFS, PFS2, and OS extrapolated using parametric functions fitted directly to data from OlympiAD. Australian lifetables applied after end of trial follow-up to capture all-cause mortality observed after the trial.
Extrapolation method	In the base case model, the submission extrapolated PFS, OS and PFS2 using a lognormal parametric function in both arms. In the ITT analysis, a lognormal function was used in all extrapolated curves, except for PFS2, which utilised a generalised gamma function in both arms.
Health related quality of life	EORTC QLQ-C30 scores from OlympiAD were mapped to EQ-5D-5L based utility values using published mapping algorithms, and the literature for the progressed disease state. The health state utilities were: • PFS1-0.817 for olaparib and 0.745 for chemotherapy; • PFS2 0.749 for olaparib and 0.717 for chemotherapy; • PD 0.53 for both treatments.
BRCA test modelling	Though *BRCA* test costs were incorporated into the model, neither the diagnostic accuracy of the g*BRCA* test nor the costs/outcomes of non-germline *BRCA* patients were captured in the model. While it was inappropriate for the submission to not have considered test performance in the economic model, it was acknowledged that *BRCA* testing has a high sensitivity and specificity, but omitting testing may have led to the ICER being underestimated as the prevalence of *BRCA*m was not considered, which has implications for the number of tests required for each patient treated.

Source: Table 3.1, p104 of the submission.
EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module; EQ-5D5L = EuroQoL 5 dimension 5 level; OS = overall survival; PFS= progression free survival; PFS2 = time to second progression or death

The economic evaluation incorporated costs of *BRCA* testing, but not accuracy, implicitly assuming 100% test accuracy.

The submission used a partitioned survival model to estimate the incremental cost-effectiveness of olaparib versus the nominated main comparator, placebo, in the proposed g*BRCA*m variant population.

The submission presented a four state partitioned survival model over a time horizon of 10 years, with a monthly cycle length. The health states are defined as follows:

- PFS1: progression-free survival: A state where patients are free from disease recurrence having received treatment with olaparib or chemotherapy as per the OlympiAD trial.
- PFS2: A state where patients have experienced recurrence after olaparib or chemotherapy. However, several active therapies are available such as sacituzumab govitecan, aromatase inhibitors, hormonal and endocrine therapy.
- Progressive disease: A state where few active treatments are available, and patients receive BSC.
- Death: Absorbing state for deaths from any cause.

The submission did not include a model structure diagram. The submission assumed that the cost of testing would be $1,200 per test based on the current fee for MBS item 73295.

The submission assumed that redacted% of the population would have progressed from early breast cancer, that 8% were HR+ *de novo* patients, and that 10% were *de novo* TNBC patients. This was based on calculations using:

- Ipsos data on HR+ (redacted%) and TNBC+ (redacted%) rates, which could not be verified. The economic model stated this was from Ipsos Q2 2022 data which was not included as an attachment. These rates were adjusted to relative proportions of HR+ (redacted%) and TNBC (redacted%);
- Stage at diagnosis data were sourced from Cancer Australia (96% Stages 1-3 i.e. eBC: 4% stage 4, i.e. mBC). The eBC estimates were then adjusted to account for progression from eBC to mBC based on the chemotherapy arm from OlympiA eBC trial at year four (96% x redacted% = redacted%). The adjusted eBC value (redacted%) and the mBC value (4%) were then adjusted again for proportional weighting of eBC (redacted%) and mBC (redacted%); and
- Of the redacted% mBC patients, 10% were calculated to be *de novo* TNBC (redacted% x redacted% = 10%), and 8% were calculated to be *de novo* HR+ (redacted% x redacted% = 8%).

However, the proportion of *de novo* patients may be higher in the Australian population than suggested. In the financial estimates, the submission assumed that 34% and 20.5% of patients with HR+ and TNBC would have *de novo* disease.

The submission assumed that of olaparib patients progressing from eBC10%% would receive g*BRCA* testing in the mBC setting. Of the *de novo* HR+ patients 95% would receive testing in the mBC setting, and of *de novo* TNBC patients, 95% would receive testing in the mBC setting. For the chemotherapy arm, the submission estimated that 0% of patients progressed from eBC would receive testing, 20% of *de novo* HR+ would receive testing and 74% of *de novo* TNBC patients would receive testing. The submission claimed that this was consistent with current testing rates the PBAC had previously considered for the olaparib in eBC submission (Table 20, olaparib PSD March 2023 PBAC meeting[11]).

