Medical Services Advisory Committee (MSAC) Public Summary Document

Application No.1716 – Germline BRCA mutation test to detect BRCA1 or BRCA2 mutations in patients with HER2- negative high risk early breast cancer to determine eligibility for PBS-listed olaparib treatment

Applicant: **AstraZeneca Pty Limited**

Date of MSAC consideration: **30-31 March 2023**

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 submission requested:

- Medicare Benefits Schedule (MBS) listing to determine the presence of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in a patient with triple negative early breast cancer (TNBC) or hormone receptor (HR) positive, HER2-negative early breast cancer with high risk characteristics of high grade tumour (Grade 3) and/or large tumour size (≥2 cm) and/or pathologically involved lymph nodes and/or high recurrence score (multigene assay), requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS).
- PBS listing of olaparib (Lynparza), for the treatment of adult patients with *BRCA*-pathogenic variant, HER2-negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy.

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 deferred its decision for public funding of germline *BRCA* testing to detect *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in patients with HER2-negative early breast cancer to determine eligibility for Pharmaceutical Benefits Scheme (PBS)-listed olaparib treatment. MSAC foreshadowed that it would reconsider this testing if the Pharmaceutical Benefits Advisory Committee (PBAC) recommended the PBS listing of olaparib for the patients in this population who have previously been treated with neoadjuvant or adjuvant chemotherapy. MSAC considered that, in order to inform a recommendation, more information would be required on the projected patient numbers, cost of the test, and other testing requirements. MSAC considered that expanding MBS item 73295 would be preferable to introducing a new MBS item for this patient population, and considered that the item could be futureproofed by generalising it to all PARP inhibitors, not just olaparib.

Consumer summary

This was an application from AstraZeneca requesting an expansion of MBS item 73295 to include a new population: people with triple-negative early breast cancer (TNBC) or hormone receptor (HR)-positive, HER2-negative, early breast cancer with high-risk characteristics of high-grade tumour, to determine if they can access a medicine called olaparib (a type of PARP inhibitor). This was a codependent submission to MSAC and the Pharmaceutical Benefits Advisory Committee (PBAC).

MBS item 73295 is for genetic testing for germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in people with advanced (FIGO III–IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, for access to PARP inhibitors.

A genetic variant is a permanent difference in a gene's DNA sequence. A genetic variant can be inherited (called a germline variant) if it is present in a person's egg or sperm, or it can be created in the cells of the body that do not pass on DNA to the person's children (called a somatic variant). If a germline variant has the potential to cause disease, it is called a pathogenic variant.

Some drugs are more likely to work better if the person has certain variants. In this case, drugs called PARP inhibitors work for people with variants in their *BRCA1* or *BRCA2* genes.

Because this test is for germline pathogenic variants, which means the variants can be inherited or passed down to children, MSAC considered it appropriate that *BRCA1/2* cascade testing be available for biological relatives, as pathogenic variants in the *BRCA* genes also increases that person's chance of developing certain types of cancer.

MSAC and the PBAC agreed that olaparib appeared to benefit this group of patients in terms of surviving longer without metastatic disease, and it appeared to be safe. MSAC considered the test itself to be effective and safe. However, MSAC noted that the PBAC did not recommend access to PARP inhibitors because they did not appear to be good value for money, and the PBAC wanted more information about this and how value for money could be improved. MSAC also wanted more information from AstraZeneca about how many people would actually need this testing, including those eligible for cascade testing, so that it had a better idea of how much this service would cost the government.

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

MSAC deferred its decision about expanding MBS item 73295 to include people with TNBC or HR-positive, HER2-negative early breast cancer with high-risk characteristics of high-grade tumour, to determine if they can access olaparib. MSAC considered the test to be safe and effective in this group of patients, but wanted more information on how much expanded testing will cost the government and clarity around the wording in the MBS item descriptor. When the PBAC reconsiders their part of the application, and when MSAC receives the extra information about costs, MSAC will reconsider the testing for this group of patients.

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

MSAC noted that this was a streamlined, codependent application from AstraZeneca Pty Ltd requesting MBS listing to determine the presence of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in a patient with triple-negative early breast cancer (TNBC) or hormone receptor (HR)-positive, HER2-negative, early breast cancer with high-risk characteristics of high-grade tumour (Grade 3) and/or large tumour size (≥2 cm) and/or pathologically involved lymph nodes and/or high recurrence score (multigene assay), requested by a specialist or consultant physician, to determine eligibility for olaparib under the PBS. MSAC recalled that the original application received in March 2022 was an application for testing of breast tumour

tissue (or germline testing if tumour testing is not feasible) to detect clinically significant gene variants of the *BRCA1* or *BRCA2* genes to determine eligibility for olaparib for the treatment of HER2-negative high-risk early breast cancer. However, the applicant modified the current proposal to include MBS listing of the g*BRCA* pathogenic/likely pathogenic variant test only, in line with the inclusion criteria of the OlympiA (the clinical utility standard) trial. MSAC also recalled that it had previously 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 (application 1380 in November 2016 and application 1554 in July 2020) and prostate cancer (application 1618 in November 2021).

MSAC noted that *BRCA1/2* testing is well established in Australia, with laboratories using next-generation sequencing (NGS) methodology. MSAC considered it reasonable that testing concordance will be high between NGS and the Sanger sequencing method used in the clinical trials.

MSAC noted that in the event that funding for the proposed *BRCA1/2* testing were approved, there were two options to consider for implementation:

- introduce a new MBS item for the testing, which may cause inconsistency in the MBS and may cause MBS items to be complex and confusing for requesting practitioners, which may in turn affect patient management
- amend existing MBS item 73295 to include the proposed population, which was the preferred option.

The MBS currently subsidises similar services to the one proposed in this application, but there is variation in the current schedule fees. MSAC recalled it had initially supported *BRCA1/2* testing at $1,200, although it noted the MSAC Executive advised in March 2022 that the fee should be reduced to $1,000, which aligns with MBS item 73304 for detection of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in a patient with metastatic castration-resistant prostate cancer. However, MSAC noted that MBS item 73295 still has a fee of $1,200, and that the department is 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.

MSAC noted the proposed descriptor and amendments to the existing descriptor for MBS item 73295. MSAC considered that the current descriptor insufficiently defined the eligible patient population, and recommended the following amendments to the descriptor's wording: "… either triple-negative early breast cancer or hormone receptor-positive, HER2-negative, early breast cancer with 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 nodes metastases.

MSAC noted that the application's intention was to identify patients that had at least one of the high-risk characteristics, and considered these amendments to better reflect the intended population.

On the question of whether the eligible testing population could be better aligned to the population for the co-dependent therapy, MSAC noted the applicant's pre-MSAC response that

not aligning the two populations would mean opening the test to a broader population (e.g., all breast cancer patients) who may not be eligible for treatment with olaparib under the proposed PBS restriction, despite knowing their *BRCA* status, which may be a cause for confusion to clinicians and disappointment to patients.

MSAC noted that the original proposed MBS descriptor included reference to a high recurrence score through multigene assays. MSAC queried whether reference to EndoPredict® should be included in the descriptor, as this is the only multigene assay supported for public funding to date. However, MSAC considered that as those eligible for testing for EndoPredict® would already be captured as eligible patients under the proposed amendments to MBS item descriptor 73295, a reference to EndoPredict® did not need to be included.

MSAC supported adding PN.0.27, which states that patients who are found to have any form of affected allele should be referred for post-test genetic counselling, to the MBS item.

MSAC noted the department's suggestion of referring to olaparib as "a PARP inhibitor", to ensure current access to treatments other than olaparib would not be adversely affected. MSAC noted that MBS item 73295 was amended on 1 September 2022 to replace the specific drug name of "olaparib" with the name of the relevant class of drugs (i.e. a PARP inhibitor). This change was recommended by the MSAC Executive to expand the use of the item to determine PBS eligibility for niraparib and other PARP inhibitors that may be approved in the future by PBAC for listing on the PBS for the treatment of the conditions listed in MBS item 73295. MSAC advised it would reconsider the potential amendments to the MBS item descriptor 73295 for any future resubmission. MSAC noted the applicant's willingness (in the pre-MSAC response) to work with the department to make suitable edits to the 73295 MBS item descriptor.

Table 1 MSAC's advice of potential amendment to MBS item descriptor 73295

	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 or HER2-negative high-risk breast cancer for whom testing of tumour tissue is not feasible, 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), where: HER2-negative high-risk breast cancer is classified as either triple negative early breast cancer or hormone receptor positive, HER2-negative, early breast cancer with at least one of the following high-risk characteristics: (i) tumour histological grading of at least 3; or (ii) tumour size of greater than 2 cm; or ~~(iii)~~ one or more axillary lymph node metastases Maximum of one test per patient's lifetime Fee: $1,200.00 Benefit: 75% = $900.00; 85% = $1106.80* (See para PN.0.27 of explanatory notes to this Category)	
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.	

* 85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of $93.20. All out-of-hospital Medicare services that have an MBS fee of $621.50 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 the proposed clinical management algorithm did not include cascade testing. However, MSAC considered that this proposed intervention would trigger cascade testing for patients found to have *BRCA1/2* pathogenic/likely pathogenic variants, which was not considered in the assessment. MSAC considered that cascade testing was appropriate for this population because it involved germline testing, and supported cascade testing of biological relatives under MBS item 73297 for those who are found to carry *BRCA1/2* pathogenic variants.

MSAC noted that in considering the funding application for the codependent therapy olaparib, the PBAC "did not recommend listing olaparib for the treatment of human epidermal growth factor 2 negative (HER2-) high risk early breast cancer with a confirmed germline *BRCA1/2* (g*BRCA1/2*) variant in patients who have previously been treated with neoadjuvant or adjuvant chemotherapy. The PBAC considered that olaparib was superior to placebo in terms of invasive disease-free survival, while noting that overall survival (OS) data remained immature, and inferior to placebo in terms of safety. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was uncertain and unacceptably high. The PBAC considered that revisions were required to the financial estimates with respect to patient estimates and duration of treatment". MSAC noted that the PBAC nominated an early re-entry resubmission pathway for this application.

MSAC noted the main clinical evidence for the codependent therapy was derived from the OlympiA trial, which compared olaparib to placebo in patients with g*BRCA1/2* pathogenic/likely pathogenic variant-associated early breast cancers and high-risk clinico-pathological features. MSAC noted that olaparib was non-inferior compared to placebo in terms of comparative safety (adverse events [AEs]: 91.8% vs 83.8%; serious AEs: 8.7% vs 8.6%; death: 0.1% vs 0.2%).