[11] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/olaparib-psd-03-2023.pdf

As the model did not incorporate test accuracy into the model, the *BRCA*m positive rate was not incorporated into the model.

Table 10 presents a summary of the key drivers of the subgroup model and ITT model. In the subgroup model, the only key drivers were efficacy inputs such as OS extrapolation and PFS2 health state assumptions. The commentary noted, however, that as the OS benefit assumed in the no prior chemotherapy subgroup may not be supported, the entire model should be considered uncertain and may not be informative.

Table 10 Key drivers of the model

Description	Method/Value	Impact
Subgroup model		**Base case: $redacted[1]/QALY gained**
OS Extrapolation	Both olaparib and chemotherapy arms extrapolated OS using the lognormal function.	*Moderate, favours olaparib.* *Use of Weibull function in both arms increased the ICER by **redacted**% to* $**redacted**[2]*/QALY gained.*
PFS2 state assumptions	The model assumed a PFS2 health state in between progression free and progressed. This state had different (treatment specific utilities) and disease monitoring costs assumed to be equal to progression free.	*Moderate, favours olaparib* *Assuming disease monitoring costs and utilities equal to those in the PD states increased the ICER by **redacted**% to* $**redacted**[2]*QALY gained.*
Differential Utilities	The submission assumed different utilities for olaparib and chemotherapy in both PFS1 (0.817 vs 0.745) and PFS2 (0.749 vs 0.717) health states.	*Assuming no differential utilities increased the ICER by **redacted**% to $**redacted**[2]/QALY*
ITT model		**Base case: $redacted[3]/ QALY gained**
OS improvement assumption	The submission extrapolated ITT OS KM data from OlympiAD, which assumed a survival increment associated with Olaparib despite no statistically significant difference being demonstrated in the trial.	High, favours olaparib. Applying the olaparib OS curve to the chemotherapy arm increases the ICER by **redacted**% to *$**redacted**[4]*
PFS2 extrapolation	The submission extrapolated PFS2 using a generalized gamma function.	High, favours olaparib Use of a lognormal function increases the ICER by **redacted**% to $ **redacted**[4]
Differential Utilities	The submission assumed different utilities for olaparib and chemotherapy in both PFS1 (0.817 vs 0.745) and PFS2 (0.749 vs 0.717) health states.	*Assuming no differential utilities increased the ICER by **redacted**% to $ **redacted**[4]/QALY*

Source: Submission's attached economic model spreadsheet
ICER = incremental cost-effectiveness ratio; ITT = intention to treat; OS = overall survival; PFS2 = time to second progression to death; PD = progressed disease; QALY = Quality adjusted life-year;
*The **redacted** values correspond to the following ranges*
[1]$45,000 to < $55,000
[2]$55,000 to < $75,000
[3]$75,000 to < $95,000
[4]$95,000 to < $115,000

Results of the economic analysis

The submission presented stepped results of the subgroup model. with the following steps:

- Trial based cost per progression free life years
- Cost per life year gained over 10 years
- Cost per QALY over 10 years.

Table 11 Results of the stepped economic evaluation of the subgroup model

Step and component	Olaparib	Chemotherapy	Increment
Step 1: trial-based costs and progression free life years			
Costs	$**redacted**	$7,917	$**redacted**
Progression-free years gained	0.79	0.51	0.28
Incremental cost/extra LYG gained			$**redacted**
Step 2: cost per LYG over 10 years			
Costs	$**redacted**	$64,625	$**redacted**
LYG	2.83	1.66	1.168
Incremental cost/extra LYG gained			$**redacted**
Step 3: cost per QALY over 10 years			
Costs	$**redacted**	$64,625	$**redacted**
QALY	1.965	1.086	0.880
Incremental cost/extra QALY gained			**$redacted**[1]

Source: Tables 3.29 -3.31, p148 of the submission. LYG = life year gained; QALY = quality adjusted life year
*The **redacted** values correspond to the following range*
[1] $45,000 to < $55,000

The submission presented results of the ITT model.

Table 12 Results of the economic evaluation in the ITT model

Component	Olaparib	Chemotherapy	Increment
Costs	$**redacted**	$65,260	$**redacted**
LYG	2.18	1.91	0.267
Incremental cost/extra LYG gained			$**redacted**[2]
Costs	$ **redacted**	$65,260	$ **redacted**
QALY	1.648	1.265	0.383
Incremental cost/extra QALY gained			**$ redacted**[1]

Source: Tables 3.29 -3.31, p148 of the submission.
LYG = life year gained; QALY = quality adjusted life year
*The **redacted** values correspond to the following ranges*
[1] $75,000 to < $95,000
[2]$95,000 to < $115,000

Sensitivity analysis

The results of key univariate sensitivity analyses of the subgroup model and the ITT model are summarised in Table 13 and Table 14, respectively.

Table 13 Key sensitivity analyses in subgroup model

Analyses	Incremental cost	Incremental QALY	ICER	% Change
Base case	**$redacted**	**0.880**	$**redacted**[2]	
Discounting rate (5% in BC)				
0%	$**redacted**	*1.025*	$**redacted**[2]	***redacted****%*
Time horizon (10 years in BC)				
15 years	$**redacted**	*0.933*	$**redacted**[1]	***redacted****%*
7 years	$***redacted***	*0.791*	$***redacted***[2]	***redacted****%*
5 years	$***redacted***	*0.670*	$***redacted***[2]	***redacted****%*
PFS2 extrapolation both arms (lognormal in BC				
Weibull used to extrapolate PFS2	$**redacted**	*0.885*	$**redacted**[2]	***redacted****%*
Gompertz used to extrapolate PFS2	$**redacted**	*0.853*	$**redacted**[2]	***redacted****%*
Gen Gamma used to extrapolate PFS2	$**redacted**	*0.940*	$**redacted**[1]	***redacted****%*
OS extrapolation both arms (log normal in BC)				
Weibull used to extrapolate OS	$**redacted**	*0.727*	$**redacted**[2]	***redacted****%*
Gen Gamma used to extrapolate OS	$**redacted**	*1.003*	$**redacted**[1]	***redacted****%*
Extended OS follow-up (Robson 2023) used to extrapolate OS	$**redacted**	*0.898*	$**redacted**[1]	***redacted****%*
Utilities				
Removal of treatment-specific utility scores in both PFS1 and PFS2	$**redacted**	*0.812*	$**redacted**[2]	***redacted****%*
Costs				
Utility in PFS2 and disease monitoring costs set to same as PD	$**redacted**	*0.816*	$**redacted**[2]	***redacted****%*
Account for BRCAm prevalence in testing [a]	$**redacted**	*0.880*	$**redacted**[2]	***redacted****%*
Using time in PFS1 to inform treatment duration (olaparib: 13.60 months, chemotherapy: 9.37 cycles/6.47 months)	$**redacted**	0.880	$**redacted**[2]	***redacted****%*
Post progression targeted therapy use set to 0%	$**redacted**	*0.880*	$**redacted**[2]	***redacted****%*

Source: Table 3.33p 151 0f the submission.
BC = base case; DCO = data cutoff; eBC = early breast cancer; ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease PFS1 = progression free survival 1: PFS2 = progression free survival 2; QALY = quality adjusted life year
a Assuming 5% prevalence (20 tests per patient treated) for HR+ mBC and 13.25% prevalence (7.5 tests per patient treated) for TNBC, and 13 tests (weighted prevalence based on 8% HR+ mBC and 10% TNBC as assumed for *de novo* mBC patients) for patients who progressed from eBC.
*The **redacted** values correspond to the following ranges*
[1]*$45,000 to < $55,000*
[2]*$55,000 to < $75,000*

Overall, the commentary considered that the subgroup model was not sensitive to most of the inputs selected by the submission.