MSAC noted that the clinical outcomes measured were (hazard ratio [95% confidence interval]):

- invasive disease-free survival (IDFS; 0.63 [0.50, 0.78])
- distant disease-free survival (DDFS; 0.61 [0.48, 0.77])
- overall survival (OS; 0.68 [0.50, 0.91]).

MSAC concluded from the above clinical outcome measures that olaparib was superior to placebo in terms of comparative effectiveness. However, MSAC noted that TNBC patients were over-represented in the OlympiA trial in comparison to the Australian setting, which could have overestimated the effectiveness of olaparib.

MSAC noted ESC's concern that the application's economic model assumed a g*BRCA*m prevalence of 13.25% of the tested population (early triple-negative or HR-positive, HER2-negative), which was likely an overestimate. MSAC noted the pre-MSAC response that "prevalence of 13.25% is appropriate given it was estimated by a simple mean calculation of three studies incorporating 1,102 patients. PBAC did not consider the rate of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant prevalence an issue". However, MSAC disagreed with the approach used to attain 13.25% (based on a simple mean from three studies. MSAC advised the PBAC may wish to consider whether 13.25% was a reasonable estimate of the prevalence of *BRCA1/2* pathogenic variants in the early triple-negative or HR-positive, HER2-negative population. MSAC also noted that the economic model assumed that 74% of patients were currently undergoing g*BRCA1/2* testing. The was likely an overestimate, as g*BRCA1/2* testing is recommended for a subset of people with breast cancer. MSAC noted the pre-MSAC response that stated that Australian IPSOS data reported that 74% of TNBC patients currently received BRCA testing. The pre-MSAC response indicated that the ICER was only marginally sensitive to this assumption (increasing from $45,000 to <$55,000to $45,000 to <$55,000 if a weighted average of 33.5% was used). MSAC noted that the IPSOS report could not be located to verify these numbers.

MSAC noted the financial impact of listing, which was from a societal and individual payer perspective. Including cascade testing, the total budget impact to the MBS was $0 to < $10 million in year 1 to $0 to < $10 million in year 6. However, MSAC noted that this was based on a fee of $1,000 and cascade testing for 1.8 biological relatives (per *BRCA1/2* positive patient). MSAC was concerned that the numbers of high-risk patients were underestimated, especially the HER2-positive cases, which means that the projected financial impacts would also be underestimated after taking account of the additional cascade testing associated with these additional patients.

MSAC accepted the claims of non-inferior safety and superior effectiveness, but considered that the descriptor wording needed to accurately reflect the intended population, and the fee and population numbers required further interrogation. MSAC also wanted more certainty about the financial impact. Considering these issues and that PBAC did not recommend listing olaparib for this indication, MSAC deferred its decision.

4. Background

MSAC has previously 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 and 1554).

MSAC initially supported MBS funding of germline *BRCA* testing to determine eligibility for olaparib (Application 1380 Public Summary Document [PSD]). MSAC recognised that germline *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) as MSAC considered that it was biologically plausible that women with a somatic or germline *BRCA* (g*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.

In March 2022, the Department of Health and Aged care received an application (MSAC 1716) seeking MBS subsidy to test breast tumour tissue (or germline testing if tumour testing is not feasible) to detect pathogenic variants of the *BRCA1* or *BRCA2* genes to determine eligibility for olaparib for the treatment of HER2-negative high risk early breast cancer. The MSAC Executive's advice was sought regarding the appropriate assessment pathway and type of codependent submission for MSAC Application 1716. The MSAC executive determined that it was appropriate for the MSAC submission to proceed via a streamlined codependent pathway. This allowed the submission to by-pass the MSAC PICO advisory sub-committee (PASC), and the MSAC Evaluation sub-committee (ESC) and progress directly to MSAC for consideration. The initial MSAC Application 1716 requested a tumour test and germline test to identify *BRCA* gene pathogenic variants, however, based on advice provided by the Department (pre-PBAC meeting and MSAC Executive) and clinicians, the applicant modified the proposal to include MBS-listing of the g*BRCA* pathogenic variant test only, in line with the inclusion criteria of the OlympiA (the clinical utility standard) trial.

5. Prerequisites to implementation of any funding advice

The submission stated that germline *BRCA1/2* pathogenic variant testing services are widely available in Australia and the current reference standard for *BRCA* pathogenic variant testing is Next Generation Sequencing (NGS). The National Pathology Accreditation Advisory Council (NPAAC) advised that *BRCA1/2* testing is well established in a number of laboratories in Australia and that an external quality assurance is available through the European Molecular Genetics Quality Network (EMQN).

At submission lodgement, the applicant stated that olaparib was under review by the TGA for *BRCA* pathogenic variant, HER2 negative, early breast cancer. A TGA submission made for this indication proceeded past the first round of assessment. A TGA decision was expected in April 2023.

6. Proposal for public funding

Table 2 Proposed MBS item descriptor

	Category 6 – Pathology Services
MBS item XXXX	Group P7 – Genetics
Detection of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants, in a patient with triple negative early breast cancer or hormone receptor positive, HER2-negative, early breast cancer with high risk characteristics (i) tumour histological grading of at least 3, (ii) tumour size of greater than 2 cm, (iii) cancer cells in any positive axillary lymph nodes, (iv) high recurrence score (multigene assay[α]), requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS) Maximum one test per lifetime Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,112.10	
Explanatory notes Patients who are found to have a pathogenic or likely pathogenic variant in *BRCA*1 or *BRCA*2 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.	

Source: Table 1.7, p30 of the submission.
BRCA = breast cancer gene, HER2 = human epidermal growth factors receptor 2, MBS = Medicare Benefits Schedule.

[α] Multigene recurrence risk assays such OncotypeDX 21 gene tests are not currently MBS-listed. EndoPredict has been recommended for public funding by MSAC (MSAC Application 1408.1)

The proposed high-risk population for olaparib differed from the population for *BRCA1/2* testing. The definition of high risk of recurrence in the proposed PBS restriction was defined as any of:

- TNBC patient who has received prior neoadjuvant chemotherapy and has residual invasive cancer in the breast and/or resected lymph nodes;
- Hormone receptor positive, HER2-negative, patient who has received prior neoadjuvant chemotherapy and has residual invasive cancer in the breast and/or resected lymph nodes;
- TNBC patient who has received prior adjuvant chemotherapy and has node positive disease or primary tumour greater than 20 mm;
- Hormone receptor positive, HER2-negative, patient who has received prior adjuvant chemotherapy and has 4 or more positive lymph nodes.

Due to the large population eligible for BRCA1/2 testing and the high associated cost, MSAC may wish to advise whether it would be appropriate to better target BRCA1/2 testing to the population eligible for olaparib treatment. If it is feasible perform BRCA1/2 testing following

surgery (and neoadjuvant chemotherapy where applicable) without delaying initiation of olaparib, this population may include:

- *TNBC patients with node positive disease or primary tumour greater than 20 mm who will commence adjuvant chemotherapy;*
- *Hormone receptor positive, HER2-negative patients with 4 or more positive lymph nodes who will commence adjuvant chemotherapy;*
- *TNBC patients with residual invasive cancer in the breast and/or resected lymph nodes following neoadjuvant chemotherapy;*
- *Hormone receptor positive, HER2-negative patients with residual invasive cancer in the breast and/or resected lymph nodes following neoadjuvant chemotherapy.*

The proposed test cost is higher ($1,200) compared to the MBS item 73304 fee ($1000) for *BRCA1/2* testing of prostate tumour tissue (Application 1618). The proposed MBS listing would likely substantially increase the number of people eligible for *BRCA1/2* testing on the MBS (refer to financial implications). 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.

The submission noted that germline *BRCA1/2* pathogenic variant testing provided information about familial risk and facilitates cascade testing in unaffected family members.

7. Population

The submission proposed detection of germline *BRCA*1 or *BRCA*2 pathogenic or likely pathogenic gene variants, in a patient with triple negative early breast cancer (eBC) or hormone receptor positive, HER2-negative, early breast cancer with high risk characteristics (i) tumour histological grading of at least 3, (ii) tumour size of greater than 2 cm, (iii) cancer cells in any positive axillary lymph nodes, (iv) high recurrence score (multigene assay), requested by a specialist or consultant physician, to determine eligibility for olaparib under the PBS.

The submission focused on germline *BRCA* pathogenic variant, HER2-negative high risk early breast cancer. This included all patients with invasive, non-metastatic breast cancer, harbouring germline pathogenic variants in one or both *BRCA* genes (*BRCA*1 and/or *BRCA*2), with the absence of the HER2 biomarker.

HER2-negative breast cancer can be either hormone receptor (HR) negative (triple negative breast cancer [TNBC]) or HR positive (i.e. HR-positive/HER2-negative). Early-stage breast cancer (Stages I to III) is defined as disease confined to the breast with or without regional lymph node involvement and in the absence of metastatic disease. Early-stage breast cancer is a heterogeneous disease and optimal treatment depends on pathological and molecular characterisation of the tumour subset to classify tumours as (1) oestrogen receptor (ER) and/or progesterone receptor (PgR) positive or negative, (2) HER2-positive or negative, or (3) triple negative. Treatment for Stages I to III breast cancer usually includes surgery and radiation therapy, often with chemotherapy or other drug therapies either before (neoadjuvant) or after (adjuvant) surgery. Studies have shown that the risk of recurrence in early breast cancer is highest during the first 5-years after diagnosis, with a significant decrease and plateauing of the recurrence rate thereafter. Based on the results from OlympiA trial, olaparib provides an oral chemotherapy-free treatment option personalised to a patient's unique *BRCA* pathogenic variant in early breast cancer. The results of the OlympiA trial highlight the value of testing for *BRCA* pathogenic variants at diagnosis, and also illustrates the importance of adjuvant therapy for patients with HER2-negaitve high risk early breast cancer in reducing recurrence.