During the evaluation, shorter time horizons were selected to be consistent with some of the recent models considered by the PBAC in breast cancer. As expected, a shorter time horizon increased the ICER, but substantial increases in the ICER were only observed by halving the time horizon from 10 to 5 years. The use of a shorter time horizon could be reasonable depending on the expected place in treatment of olaparib, which remains uncertain. Should olaparib be positioned after pembrolizumab plus chemotherapy in TNBC, for example, a shorter time horizon may be appropriate.

Given that patients will not be assessed for progression as frequently in clinical practice than in the clinical trial setting and may remain on treatment for longer, a sensitivity analysis using mean time spent in PFS1 to inform treatment duration was conducted. The subgroup model was only slightly sensitive to this change (redacted%).

Table 14 Results of key sensitivity analyses in the ITT model

Analyses	Incremental cost	Incremental QALY	ICER	% Change
Base case	**$redacted**	**0.383**	**$redacted[3]**	**–**
Discounting rate (5% in BC)				
0%	**$redacted**	*0.439*	**$redacted[2]**	***redacted***
Time horizon (10 years in BC)				
15 years	**$redacted**	*0.430*	**$redacted[2]**	***redacted***
7 years	**$redacted**	*0.335*	**$redacted[3]**	***redacted***
5 years	**$redacted**	*0.293*	**$redacted[4]**	***redacted***
PFS extrapolation both arms (lognormal in BC)				
Weibull used to extrapolate PFS	**$redacted**	*0.378*	**$redacted[3]**	***redacted***
Exponential used to extrapolate PFS	**$redacted**	*0.380*	**$redacted[3]**	***redacted***
Gen Gamma used to extrapolate PFS	**$redacted**	*0.736*	**$redacted[1]**	***redacted***
PFS2 extrapolation both arms (Generalised Gamma in BC)				
Weibull used to extrapolate PFS2	**$redacted**	*0.304*	**$redacted[4]**	***redacted***
Exponential used to extrapolate PFS2	**$redacted**	*0.319*	**$redacted[4]**	***redacted***
Loglogistic used to extrapolate PFS2	**$redacted**	*0.316*	**$redacted[4]**	***redacted***
Gompertz used to extrapolate PFS2	**$redacted**	*0.303*	**$redacted[4]**	***redacted***
Lognormal used to extrapolate PFS2	**$redacted**	*0.312*	**$redacted[4]**	***redacted***
OS extrapolation both arms (log normal in BC)				
Weibull used to extrapolate OS	**$redacted**	*0.372*	**$redacted[3]**	***redacted***
Loglogistic used to extrapolate OS	**$redacted**	*0.361*	**$redacted[3]**	***redacted***
Extended OS follow-up (Robson 2023) used to extrapolate OS	**$redacted**	*0.397*	**$redacted[3]**	***redacted***
Utilities				
Removal of treatment-specific utility scores in both PFS1 and PFS2	**$redacted**	*0.311*	**$redacted[4]**	***redacted***
Removal of treatment-specific utility scores in PFS2 only	**$redacted**	*0.355*	**$redacted[3]**	***redacted***
Utility in PFS2 set to same as PD	**$redacted**	*0.308*	**$redacted[4]**	***redacted***
Costs				
Account for BRCAm prevalence in testing [a]	**$redacted**	*0.383*	**$redacted[3]**	***redacted***
Using time in PFS1 to inform treatment duration (olaparib: 11.85 months, chemotherapy: 8.81cycles/6.08 months)	**$redacted**	0.282	**$redacted[3]**	***redacted***
Post progression targeted therapy use set to 0%	**$redacted**	*0.383*	**$redacted[3]**	***redacted***
OS in chemotherapy set equal to OS in Olaparib arm [b]	**$redacted**	*0.241*	**$redacted[4]**	***redacted***

Source: Calculated during the evaluation using the attached economic model.

BC = base case; DCO = data cutoff; eBC = early breast cancer; ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease PFS1 = progression free survival 1: PFS2 = progression free survival 2; QALY = quality adjusted life year

a Assuming 5% prevalence (20 tests per patient treated) for HR+ mBC and 13.25% prevalence (7.5 tests per patient treated) for TNBC, and 13 tests (weighted prevalence based on 8% HR+ mBC and 10% TNBC as assumed for *de novo* mBC patients) for patients who progressed from eBC.