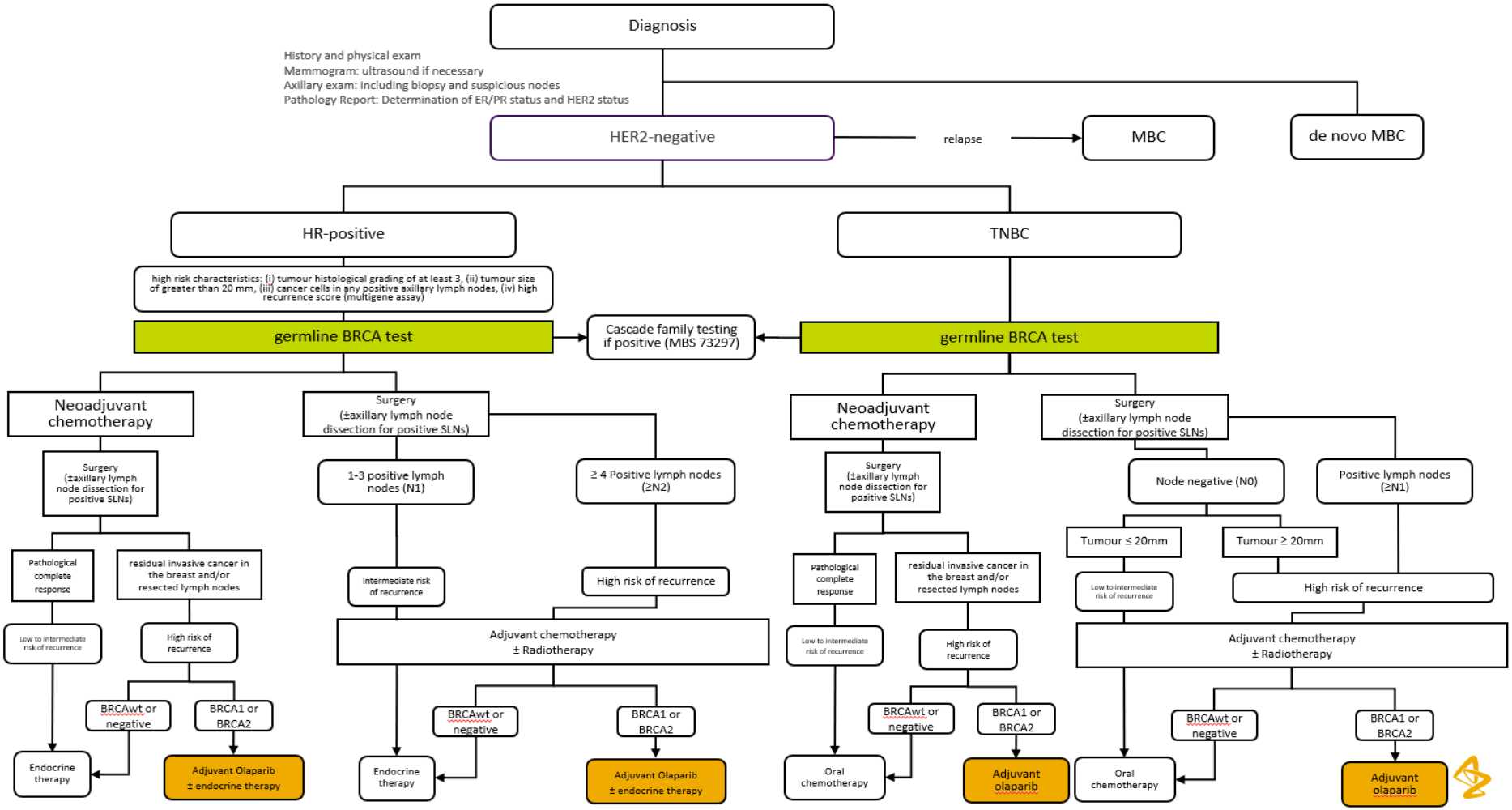
The current and proposed treatment algorithm for a patient newly diagnosed with *BRCA1* or *BRCA* 2 pathogenic variant, HER2-negative high risk early breast cancer is shown in Figure 1. At present there are no specific guidelines to treat women newly diagnosed *BRCA1* and/or *BRCA*2 pathogenic variant HER2-negative high risk early breast cancer, which was the population of focus in the submission.

The current algorithm is based on local and international clinical practice guidelines for patients newly diagnosed with *BRCA*1 and/or *BRCA*2 pathogenic variant HER2-negative high risk early breast cancer. The current clinical management does not have a recommendation to test TNBC and HR-positive, HER2-negative early breast cancer patients with high risk tumour characteristics to test for the presence of a *BRCA*1 or *BRCA*2 pathogenic variant at diagnosis. Patients who are identified to be high risk of recurrence of cancer receives neoadjuvant or adjuvant chemotherapy (with anthracyclines and/or taxanes) followed by oral chemotherapy and endocrine therapy if HR-positive.

The proposed clinical management algorithm included the proposed medical service (germline *BRCA* variant test) at diagnosis of Immunohistochemistry (IHC) status of breast cancer. It is proposed olaparib treatment be provided in adult patients with HER2-negative high risk early breast cancer with a confirmed *BRCA*1 and/or *BRCA*2 variant, who must have completed definitive local treatment and have previously been treated with neoadjuvant or adjuvant chemotherapy (containing anthracyclines and/or taxanes). Patients who received prior neoadjuvant chemotherapy; both TNBC patients and HR-positive patients must have had residual invasive cancer in the breast and/or resected lymph nodes. Patients who had received prior adjuvant chemotherapy; TNBC patients must have had node positive disease or primary tumour greater than 2 cm, HR-positive patients must have had 4 or more positive lymph nodes.

Those patients who test negative to *BRCA* variants or test positive to *BRCA* wild type (*BRCA*wt) variant will receive similar treatment options under the current clinical management algorithm i.e. oral chemotherapy and endocrine therapy, if HR-positive.

Figure 1 **Proposed clinical treatment algorithm**



Abbreviations: *BRCA*, BReast CAncer gene; *BRCA*wt, BReast CAncer gene wild type; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; MBS, Medicare Benefits Schedule; PR, progesterone receptor; SLN, sentinel lymph node biopsy; TNBC, triple negative breast cancer

8. Comparator

Test

The comparator for *BRCA*1/2 testing was 'no testing'. The MSAC executive noted that germline *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 *BRCA*1 and *BRCA*2 genes, 2020), to identify suitable candidates for germline *BRCA* pathogenic variant testing for the purpose of familial cancer risk assessment. The eviQ guidelines currently recommend *BRCA* pathogenic variant testing for the purpose of familial cancer risk assessment in individuals with a greater than 10% probability of carrying a 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 *BRCA*1/2 testing would be a comparator. *This was appropriate.*

Codependent drug

The nominated comparator for olaparib was placebo ("watch and wait").

9. Summary of public consultation input

Consultation feedback was received from five (5) organisations and one individual specialist. The organisations included a consumer group, medical and a genomics organisation:

- Pink Hope
- The Medical Oncology Group of Australia (MOGA)
- The Royal College of Pathologists of Australasia (RCPA)
- Australian Genomics (AG)
- Omico

All feedback received was supportive of public funding for the proposal and acknowledged that it would grant more patients the opportunity to better inform their treatment options. All input agreed that funding the test will increase equity of access as many patients with TNBC currently fund their own test.

Half of the input noted the OlympiA study to support the benefits to patients with PARP inhibitors with proven germline BRCA 1/2 mutations through testing. MOGA noted the current MBS items for germline genetic testing for BRCA 1/2 requires patients to have a 10% chance of having a pathogenic/likely pathogenic variant. They considered this threshold to be inappropriate in the setting of new targeted therapies that improve survival for patients in this population. MOGA strongly supported the indication being for germline testing using blood not tumour tissue.

Pink Hope supported expanding access to the test for a wider cohort of patients as it will allow more patients to be eligible to PBS subsidised treatments that are more personalised which gives

greater access to treatment options and may improve survival outcomes for these patients. They considered more patients should have access to this test to inform their decision making in regards to treatment options and may benefit other family members in being aware of their cancer risk and how to manage it. They noted however, that passing this information onto some family members may cause anxiety but that genetic counselling should be accessible to support these patients and their families in understanding the information and managing the potential anxiety caused.

Australian Genomics noted there may be increases in workload for diagnostic testing laboratories and for clinical genetic services with the public funding of the proposal that would need to be managed. They suggested that BRCA testing for women with breast cancer for any indication may be more appropriate as part of a broader gene panel so that families of the patient would benefit from this information as well. They also considered that amending MBS item numbers as opposed to creating new item numbers would be beneficial in practice, so as to avoid the risk of introducing complexities and making it confusing for the clinician ordering the test.

RCPA did not agree that 'high risk early breast cancer' was well defined in the application. They considered the application proposes to target eligibility for the test beyond TNBC, despite lacking evidence to justify expanding the population. Conversely, MOGA recommended that 'high risk' not be limited to the definition used in the OlympiA clinical trial considering it too restrictive. They considered that medical oncologists are well placed to quantify risk of recurrence and death for each individual patient so the indication should not restrict their ability to define a patient as 'high risk'.

10. Characteristics of the evidence base

The clinical evidence for this submission was based on the pivotal OlympiA trial comparing olaparib to placebo (watch and wait). Key features of the randomised trial are summarised in Table 3.

Table 3 Key features of the included evidence

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
olaparib vs. placebo						
OlympiA	1836 (1830 women and 6 men)	R, DB, PC, MC 3.5 years	*Low*	HER2 negative, *BRCA* pathogenic variant positive, eBC[1] previously treated with chemotherapy.	Primary outcome: IDFS. Secondary outcomes: OS, DDFS, FACIT-Fatigue, EORTC QLQ-C30, safety	IDFS EORTC QLQ-C30

Source: Figure 2.2, p41, table 2.4, pp43-44, table 2.8 pp50-54, table 2.14, pp64-66, table 2.11, p58 of the submission.
BRCA = breast cancer gene, DB = double blind, DDFS = distant disease-free survival, eBC = early breast cancer, EORTC = European Organisation for the Research and Treatment of Cancer, FACIT = functional assessment of chronic illness therapy, IDFS = invasive disease-free survival, MC = multi-centre, OS = overall survival, PC = placebo controlled, QLQ-C30 = quality of life questionnaire core 30, R = randomised.

[1] Patients could be positive or negative for hormone receptors. This was a stratification factor during randomisation.

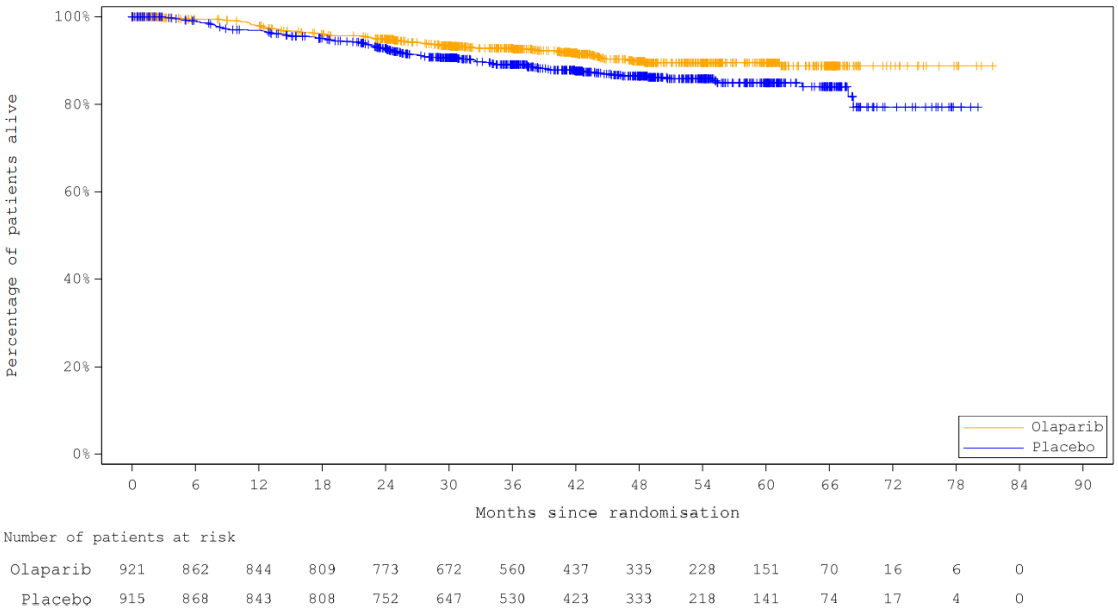
The clinical evidence based on the pivotal OlympiA trial comparing olaparib to placebo ('watch and wait') in patients with HER2-negative high risk early breast cancer compared the efficacy of the poly (adenosine diphosphate-ribose) polymerase inhibitor (PARPi), olaparib, in patients with HER2-negative high risk early breast cancer with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants and high risk clinicopathological factors who had received local treatment and ≥ six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines and/or taxanes[2].

The trial was designed to include only patients with g*BRCA*1/2 pathogenic variant-associated early breast cancers and high-risk clinico-pathological features as these patients remain at an increased risk for recurrence following standard multimodality therapies and are predicted to benefit from adjuvant PARP inhibitor therapy with olaparib[3].Treatment with olaparib was administered for up to 12 months and the results, at a median follow-up of 3.5 years and 3.6 years for olaparib and placebo arms respectively, showed that treatment with olaparib resulted in a statistically significant and clinically meaningful reduction of 37.2% in the risk of invasive disease recurrence or death compared with placebo (HR 0.628; 95% CI: 0.504, 0.779; p=0.0000233) (Figure 4). Subgroup analyses of the IDFS outcome were consistent with the primary analysis, with the treatment benefit of olaparib over placebo evidenced across most of the predefined subgroups. Notably, there was no evidence to indicate a differential treatment effect based on HR status, such that subgroup analyses demonstrated no difference in response between the HR-positive, HER2-negative and TNBC population for the primary outcome (p=0.754). The OS (Figure 5) results showed a statistically significant 32.2% risk reduction in the olaparib arm compared to the placebo arm (HR 0.678; 95% CI: 0.503, 0.907; p=0.0091). Similarly, there was a statistically significant and clinically meaningful 39.3% reduction in the risk of distant disease recurrence or death for olaparib versus placebo (HR 0.607; 95% CI: 0.476, 0.771; p=0.0000421).

[2] Tutt ANJ et al. 2021 OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. *N Engl J Med*.384(25):2394-2405.

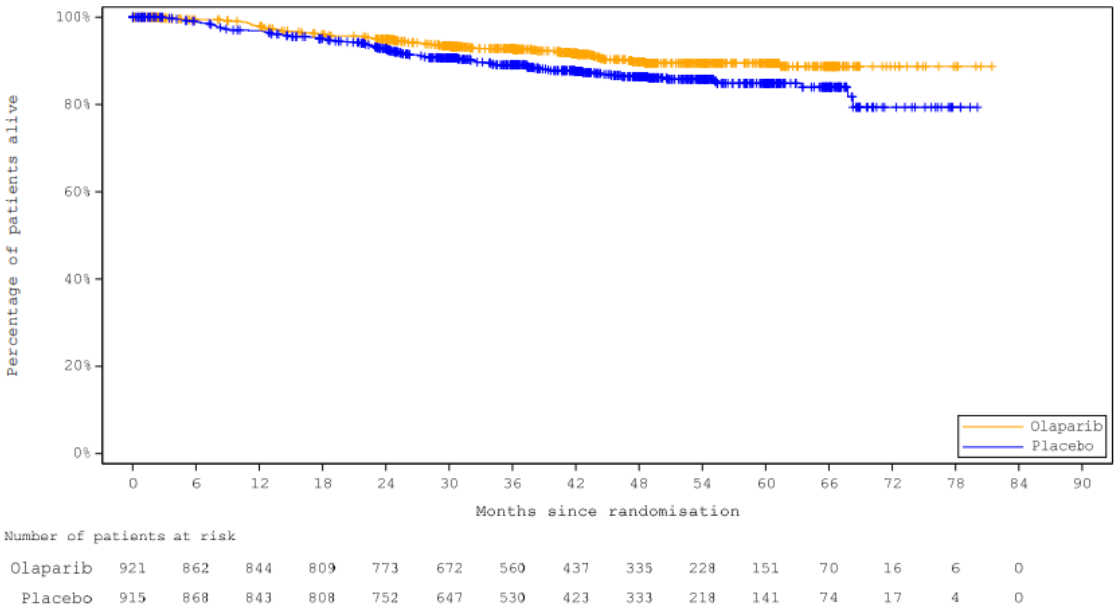
[3] Kurian, Allison W., et al. 2021 "Predicted chemotherapy benefit for breast cancer patients with germline pathogenic variants in cancer susceptibility genes." *JNCI Cancer Spectrum* 5.1 pkaa083.

Figure 2: Kaplan-Meier Plot for IDFS (ITT Population) in OlympiA at median follow-up of 3.5 and 3.6 years (olaparib and placebo respectively)



Source: Figure 2.3, p68 of the submission.
IDFS = Invasive disease-free survival, ITT = Intention-to-treat

Figure 3: Kaplan-Meier Plot for OS (ITT Population) in OlympiA at median follow-up of 3.5 and 3.6 years



Source: Figure 2.5, p71 of the submission.
ITT = intention to treat, OS = overall survival.

Overall, the incidence of AEs was higher in the olaparib arm than the placebo arm (91.8% vs 83.8%, respectively). However, the incidence of serious adverse events (SAEs) remained similar across the olaparib and placebo arms (8.7% vs 8.6%, respectively). A greater proportion of patients in the olaparib arm experienced AEs leading to discontinuation of study treatment (10.8% for olaparib vs 4.6% for placebo), dose reduction (23.4% for olaparib vs 3.7% for placebo) and dose interruption (31.4% for olaparib vs 11.0% for placebo). It is important to note that

despite this increased occurrence of AEs observed among patients receiving olaparib, the rate of AEs resulting in death during study treatment, or 30-day safety follow-up remained balanced between both treatment groups, which occurred in one patient in the olaparib arm (0.1%) and two patients in the placebo arm (0.2%).

The clinical evaluation demonstrated that, in patients with HER2-negative high-risk early breast cancer with confirmed *BRCA*1 and/or *BRCA*2 pathogenic variant who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (with anthracyclines and/or taxane), olaparib was superior compared to placebo in terms of comparative efficacy (IDFS, DDFS, OS) and olaparib was noninferior compared to placebo in terms of comparative safety. Results of key outcomes in the OlympiA trial DCO2 (median follow up of 3.5 years) are shown in Table 4.

Table 4: Results of key outcomes in the OlympiA trial DCO2 (median follow up of 3.5 years)

Outcome	Olaparib n/N (%)	Placebo n/N (%)	Relative risk (95% CI)	Hazard ratio (95% CI)	Median time to event
IDFS	134 /921 (14.5%)	207/ 915 (22.6%)	**0.64 (0.53, 0.78)**	**0.63 (0.50, 0.78)**	**NR**
OS	75/921 (8.1%)	109/ 915 (11.9%)	**0.68 (0.52, 0.90)**	**0.68 (0.50, 0.91)**	**NR**
DDFS	107/921 (11.6%)	172/ 915 (18.8%)	**0.62 (0.49. 0.77)**	**0.61 (0.48, 0.77)**	**NR**

Source: Table 2.16, p68, table 2.17, p69, and table 2.18, p71 of the submission).
CI = confidence interval, DDFS = distant disease-free survival, IDFS = invasive disease-free survival, n = number of participants with event, N = total participants in group, NR = not reached; OS = overall survival. **Bold** indicates statistically significant results.

11. Comparative safety

Test

The submission did not make an explicit clinical claim with respective to comparative safety. The submission stated that germline *BRCA* pathogenic variant testing is currently offered by several Australian pathology providers using in-house developed NGS-based testing methods*. It is unlikely that there will be adverse events from the testing procedure. BRCA1/2* testing using NGS is highly accurate and is unlikely to have downstream safety concerns from false positive or false negative test results.

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 compared to placebo. The PBAC commentary considered that the claim was not adequately supported as the olaparib arm had a higher incidence of all AEs, a higher incidence of grade 3 or higher AEs, and a higher incidence of AEs leading to dose reduction, interruption, or discontinuation, compared to the placebo arm and also the long-term risk of MDS/AML. As the comparator was placebo, this is a reasonable outcome. Furthermore, the PBAC commentary considered the safety profile of olaparib in the OlympiA trial aligns with what is already established for olaparib in the indications for which it has received PBAC and TGA approval.