B calculated during the evaluation by pasting values from Column H of 'olaparib trace' to Column H of 'chemo trace'

*The **redacted** values correspond to the following ranges*

[1]$25,000 to < $45,000

[2]$55,000 to < $75,000

[3]$75,000 to < $95,000

[4]$95,000 to < $115,000

Overall, the ITT model was highly sensitive to the choice of extrapolation of PFS2. Though the generalised gamma extrapolation was the best fitting by total AIC and BIC score, the others were also well fitting and the generalised gamma extrapolation reported the most optimistic ICER.

Additionally, the model was sensitive to the utility in PFS2 and setting disease monitoring costs in PFS2 equal to PD, suggesting that the modelling of benefit associated with PFS2 may be uncertain and overestimated. Using time in PFS1 to inform treatment duration also increased the ICER by redacted%.

Assuming OS in the chemotherapy arm to be the same as that in the olaparib arm, consistent with the lack of statistically significant improvement in the OlympiAD trial, increased the ICER by redacted%.

Additionally, the ITT model was more sensitive to changing the duration of treatment to be the mean time in PFS1 (increased ICER by redacted%). The ITT model was also more sensitive to time horizon than the subgroup model.

Overall, the commentary considered that the ITT model's ICER appeared underestimated and may be optimistic, as an OS benefit was modelled even though it was not reported in OlympiAD, and differential utilities by treatment arm were applied. The ITT model was more sensitive to changes in several variables compared to the subgroup model and may be more uncertain. This was likely due to the smaller incremental benefit in the base case of the ITT model and smaller changes in the modelled benefit may have greater impacts.

14. Financial/budgetary impacts

The submission took an epidemiological approach to estimating use and financial implications.

The financial implications to the PBS and MBS resulting from the proposed listing of *BRCA* testing and olaparib are summarised in Table 15.

Table 15: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
% of patients with recurrent mBC	66%	Average of Kisqali Access Registry for Metastatic Breast Cancer in Australia (KARMA, n=160) registry and ARORA registry.	The ARORA registry considered that 59% of HR+ patients had relapsed as opposed to *de novo* metastatic disease and the KARMA registry considered that 74% would have relapsed or recurrent disease.
% of HR + patients with prior (neo)adjuvant chemotherapy	63%	Taken from KARMA registry	The PBAC considered that 25% would be more appropriate. (Table 19, olaparib PSD March 2023 PBAC meeting).
Germline *BRCA* mutation testing rates	TNBC: 75-90% HR+: 50-90%	Table 20 olaparib PSD March 2023 PBAC meeting	In the eBC setting, DUSC had considered rates ranging from 80% to 95% to be appropriate, but that initially uptake may be higher. It was unclear how applicable uptake rates from the eBC setting would be to the metastatic setting.
Germline *BRCA* mutation test positive to *BRCA1* or *BRCA2* mutation, TNBC	13.25%	Table 20 olaparib PSD March 2023 PBAC meeting	*Reasonable*
Germline *BRCA* mutation test positive to	5%	Assumption to align with in the OlympiA trial, estimates from population based studies	This was consistent with previous MSAC considerations (Table 1and 6, 1716 PSD November 2023 MSAC meeting).

Data	Value	Source	Comment
BRCA1 or *BRCA2* mutation, HR+		(Armstrong 2019) and IPSOS report, showing that testing is less established in this population	
Proportion of TNBC patients	15%	paragraph 6.71 sacituzumab govitecan PSD March 2022 PBAC meeting	Reasonable. This was consistent with DUSC recommendations.
Estimate of TNBC patients that are metastatic	54.80%	Table 16 trastuzumab deruxtecan PSD November 2023 PBAC meeting	In its consideration of trastuzumab deruxtecan at the July 2022 PBAC meeting DUSC stated: "DUSC agrees with the commentary that this is likely an overestimate. However, DUSC noted that this employs similar rationale to other submissions (atezolizumab March 2020 and SG for triple negative breast cancer). In prior submissions, for atezolizumab March 2020 and pembrolizumab March 2023, this has also taken into account the mortality rate of (44% for all stages of breast cancer from Lin 2012[e]) into the estimates" (Table 14, trastuzumab deruxtecan PSD November 2023 PBAC meeting)
Proportion of *de novo* / recurrent patients in HER2-/HR+	34%	Average of ARORA registry and Karma Registry average	Substantially greater than the 12.6% *de novo* patients in the OlympiAD trial, see paragraph 0
Proportion of *de novo* TNBC patients	20.5%	Midpoint of North Carolina mBC registry (File 2022) and PRAEGNANT (Muller 2022), a German prospective breast cancer registry to assess treatment patterns and quality of life and to identify patients who may be eligible for clinical trials or specific targeted treatments.	It was unclear to what extent these estimates would be applicable to the Australian setting. 34.8% of TNBC patients were assumed to be diagnosed with unresectable locally advanced or *de novo* metastatic TNBC (Table 15 sacituzumab govitecan PSD November 2021 PBAC meeting)
Treatment utilisation			
Average duration of Olaparib treatment	373.06 days	Submission economic evaluation	This was consistent with the economic evaluation for the no prior chemotherapy subgroup. However may be underestimated as patients will not be assessed for progression as frequently in clinical practice and may remain on treatment for longer.
Cost of germline BRCA1 or BRCA2 mutation testing	$1,200	MBS item 73295	Consistent with existing MBS item

Source: Tables 4.1, p157 of the submission.
AIHW = Australian Institute for Health and Wellness; CDK = cyclin-dependent kinase; DPMQ = dispensed price per maximum quantity; DUSC = Drug utilisation Sub Committee; eBC = early breast cancer; HER2 = Human epidermal growth factor receptor; HR + = hormone receptor positive; mBC = metastatic breast cancer; MBS = Medicare benefits schedule; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; TNBC = triple negative breast cancer;

Table 16 presents the estimated number of patients eligible for olaparib, which ranged from <500 in Year 1 to <500 in Year 6. The submission assumed that 100% of eligible patients would receive treatment with olaparib.

Table 16: Estimated number of TNBC and HR+ HER2-negative patients eligible for Olaparib

	2025	2026	2027	2028	2029	2030
TNBC patients						
Incident population	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Triple negative patients (15%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Metastatic/ unresectable (54.8%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Recurrent population (79.5%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Proportion tested for *BRCA*	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%
Recurrent population tested for *BRCA*	**redacted**[2]	**redacted**[2,b]	**redacted**[2]	**redacted**[2]	**redacted**[2,c]	**redacted**[2]
Recurrent *BRCA*m (13.25%)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
De novo metastatic breast cancer (20.5%)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Proportion tested for *BRCA*	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%
De novo population tested for *BRCA*	**redacted**[3,a]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
*De novo BRCA*m (13.25%)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Total eligible TNBC patients	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
HR+ HER2-negative patients						
Incident population (CDK 4/6 inhibitor population)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Recurrent population (66%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Proportion tested for *BRCA*	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%
Recurrent metastatic cancer tested for *BRCA*	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Recurrent metastatic cancer who have received (neo)adjuvant chemotherapy (63%), and tested for *BRCA*	**redacted**[3]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Recurrent metastatic cancer who have received (neo)adjuvant chemotherapy, and *BRCA*m (5%)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
De novo metastatic breast cancer (34%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Proportion tested for *BRCA*	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%
De novo population tested for *BRCA*	**redacted**[3]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
*De novo BRCA*m (5%)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Total eligible HR+ HER2-negative patients	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Total patients eligible for olaparib	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]

Source: Tables 4.2-4.10, pp159-164 of the submission, Table 4.22 and 4.23, pp171-172 of the submission and attached financial spreadsheet.

DUSC = drug utilisation Sub Committee; HER2-negative = human epidermal growth factor receptor negative; HR + = hormone receptor positive; TNBC = triple negative breast cancer

[a] The submission presented an estimate of < 500 which was inconsistent with estimates in the financial spreadsheet and testing considerations in Section 4.5 of the submission.

[b] The submission presented an estimate of 500 to < 5,000 which was inconsistent with estimates in the financial spreadsheet and testing considerations in Section 4.5 of the submission.