12. Comparative effectiveness

The primary outcome for the OlympiA trial was IDFS. This involved investigator assessed recurrence of invasive disease or death. The results of IDFS from the OlympiA trial are shown in Table 4. The olaparib arm of the trial showed a statistically significant reduction in recurrence

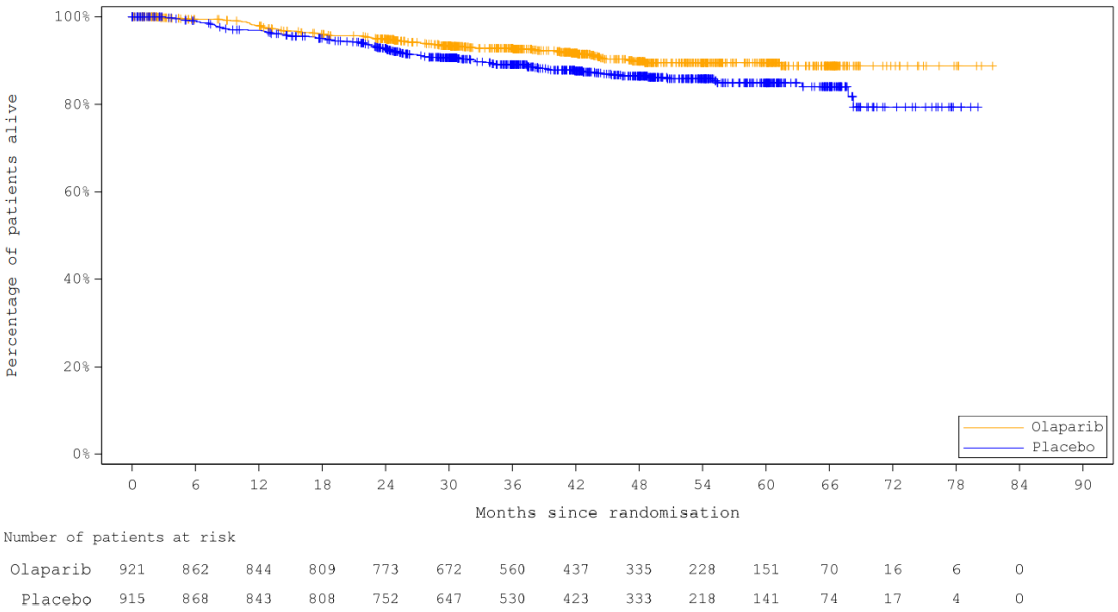
when compared to placebo (14.5% in olaparib, 22.6% in placebo hazard ratio 0.63 (95% CI 0.50, 0.78) at DCO2). The Kaplan-Meier curves for IDFS in the OlympiA trial are presented in Figure 4.

Secondary outcomes included OS and DDFS. *The OS data were immature at DCO2 (75 (8.1%) deaths in olaparib and 109 (11.9%) deaths in placebo) owing to the long survival seen in eBC patients.* The submission stated that the deaths observed in the OlympiA trial were from "early progressors" and the likely full extent of OS gain had not been realised and likely will not be observed for many years after the trial has concluded. The OS results from the OlympiA trial are displayed in Table 4. At the most recent data cut off (12th of July, 2021, median follow-up 3.5 years), there was a statistically significant difference in OS (hazard ratio 0.68 (95% CI 0.50, 0.91)). *The median OS had not been reached.* The Kaplan-Meier curves for OS in the OlympiA trial are presented in Figure 5.

The DDFS data from the OlympiA trial are also presented in Table 4 and these findings align with the results for IDFS. The olaparib arm had a distant recurrence rate of 11.6% while the placebo arm had a distant recurrence rate of 18.8% at DCO2. This was a statistically significant difference (11.6% in olaparib vs. 18.8% in placebo, hazard ratio 0.61 (95% CI 0.48, 0.77).

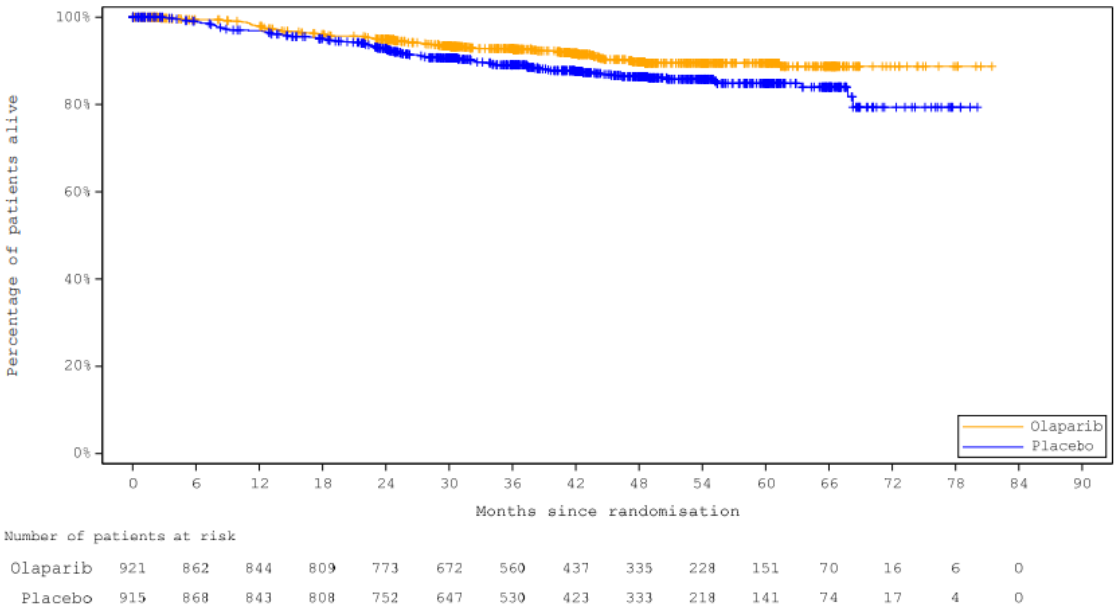
Treatment with olaparib was administered for up to 12 months and the results, at a median follow-up of 3.5 years and 3.6 years for olaparib and placebo arms respectively, showed that treatment with olaparib resulted in a statistically significant and clinically meaningful reduction of 37.2% in the risk of invasive disease recurrence or death compared with placebo (HR 0.628; 95% CI: 0.504, 0.779; p=0.0000233) (Figure 4). Subgroup analyses of the IDFS outcome were consistent with the primary analysis, with the treatment benefit of olaparib over placebo evidenced across most of the predefined subgroups. Notably, there was no evidence to indicate a differential treatment effect based on HR status, such that subgroup analyses demonstrated no difference in response between the HR-positive, HER2-negative and TNBC population for the primary outcome (p=0.754). The OS (Figure 5) results showed a statistically significant 32.2% risk reduction in the olaparib arm compared to the placebo arm (HR 0.678; 95% CI: 0.503, 0.907; p=0.0091). Similarly, there was a statistically significant and clinically meaningful 39.3% reduction in the risk of distant disease recurrence or death for olaparib versus placebo (HR 0.607; 95% CI: 0.476, 0.771; p=0.0000421).

Figure 4: Kaplan-Meier Plot for IDFS (ITT Population) in OlympiA at median follow-up of 3.5 and 3.6 years (olaparib and placebo respectively)



Source: Figure 2.3, p68 of the submission.
IDFS = Invasive disease-free survival, ITT = Intention-to-treat

Figure 5: Kaplan-Meier Plot for OS (ITT Population) in OlympiA at median follow-up of 3.5 and 3.6 years



Source: Figure 2.5, p71 of the submission.
ITT = intention to treat, OS = overall survival.

Overall, the incidence of AEs was higher in the olaparib arm than the placebo arm (91.8% vs 83.8%, respectively). However, the incidence of serious adverse events (SAEs) remained similar across the olaparib and placebo arms (8.7% vs 8.6%, respectively). A greater proportion of patients in the olaparib arm experienced AEs leading to discontinuation of study treatment (10.8% for olaparib vs 4.6% for placebo), dose reduction (23.4% for olaparib vs 3.7% for placebo)

and dose interruption (31.4% for olaparib vs 11.0% for placebo). It is important to note that despite this increased occurrence of AEs observed among patients receiving olaparib, the rate of AEs resulting in death during study treatment, or 30-day safety follow-up remained balanced between both treatment groups, which occurred in one patient in the olaparib arm (0.1%) and two patients in the placebo arm (0.2%).

The clinical evaluation demonstrated that, in patients with HER2-negative high-risk early breast cancer with confirmed *BRCA*1 and/or *BRCA*2 pathogenic variant who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (with anthracyclines and/or taxane), olaparib was superior compared to placebo in terms of comparative efficacy (IDFS, DDFS, OS) and olaparib was noninferior compared to placebo in terms of comparative safety. Results of key outcomes in the OlympiA trial DCO2 (median follow up of 3.5 years) are shown in Table 5.

Table 5: Results of key outcomes in the OlympiA trial DCO2 (median follow up of 3.5 years)

Outcome	Olaparib n/N (%)	Placebo n/N (%)	Relative risk (95% CI)	Hazard ratio (95% CI)	Median time to event
IDFS	134 /921 (14.5%)	207/ 915 (22.6%)	**0.64 (0.53, 0.78)**	**0.63 (0.50, 0.78)**	**NR**
OS	75/921 (8.1%)	109/ 915 (11.9%)	**0.68 (0.52, 0.90)**	**0.68 (0.50, 0.91)**	**NR**
DDFS	107/921 (11.6%)	172/ 915 (18.8%)	**0.62 (0.49. 0.77)**	**0.61 (0.48, 0.77)**	**NR**

Source: Table 2.16, p68, table 2.17, p69, and table 2.18, p71 of the submission.
CI = confidence interval, DDFS = distant disease-free survival, IDFS = invasive disease-free survival, n = number of participants with event, N = total participants in group, NR = not reached; OS = overall survival. **Bold** indicates statistically significant results.

Hormone receptor status was a stratification factor in the OlympiA trial, which included a smaller proportion of HR-positive, HER2-negative patients (17.7%) compared to the TNBC population (82.3%). In contrast, the proportion of HR-positive, HER2-negative patients in Australian clinical practice is estimated to be approximately 56.9 to 79.6% compared with 12 to 24% for TNBC.

Subgroup analyses by HR status are summarised in Table 6. In the OlympiA trial, the treatment effect of olaparib versus placebo was slightly higher in the TNBC subgroup than in the HR+ subgroup, in terms of IDFS and DDFS and OS. Although the difference in treatment effect was not statistically significant across subgroups, the test for interaction was not statistically powered. As TNBC patients were over-represented in the OlympiA trial in comparison to the Australian setting, this may overestimate the effectiveness of olaparib.