[c] The submission presented an estimate of 500 to < 5,000 which was inconsistent with estimates in the financial spreadsheet and testing considerations in Section 4.5 of the submission.

*The **redacted** values correspond to the following ranges*

[1] 20,000 to < 30,000

[2] 500 to < 5,000

[3] < 500

Table 16 presents the estimated number of new *BRCA* tests required as a result of the proposed listing, which ranged from 500 to < 5,000 in Year 1 to 500 to < 5,000 in Year 6. The submission estimated that an increasing proportion of recurrent patients would already know their *BRCA* status from testing in eBC, and would not require testing after diagnosis of mBC. For the TNBC population, the submission stated that recurrence from eBC usually occurs within the first three years (Soares 2021) and estimated that an increasing proportion of the recurrent TNBC population would already know their *BRCA* status at diagnosis of mBC (from redacted% in Year 1 to redacted% in Years 5 and 6). This reduced the estimated number of new *BRCA* tests by up to 500 to < 5,000 tests per year. For the HER2-negative/HR+ population, the submission stated that recurrence from eBC for patients with a known *BRCA* status was not expected within the 6-year time horizon, given HER2-/HR+ patients commonly have recurrence after 5 years and will spend approximately 2 years on CDK4/6 inhibitors. Therefore, the submission assumed a declining rate of new *BRCA* tests performed after mBC diagnosis in the TNBC population (proportion decreases from redacted% in Year 1 to redacted% in Years 5 and 6), but not for the HER2-/HR+ population (proportion increases from redacted% in Year 1 to redacted% testing in mBC from Year 4 onwards).

Table 17: Total uptake of *BRCA* tests

	2025	2026	2027	2028	2029	2030
TNBC Patients						
De novo TNBC taking up *BRCA* testing	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Recurrent TNBC taking up *BRCA* testing	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Total TNBC patients taking up *BRCA* testing	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Proportion of recurrent TNBC who know their *BRCA* status due to eBC testing	**redacted**%	**redacted** %	**redacted** %	**redacted** %	**redacted** %	**redacted** %
Estimated patients who know their status from testing in eBC	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Estimated recurrent patients who take up testing in mBC	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Total TNBC patients requiring test in mBC	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[1]	**redacted**[1]
HR+ HER2- negative patients						
De novo HR+ patients taking up *BRCA* testing	**redacted**[1]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Recurrent HR+ patients taking up *BRCA* testing	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Total number of HR+ patients taking up *BRCA* testing	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Total new *BRCA* tests	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
De novo patients only	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]

Source: Table 4.22 and 4.23, pp171-172 of the submission and attached financial spreadsheet.
HR+ = hormone receptor positive; TNBC = triple negative breast cancer
*The **redacted** values correspond to the following ranges*
[1] *< 500*
[2] *500 to < 5,000*

The submission assumed a test cost of $1,200 based on Item 73295 for g*BRCA* test and applied a MBS rebate of 80%. This was not appropriate as the Greatest permissible gap (GPG) of $98.70

applies. Consequently, applying an 80% rebate (cost of $960 to the MBS) underestimated costs to the MBS compared to a cost considering GPG ($1,101.30) by $141.30 per test. MBS costs adjusted for GPG have been calculated and are presented alongside the financial estimates. Additionally, the submission did not consider the costs of cascade testing, underestimating the costs of testing.

Table 18 presents the estimated use and financial implications in the submission. During the evaluation, two errors were identified. First, the submission financial spreadsheet assumed no usage of olaparib in HR+ *de novo* patients. Second, Cell H111 of the 2d. Patients DTG worksheet included the word "remove" instead of the appropriate number [3] in the cell. Both of these errors were addressed and corrected results are presented below.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of olaparib						
TNBC patients						
Recurrent	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
De novo	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Total treated TNBC patients	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
HR+						
Recurrent metastatic cancer who received (neo)adjuvant chemotherapy	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
De novo	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Total treated HR+ HER2-negative patients	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Total olaparib prescriptions[a]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Total no. patients identified with gBRCA variants following olaparib listing (i.e estimated gBRCA positive patients)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
No. cascade tests (1.8 per patient with gBRCA variants identified)[c]	**redacted**[1]	**redacted**[1]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Recurrent scripts only	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
De novo scripts only	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Net financial implications						
Net cost to PBS/RPBS	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]
Total costs to the MBS for *BRCA* testing (80% rebate)	**redacted**[3]	**redacted**[3]	**redacted**[3,b]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Total costs to the MBS (adjusted for GPG)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Cost of cascade testing to the MBS 73297 ($340 per relative tested)[d]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Total costs to Government	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]
Total cost to Government (adjusted for GPG)	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[5]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total cost to Government (adjusted for GPG and including cascade testing)	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[4]	**redacted**[5]