Table 6: Comparison of IDFS, DDFS and OS by HR status in OlympiA at DCO2

HR status	Olaparib n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Interaction p-value
IDFS				
HR-positive, HER2-negative	25/168 (14.9%)	34/157 (21.7%)	0.680 (0.402, 1.134)	0.754
TNBC	109/751 (14.5%)	173/758 (22.8%)	**0.620 (0.487, 0.787)**	
DDFS				
HR-positive, HER2-negative	23/168 (13.7%)	31/157 (19.7%)	0.692 (0.399, 1.182)	0.608
TNBC	84/751 (11.2%)	141/758 (18.6%)	**0.591 (0.450, 0.772)**	
OS				
HR-positive, HER2-negative	16/168 (9.5%)	17/157 (10.8%)	0.897 (0.449, 1.784)	0.381
TNBC	59/751 (7.9%)	92/758 (12.1%)	**0.640 (0.459, 0.884)**	

Source: Table 2.32, p 91 of the submission.
CI = confidence interval; DDFS = distance disease-free survival; HER2 = human epidermal receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; N = number; OS = overall survival; TNBC = triple negative breast cancer.
Bold indicates a statistically significant result.

Comparative analytical performance

The submission assumed that the germline *BRCA* test used in Australia is concordant with that used in the key study, and therefore effectively had 100% sensitivity and 100% specificity.

The submission stated that germline *BRCA* testing conducted for OlympiA by Myriad was performed either using their CLIA-based assay, the Myriad Integrated BRCA Analysis® test or the Myriad BRCA Analysis CDX® test. The Myriad test uses Sanger sequencing (the reference standard in the submission). Germline *BRCA* pathogenic variant testing offered by several Australian pathology providers are NGS-based methods. Close concordance between NGS-methods and Sanger sequencing was previously demonstrated in the platinum sensitive relapse HGSOC submission in 2016. The germline *BRCA* test used to determine eligibility for olaparib would be identical to the currently available tests in Australia, thus, it was reasonable to assume the tests were fully concordant. MSAC has previously assessed the comparative analytical performance of germline *BRCA1/2* testing in applications 1380 and 1554.*).*

Clinical claim

The submission concluded that the results of OlympiA trial:

- supported the codependence of testing of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants in patients with triple negative early breast cancer (TNBC) or hormone receptor (HR) positive and treatment benefit from olaparib. *This was appropriate.*
- demonstrated olaparib as superior in terms of effectiveness compared to placebo. *This claim was appeared to be adequately supported and will be considered by the PBAC.*

As the OlympiA trial enrolled people with early breast cancer who have germline pathogenic or likely pathogenic variants in BRCA1 or BRCA2m, submission did not present evidence on the treatment effect of olaparib + bevacizumab for patients who were gBRCA1/2 positive versus patients who were not gBRCA1/2 positive. Thus, an estimate of the variation in this treatment effect due to gBRCA1/2 positivity could not be established from the evidence presented.

13. Economic evaluation

Structure of the economic model

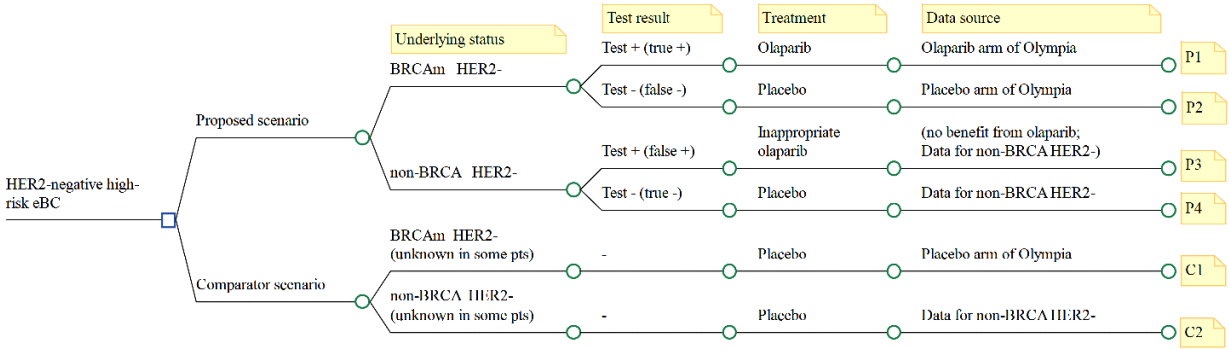
The submission to PBAC presented an economic evaluation based on the direct randomised trial OlympiA and external data. The type of economic evaluation was a cost-effectiveness (cost per LY) and cost-utility (cost per QALY) analysis. The economic evaluation incorporated the codependency of olaparib with g*BRCA* testing, and the model began at g*BRCA* testing.

As the submission assumed the g*BRCA* test used in Australia was concordant with that used in the key study, and therefore effectively had 100% sensitivity and 100% specificity, the model reduced to a comparison of olaparib vs placebo (as per OlympiA) with front-loaded costs associated with the incremental costs for the test applied to 100% of the population.

The submission used a semi-Markov model to estimate the incremental cost-effectiveness of olaparib versus the nominated main comparator, placebo, in the proposed g*BRCA*-pathogenic variant population. The proposed *MSAC* scenario (g*BRCA* testing and olaparib available for g*BRCA*-pathogenic variant patients) was compared with the comparator scenario in which some g*BRCA*

testing occurred as per current clinical practice, but patients received placebo despite their *BRCA* status (Figure 6).

Figure 6 Structure of testing component of the model



Note: *BRCA* unknown patients were assumed to be combined with non-*BRCA* patients

The semi-Markov model at the end of each branch had five health states: iDFS, non-mBC recurrence, early-onset mBC, late-onset mBC and death. The analysis using a 40-year time horizon was consistent with the mean age at entry into OlympiA, the curative aim of treatments in the eBC setting, and previous PBAC-approved models in this setting (Trastuzumab emtansine PSD November 2019). Patients progressed through the model in monthly cycles. Transition probabilities for the earlier health states (i.e. rates of non-mBC and mBC recurrence, and rates of death from iDFS, non-mBC and early-onset mBC) were derived from the OlympiA trial. However, due to limited long-term OS follow-up in OlympiA, survival rates after late-onset mBC were taken from external sources and reflected the outcomes of treatments administered in the mBC setting (e.g. CDk4/6 inhibitors for HER2-HR+ patients and sacituzumab govitecan for TNBC patients among others). The efficacy of placebo in the non-*BRCA* branches of the co-dependent test/treatment model had been estimated by applying published hazard ratios to the transition probabilities for g*BRCA*-pathogenic variant patients.

The model assumed that 95% of the proposed scenario underwent g*BRCA* testing at or soon after diagnosis. Consistent with current clinical practice, some patients in the comparator scenario underwent g*BRCA* testing, which usually occurred at familial cancer centres. Australian IpSOS data reported that 74% of TNBC patients currently received g*BRCA* testing. Given that high-risk HER2-/HR+ patients presented with clinical symptoms similar to those with TNBC, it was assumed that update of *BRCA* testing in high-risk HER2-/HR+ patients was likely to be comparable to the rate of testing in TNBC patients (thus assumed to be 74%). Therefore, test costs were calculated only for the incremental 21% of patients. *This approach was based on the current usage of gBRCA testing in patients with TNBC. Testing in patients with HR+, HER2- cancers might be less common. Furthermore, this assumed that there would be no leakage of testing into lower risk eBC patients if an MBS item number became available.*

The prevalence of g*BRCA*-pathogenic variant in the model (13.25%) was based on an average of three published sources. Germline *BRCA* pathogenic variant testing offered by several Australian pathology providers uses NGS-based methods with diagnostic accuracy (sensitivity/specificity) of the germline *BRCA* test assumed to be 100%.

The IpSOS data for HR-positive, HER2-negative patients could not be located in the submission. Germline BRCA testing is currently recommended by the Cancer Council[4] in patients with TNBC diagnosed under the age of 50 years, or who fulfil the CanRisk or Manchester score criteria for germline testing. EviQ[5] also recommends testing in TNBC diagnosed ≤50 years and for other high-risk characteristics including breast cancer diagnosed ≤40 years.

According to the IpSOS data in the submission, BRCA testing has increased rapidly in TNBC from 2020 to 2022, from 38% to 74%. It was unclear what had driven this increase or whether it was expected to be sustained at 74%.

The structure of the model presented in the current submission appeared consistent with previous models presented to PBAC.

Results of the economic analysis

The submission presented the following steps in a stepped analysis.

- Trial based costs
- Costs incurred in the modelled economic evaluation
- Disease-free years gained during the trial period (79 months)
- Final outcomes accrued over the full time horizon (40 years)

Results of the stepped evaluation are presented in Table 7

[4] Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with breast cancer, 2nd edn, Cancer Council Victoria, Melbourne

[5] https://www.eviq.org.au/cancer-genetics/referral-guidelines/1620-breast-cancer-referring-to-genetics

Table 7: Results of the stepped economic evaluation

Data	Costs			Health outcomes			Incremental cost-effectiveness ratio
	Proposed medicine	Comparator	Incremental	Proposed medicine	Comparator	Incremental	
	Test costs, olaparib costs and adverse events costs			*Invasive disease-free years*			
Step 1: Trial based analysis	$[redacted]	$1,693	$[redacted]	5.71	5.24	0.47	$[redacted][1] per disease-free year gained
				Increment in recurrence at 79 months (per modelled data)			
Step 1a: Trial based analysis	*As above*			*78.0%*	*69.7%*	*8.3%*	$[redacted][2] *per avoided recurrence*
	As above plus cost of disease monitoring, subsequent therapies, and palliative care			Discounted life years			
Step 2: Modelled analysis (LYs)[a]	$[redacted]	$37,929	$[redacted]	14.32	13.15	1.169	$[redacted][3]/LYG
	As above			Transformation using utility values for IDFS, non-mBC and mBC health states			
Step 3: Modelled analysis (QALYs)[a]	$[redacted]	$37,929	$[redacted]	12.360	11.321	1.039	$[redacted][4]/QALY

Source: Generated during the evaluation from the economic evaluation spreadsheet.

[a] *Modelled costs and outcomes are for the 'trial population' and do not include patients without* BRCA *pathogenic variants. This has been done so that the costs relate to a full course of olaparib per patient vs a full course of placebo per patient. The cost per patient in the testing population relates to only 12.6% of the cost of olaparib. The ICER remains the same as the benefits are also only 12.6% of the whole population. However, the numbers are not intuitive.*

IDFS = invasive disease-free survival; LY = life years; LYG = life years gained; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; QALY = quality-adjusted life years.