Source: Table 4.17, p169 of the submission and the attached financial model, corrected during evaluation.
Data in *italics* indicated the Assessment Group's calculated values during its evaluation of the submission which erroneously assumed no usage in HR + *de novo* mBC.
Data in *italics* and underlined indicated the department's calculated values pre-MSAC incorporating the cost of cascade testing/
GPG = Greatest Permissible Gap; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Assumed 13.3 scripts per patient per year.
[b] reported as **redacted** in Table 4.27 of submission, but could not be duplicated and an error was identified during the evaluation.
[c] Number of first degree relatives based on MSAC 1716 - Application for early breast cancer (eBC) *gBRCA* testing considered by MSAC in Nov 2023
[d] Source: MBS online (accessed 26 July 2024).
*The **redacted** values correspond to the following ranges*
[1] < 500
[2] 500 to < 5,000
[3] $0 to < $10 million
[4] $10 million to < $20 million
[5] $20 million to < $30 million.

Table 19 presents the estimated use and financial implications for the *de novo* portion of the population only.

Table 19: Estimated use and financial implications – *de novo* patients only

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost to PBS/RPBS for olaparib	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Net cost to MBS for *BRCA* testing	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Total costs to the MBS (adjusted for GPG)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Net cost to PBS/RPBS/MBS	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Net cost to PBS/RPBS/MBS (adjusted for GPG)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]

Source: attached financial model, corrected
Text in *italics* indicate values calculated during evaluation. The submission erroneously assumed no usage in HR + *de novo* mBC
GPG = Greatest Permissible Gap; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
*The **redacted** values correspond to the following ranges*
[1] $0 to < $10 million

The total cost to the PBS/RPBS of listing olaparib was estimated to be $10 million to < $20 million in Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $90 million to < $100 million in the first 6 years of listing.

The total costs to the MBS, adjusted for GPG was $0 to < $10million in Year 1, increasing to $0 to < $10 million in year 6 and a total of $10 to < $20 million in the first 6 years of listing.

The submission assumed <500 grandfathered patients based on an access program. These patients were added to the incident population in Year 1 of listing. The commentary considered this was reasonable.

The commentary considered that the financial estimates presented may be uncertain as:

- The number of packs of olaparib used may be underestimated as the duration of treatment of olaparib (based on mean usage in OlympiAD) may be underestimated as assessment for progression in clinical practice may be less frequent than in clinical trials therefore patients were less likely to discontinue precisely at progression;
- However the number of eligible patients may be overestimated at it was assumed that 63% of recurrent HR+ mBC patients would have had any (neo)adjuvant chemotherapy in the eBC setting whereas the PBAC had previously considered that 25% may be more reasonable (Table 19, olaparib PSD March 2023 PBAC meeting[12]);
- The submission also did not calculate cost offsets for treatments replaced, which would overestimate total net costs. There is uncertainty if olaparib will replace other costly targeted therapies such as CDK4/6 inhibitors, pembrolizumab or sacituzumab govitecan, or be used sequentially. However, if in practice the more expensive therapies were replaced, cost offsets may be substantial and therefore total net costs would be overestimated; and
- The proportion of *de novo* mBC patients was uncertain. The OlympiAD trial (12.6%) reported a lower proportion of *de novo* patients than the KARMA registry (26%) or ARORA registry (41%). In the base case of the financial estimates the submission used the average of KARMA and AURORA (34%). Should the proportion of patients with *de novo* disease be lower than expected then the number of *BRCA* tests may be overestimated, and vice versa.

15. Other relevant information

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

[12] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/olaparib-psd-03-2023.pdf