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$655,000 to < $755,000*

[3] *$35,000 to < $45,000*

[4] *$45,000 to < $55,000*

The submission based the cost of g*BRCA* testing on the existing MBS item 73296 ($1,200).

The precise uptake of germline BRCA *testing was unknown. However, there were several circumstances in which patients could access testing:*

1. *Patients diagnosed with breast cancer at a young age and meeting the eligibility criteria for MBS item 73296*
2. *Patients with a germline BRCA gene already know of their status due to cascade testing of family members*
3. *Patients diagnosed with breast cancer and are offered germline BRCA testing through a State or Territory funded program*

While the trial-based estimates presented in the submission related to a comparison of olaparib vs placebo, the modelled economic evaluation costs and outcomes related to the testing population. Therefore, the costs were 'diluted' by the large number of non-BRCA patients within the model. The evaluation presented modelled costs and outcomes for the trial population.

The ICER for the trial population modelled over 40 years was the same as for the testing population, as the model assumed 100% specificity and therefore contained no false positives. All other populations in the model had identical costs and outcomes across both arms.

The undiscounted cost of a course of olaparib was $[redacted] per treated patient (based on time-on-treatment curve from OlympiA). However, only 12.6% of patients in the proposed scenario had a true positive test result and thus received olaparib. Therefore, the average undiscounted cost of olaparib for patients in the proposed scenario was $[redacted] (= $[redacted] x 12.6%). The base-case ICER was $45,000 to < $55,000 (Table 8).

Table 8 Discounted costs and ICER from the modelled economic evaluation

	Proposed scenario	Current scenario	Incremental
Olaparib drug cost	$[redacted]	$[redacted]	$[redacted]
Subsequent anti-cancer treatment (local and metastatic recurrence), including cost of managing adverse events	$8,392	$8,862	-$470
Surgery/radiotherapy post recurrence	$1,018	$1,071	-$53
Management of adverse events	$827	$805	$22
Disease monitoring	$5,892	$5,919	-$27
Terminal care	$6,038	$6,256	-$218
Testing costs	$1,283	$999	$284
Total	$	$[redacted]	$[redacted]
Discounted QALYs	12.83	12.70	0.13
ICER	$[redacted][1]		

The redacted value corresponds to the following ranges:
[1]$45,000 to < $55,000

Sensitivity analysis

Sensitivity analyses suggested the model was most sensitive to the time horizon, the discount rate, and the parametric distribution used to model iDFS (Figure 7). However, the ICER around the base case model was robust, with the ICER ranging from $15,000 to < $25,000 (using a 0% discount rate) to $45,000 to < $55,000 (assuming the annual risk of recurrence plateaued at a conservative estimate of 5%). Given the Strategic Arrangement's intention to review the discount rate, it was noteworthy that the ICER decreased to $25,000 to < $35,000when a 1.5% discount rate was used (as proposed by Medicines Australia in their Discount Review fact sheet[6]).

*The model was moderately sensitive to the current rate of germline BRCA testing. For every 10% drop in g*BRCA *testing currently performed, the ICER in the base case model increased by approximately 2%. Reducing the rate of current testing in patients with HR+ disease to 25% (base case 74%) increased the ICER by about 5%.*

Ipsos data appeared to indicate a recent increase in gBRCA testing in Stage I-IIIa TNBC, to 74% in the first quarter of 2022. This estimate was based on small numbers and increased rapidly from 38% in the first quarter of 2020. Whether the estimate of 74% was an indication of future

[6] https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2022/02/Fact-sheet-discount-rate-feb22.pdf

rates was unclear. The rate of gBRCA testing for HR-positive patients was uncertain. The rate of gBRCA testing was varied in sensitivity analyses.

Figure 7 Tornado diagram of sensitivity analyses

The commentary presented a revised base case as several inputs were not adequately justified in the submission, and for which there could be a more reasonable approach (Table 9). The pre-PBAC response stated that the IpSOS data suggests that 10% of HR+ patients currently undergo *BRCA1/2* testing, this data includes both low-risk HR+ patients (who are less likely to be tested) and high-risk HR+ patients (who are more likely to be tested). The applicant considered that while the rate of testing within the high-risk population meeting the current defined risk criteria for BRCA testing could be as high as current testing rates of TNBC, the ICER is only marginally sensitive to this assumption (increasing between $45,000 to < $55,000).

Table 9: Stepwise multivariate sensitivity analyses to generate the evaluation alternative base case

Ref[a]	Variable or assumption	ICER ($)	Percent change from base case
	Base case	$[redacted][1]	0.0%
	ALTERNATIVE BASE CASE		
1	Increase the age in the model to 50	$[redacted][1]	6.35%
2	Apply a lower rate of current testing for HR+ patients (33.5% weighted average)	$[redacted][2]	15.51%
3	Type of recurrence equal across the arms in the model	$[redacted][2]	17.53%
4	60 month truncation point for the use of observed data	$[redacted][3]	64.97%
5	Risk of death from early-onset mBC different across arms	$[redacted][3]	78.04%

6	Reduced rate of treatment in the mBC health state	$[redacted][3]	80.64%
7	Relative dose intensity applied to sacituzumab govitecan (TNBC, mBC)	$[redacted][3]	81.37%
8	Cost of echocardiography removed from monitoring costs	$[redacted][3]	81.99%
9	Disutility applied to treatment with olaparib (5%)	$[redacted][3]	94.62%
10	Health state utilities applied using real-world EQ-5D results for patients receiving adjuvant treatments	$[redacted][4]	106.90%
	ADDITIONAL STRUCTURAL STEP		
1-10 +11	Delaying the reduction in recurrence from 5 years to 6 years in the olaparib arm	$[redacted][5]	161.86%
	ADDITIONAL *BRCA* MORTALITY RATIO		
1-10 +12	Increasing the background mortality for g*BRCA* variant patients to account for other cancer deaths	$[redacted][4]	115.68%

Source: Generated during the evaluation from the economic evaluation spreadsheet.
[a]Ref = the reference number from the univariate analyses table

EQ-5D = EuroQol five dimension scale questionnaire; g*BRCA* = germline breast cancer gene; HR+ = hormone receptor positive; ICER = incremental cost-effectiveness ratio; mBC = metastatic breast cancer recurrence; TNBC = triple-negative breast cancer.
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*
[5] *$115,000 to < $135,000*

14. Financial/budgetary impacts

Estimation of use and financial impact of the proposed medicine

The submission used an epidemiological approach to estimate the utilisation and financial estimates of *BRCA1/2* testing and Olaparib treatment on the MBS and PBS, respectively. The financial implications were considered by the Drug Utilisation Sub-Committee of the PBAC.

The Pre-Sub-Committee Response (PSCR) to the PBAC ESC and DUSC to correct the financial estimated for an error related to the number of prescriptions. These are presented in the Departmental Overview.

Table 10 presents the assumptions the submission stated it used to estimate the utilisation and financial estimates associated with *BRCA1/2* testing. *The basis for increased BRCA1/2 testing did not align with the assumptions stated. Although the commentary highlighted that total number of gBRCA1/2 tests appeared to be erroneously divided by two, the revised financial implications did not address the underestimated BRCA1/2 tests.*

Table 10 Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Commentary on the submission	*DUSC comments*
Eligible population				
Incident cases of breast cancer	21,233 in Year 1 of listing, increasing to 23,678 in Year 6	AIHW Cancer data in Australia (Updated 04-Oct-2022)	The incidence projections for 2022 to 2031 sourced from 'Cancer in Australia 2021' Supplementary Table S3.1 was appropriate.	*DUSC considered this to be appropriate.*

Data	Value	Source	Commentary on the submission	*DUSC comments*
Incidence of early (Stage I-III) breast cancer	89.81%	AIHW Australian Cancer Database 2014 Table S3.1	This data for staging distribution based on patients diagnosed in 2011 was not adjusted for patients of unknown disease stage (5.5%).	*DUSC agreed with the commentary and considered the sponsor's approach in the Pre-Sub-Committee Response (PSCR, Appendix Table 1) to be more appropriate.*
Proportion of patients with TNBC	12.10%	Stuart-Harris et al 2019	This is lower than the estimate for both March 2020 atezolizumab submission and March 2021 resubmission for locally advanced or metastatic TNBC that assumed 15% (Source: Cancer Council Australia).	*DUSC agreed with the commentary in that 12.10% is likely an underestimate.*
Proportion of patients with HR-positive breast cancer	81.8%	Stuart-Harris et al 2019	Overall, the combined probability of 69.3% (= 81.8% x 84.7%) for the proportion of HR-positive, HER2-negative breast cancer was reasonable.	*DUSC considered this to be appropriate.*
Proportion of patients with HER2-negative breast cancer	84.7%			
Proportion of high risk HR-positive, and HER2-negative breast cancer patients	49.0% The sum of neoadjuvant (4.43%) and adjuvant chemotherapy (44.57%)	Patiniott et al 2019	The approach of using proportions of patients on (neo)adjuvant treatments to estimate patients at high risk was reasonable.	*DUSC considered this to be appropriate.*
Germline BRCA pathogenic variant testing uptake rates	<u>Current:</u> 74% (Stage I-IIIa) 64% (Stage IIIb-IV) 67% (overall)	IPSOS report for BRCA testing in Q1 2022 for patients with TNBC.	This is uncertain and likely overestimated as the early breast cancer (eBC) incident patients include Stage I-III, not only Stages I-IIIa.	*DUSC agreed with the commentary and noted that this input may be biased as it was taken from a TNBC population where testing would be higher compared to hormone receptor positive patients.*
	Ranging from 80% (Year 1) to 95% (Year 6)	Assumption for both subgroup populations	The assumption is uncertain, and there is no data to support this assumption in particular for patients with HR(+)/HER2(-) eBC.	*DUSC considered this to be appropriate however noted it may be higher in initial years.*
Germline BRCA pathogenic variant test positive to BRCA1 or BRCA2 pathogenic variant	13.25% = (9.34%+15%+15.4%)/3	Simple mean of Australian evidence from IPSOS report (15%), Wong-Brown et al 2015 (9.34%), Armstrong et al 2019 (9.3%-15.4%).	IPSOS data (15%) could not be located, and uncertain. The US data for gBRCA variant (15.4%) is not representative of Australian population. The estimate of 9.34% appears to be appropriate for TNBC patients.	*DUSC considered this to be appropriate.*

Data	Value	Source	Commentary on the submission	*DUSC comments*
MBS costs				
Germline BRCA pathogenic variant testing	$1,200 (Schedule fee) $960 (Benefit at 80%)	Proposed schedule fee based on MBS item 73296 Benefit at 80% rebate rate used in the financial analysis.	Similar to the number of scripts, the total number of germline BRCA pathogenic variant testing services appear to be erroneously divided by two in the submission. As majority of the patients might receive germline BRCA pathogenic variant test at out-of-hospital setting, benefits at 85% rebate rate might be more reasonable. The Greatest Permissible Gap (GPG)[a] amount was not taken into account in the submission.	*DUSC agreed with the commentary that these costs were underestimated.*
Germline BRCA pathogenic variant cascade testing	Not costed	Cascade testing was not discussed.	MBS costs likely underestimated.	
Genetic counselling	Not costed	Not discussed.		

Source: Table 1, DUSC Advice to the PBAC. Compiled during the evaluation from information provided in Section 4 of the submission and the Excel workbook 'Att_4.1_OlympiA UCM_FINAL'.

2L = second-line treatment AE = adverse event; AIHW = Australian Institute of Health and Welfare; gBRCA = germline Breast Cancer gene t; CSR = clinical study report; DoT = duration of treatment; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; eBC = early breast cancer; GPG = Greatest Permissible Gap; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; MBS = Medicare Benefits Schedule; PSD = Public Summary Document; TNBC = triple-negative breast cancer

[a] From 1 November 2022, the GPG and the GPG threshold values are set at $93.20, $621.50, respectively.

Table 11 presents the revised estimates of utilisation and financial implications of *BRCA1/2* testing from the PSCR. The estimated utilisation and financial implications were likely underestimated and uninformative as:

- The current utilisation of *BRCA1/2* testing was likely overestimated, particularly in the HR+/HER2- population (74%);
- The financial estimates did not consider cost shifting from non-MBS funding of testing to MBS funding. In 2022, there were 3,529 claims for germline BRCA1/2 testing under MBS item 73296 (breast and ovarian cancer), however it was estimated that 5,000 to < 10,000 patients with early TNBC and early HR+ HER2- patients are currently being tested;
- The estimated number of *BRCA1/2* used to calculate MBS implications were not those estimated using the epidemiological approach; and
- Cost-offsets for *BRCA1/2* testing that were not justified when the proposed MBS listing would likely increase the number of people eligible for *BRCA1/2* testing.

Table 11 Estimated use and financial implications presented in the PBAC PSCR

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	Incidence early breast cancer	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
	Estimated extent of use *BRCA1/2* pathogenic gene variant test						
A	g*BRCA* pathogenic variant tests in TNBC patients (olaparib available), Proposed uptake Years 1−6: 80−95%	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
B	gBRCA pathogenic variant tests in TNBC patients (olaparib not available), Current uptake Years 1−6: 74%	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
C	Incremental gBRCA pathogenic variant tests in TNBC patients (C = A – B)	[redacted][3]	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
D	gBRCA pathogenic variant tests in HR(+)/ HER2(-) high risk eBC patients (olaparib available), Proposed uptake Years 1−6: 80−95%	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
E	gBRCA pathogenic variant tests in HR(+)/ HER2(-) high risk eBC patients (olaparib not available), Current Uptake Years 1−6: 74%	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
F	Incremental gBRCA pathogenic variant tests in high-risk HR+/HER2- patients (F = D – E)	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
G	Total number of patients tested (proposed) (olaparib available) (G = A + D)	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
H	Total no. patients currently tested (olaparib not available) (H = B + E)	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
I	PSCR's estimate of change in testing [I = (G – H)] [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Utilisation used to calculate MBS implications [b]							
J	PSCR's estimated increase in *BRCA* testing (derivation unclear)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
K	PSCR's estimated decrease in *BRCA* testing (derivation unclear)	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted]	-[redacted]	-[redacted]
L	PSCR's estimated decrease in BRCA testing (J-K)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]
	Estimated financial implications of the *BRCA1/2* pathogenic gene variant test to the MBS						
M	PSCR Net Cost to MBS($)	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
N	Submission's Net Cost to MBS ($) (K = I x $960.00 per patient)	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
O	Revised (commentary) [c] ($) (L = J x $1,106.80 per patient)	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]

Source: Table 20 pp37-38 of Commentary

gBRCA = germline breast cancer gene; GPG = Greatest Permissible Gap; HR(+) = hormone receptor positive; HER2 (-) = human epidermal growth factor receptor 2 negative; PSCR = PBAC pre-sub-committee response; TNBC = triple-negative breast cancer;

[a] From the 'Calculation' tab of Att_3 of the PSCR.

[b] The PSCR's estimated volume changes to the MBS item was calculated using '7. Net changes – MBS' spreadsheet in Excel workbook (Att_3) of the PSCR. This is calculated by multiplying the change in use of germline BRCA testing services (i.e. [redacted][2] in Year 1, rather than [redacted][3] in Year 1 which was erroneously calculated in the '7. Net changes – MBS' spreadsheet) by the MBS fee ($1,106.80) at 85% rebate rate accounting for the GPG, compared to $960 at 80% rebate rate in the submission.

The redacted values correspond to the following ranges:

[1] *20,000 to < 30,000*

[2] *500 to < 5,000*

[3] *< 500*

[4] *5,000 to < 10,000*

[5] *10,000 to < 20,000*

[6] *$0 to < $10 million*

Revised estimates of MBS utilisation and financial implications were calculated for the Departmental Overview. It was assumed that patients that all germline *BRCA1/2* testing for the proposed population would be provided on the MBS as a result of the new MBS item.

It was assumed that all existing use of germline *BRCA1/2* testing under MBS item 73296 was for people with early breast cancer and the utilisation of this item was predicted to increase at the rate of increasing breast cancer incidence. This likely overestimated existing MBS use (and underestimated net cost to MBS) of germline *BRCA1/2* testing for early TNBC and HR+/HER2- breast cancer as the MBS item is for people with breast and ovarian cancer who meet certain eligibility criteria.

The revised financial estimates (Table 11) estimated a net cost to the MBS of $30 million to < $40 million over 6 years. This was based on a lower MBS $1,000 fee and cascade testing for 1.8 biological relatives for each *BRCA1/2* positive individual. This was substantially higher than the financial implications estimated in the submission, PBAC commentary or PBAC PSCR. This estimate likely remains an underestimate as it assumed all current use of MBS testing was for germline *BRCA1/2* was assumed to be for people with early TNBC and HR+/HER2- breast cancer.

Table 12 Revised utilisation and financial implications

	2023	2024	2025	2026	2027	2028
Eligible patients [a]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
g*BRCA1/2* testing uptake (Years 1–6: 80–95%)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Forecast MBS testing (Without new MBS item) [b]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net increase in MBS g*BRCA* tests	[redacted][3]	[redacted][3]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
BRCA1/2 testing cost to MBS ($) ($1000 fee + GPG applied) [c]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Cascade testing						
People with a *BRCA1/2* variant (13%) [d]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Cascade tests (1.8 tests per *BRCA1/2* positive proband) [e]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Cascade testing cost to MBS [f] ($)	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Revised net cost to MBS ($)	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]

Source: Calculated for the Departmental Overview using the PSCR revised financial estimates.
gBRCA = germline breast cancer gene; GPG = Greatest Permissible Gap; PSCR = PBAC pre-sub-committee response;
[a] Att_3 of the PSCR, 'Calculation' rows 35+ 48
[b] 2022 utilisation of MBS item 73296 inflated by change in incidence of breast cancer. Calculated as 3529x(D25/C25) for Year 1.
[c] $906.80 cost to MBS per test based on GPG of $93.20
[d] As estimated in the submission. Likely overestimate
[e] Number of first degree relatives based on Application 1411.1 Economic evaluation report (p5).
[f] MBS item 73302
The redacted values correspond to the following ranges:
[1] *5,000 to < 10,000*
[2] *10,000 to < 20,000*
[3] *500 to < 5,000*
[4] *$0 to < $10 million*

15. Other relevant information

Nil

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The key trial (OlympiA) enrolled people with early breast cancer who have germline pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 (g*BRCA*1/2). Therefore, submission did not present evidence on the treatment effect of olaparib + bevacizumab for patients who were g*BRCA*1/2 positive versus patients who were not g*BRCA*1/2 positive. Thus, an estimate of the variation in this treatment effect due to g*BRCA*1/2 positivity could not be established from the evidence presented.
- *HER2* is the legacy gene symbol for *ERBB2 (*erb-b2 receptor tyrosine kinase 2). MSAC may wish to consider whether the item descriptor should be amended to reflect current nomenclature. This may require corresponding amendments to other MBS and PBS listings for consistency.

Item descriptor:

- Whether the eligible population for testing can be more closely aligned to the population eligible for olaparib treatment which includes patients with residual disease following neoadjuvant chemotherapy.
- The proposed MBS fee of $1,200 is higher than the MSAC-supported $1,000 fee for the MBS item 73303 to test for pathogenic or likely pathogenic variants in the *BRCA1* and *BRCA2* genes in people with metastatic castration-resistant prostate cancer to determine eligibility for olaparib treatment (Application 1618).The proposed MBS item is likely to substantially increase the number of germline *BRCA1/2* tests performed by pathology providers and therefore reduce the testing costs.

Economic issues:

- The economic model assumed 13.25% of the tested population (early triple negative or hormone receptor positive, HER2-negative) which is likely an overestimate. MSAC may wish to advise whether a lower value should be used a respecified base case.
- The economic model assumed 74% of patients were currently undergoing g*BRCA1/2* testing. The was likely an overestimate as *gBRCA1/2* testing is recommended for a subset of people with breast cancer. The incremental cost-effectiveness ratio increased by 15.5% (between $45,000 to <$55,000) when using a weighted average of 33.5%.

Financial issues:

- The estimated use and financial impact to the MBS the additional g*BRCA1/2* testing presented in the submission and revised in the PBAC pre-sub-committee response (PSCR) were likely underestimated and uninformative. It was estimated that fewer than 500 to < 5,000 additional g*BRCA* test would be funded on the MBS, despite over 20,000 people being diagnosed with early breast cancer annually. The financial estimates were revised in for the Departmental Overview. It was estimated that the additional g*BRCA1/2* testing would cost $0 to < $10 million in Year 1, increasing $0 to < $10 million in Year 6 (using a $1,000 MBS test fee and including cascade testing).

17. Applicant comments on MSAC's Public Summary Document

The applicant had no comments.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website