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: **23–24 November 2023**

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

1. Purpose of application

A streamlined codependent standard re-entry submission requested:

- A Medicare Benefits Schedule (MBS) item for germline *BReast CAncer gene 1 and 2* (g*BRCA*) testing to determine eligibility for access to PBS-subsidised adjuvant olaparib in patients with human epidermal growth factor receptor 2 negative (HER2−) high risk early breast cancer.
- A Pharmaceutical Benefits Scheme (PBS) listing for adjuvant olaparib in HER2− high risk early breast cancer with confirmed g*BRCA* pathogenic or likely pathogenic variants (g*BRCA* variants).

The Commentary Executive Summary refers to the 'PBAC resubmission' where relevant information was sourced from the resubmission to the Pharmaceutical Benefits Advisory Committee (PBAC).

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 an existing MBS item (item 73295) to detect germline *BReast CAncer gene 1 and 2* (g*BRCA*) pathogenic or likely pathogenic gene variants to determine eligibility for access to PBS-subsidised adjuvant olaparib (a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor) in patients with hormone receptor positive human epidermal growth factor receptor 2 negative (HER2−) high risk early breast cancer (eBC) or triple negative early breast cancer (TNBC). MSAC noted the clinical claim of superior comparative efficacy and inferior, but manageable safety for olaparib. MSAC considered the comparative claims of safety and effectiveness to be reasonable. MSAC noted that the testing population is at a high risk of poor outcomes and g*BRCA1* and g*BRCA2* testing is required to determine eligibility for PARP inhibitors.

MSAC noted that PBAC recommended PBS listing of olaparib (a type of PARP inhibitor) at its November 2023 meeting. MSAC considered that it was appropriate for the eligible testing population to remain broader than the eligible population for PBS-subsidised olaparib as aligning the two populations may lead to delays in treatment initiation. Concerns were noted by MSAC

previously that misalignment of the testing and treatment populations may be a cause for confusion in clinicians and disappointment in patients, despite knowing their gBRCA status. MSAC considered that in light of PBAC's support for PBS listing of olaparib, the amended item descriptor to include gBRCA testing to determine eligibility for PARP inhibitors with a fee of $1200 as proposed by the Department of Health and Aged Care was appropriate and did not require further amendment.

	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: i. 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 ii. triple negative early breast cancer; or iii. hormone receptor positive, *HER2*-negative, early breast cancer with one or more high-risk characteristics 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% = $1,106.80 $1,101.30 (See para PN.0.23 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.	

Consumer summary

This was the second submission (resubmission) from AstraZeneca requesting an expansion of Medicare Benefits Schedule (MBS) item 73295 to include 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 are eligible for a medicine called olaparib (a type of PARP inhibitor). This was a codependent submission to MSAC and the Pharmaceutical Benefits Advisory Committee (PBAC). The was first considered by MSAC in March 2023.

MBS item 73295 is for genetic testing for germline (inherited) *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 funded 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, and becomes incorporated into the DNA of cells throughout the body of their children, or it can develop during an individual's lifetime in the cells of the body that do not pass on DNA to the person's children (called a somatic variant). 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). Olaparib comes from a family of medications called PARP inhibitors. Some drugs 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 pathogenic variants in their *BRCA1* or *BRCA2* genes.

Consumer summary

Because this test is for germline pathogenic variants, MSAC considered it appropriate that testing for the particular *BRCA1* and *BRCA2* variant is available for biological relatives (cascade testing). This is because relatives who carry pathogenic variants in their germline *BRCA* genes have an increased chance of developing certain types of cancer.

MSAC and the PBAC agreed that olaparib appeared to help this group of patients survive longer, and it appeared to be safe. MSAC considered the test itself to be effective and safe. MSAC also noted that the PBAC supported Pharmaceutical Benefits Scheme (PBS) listing of olaparib at its November 2023 meeting, prompting MSAC to support expanding MBS item 73295 for public funding of the accompanying genetic test to determine eligibility for olaparib.

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

MSAC supported expanding MBS item 73295 to include 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 olaparib on the PBS. MSAC considered the genetic testing to be safe, effective and good value for money.

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 detect germline *BRCA1* or *BRCA2* (*gBRCA1/2*) pathogenic or likely pathogenic (P/LP) 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). MSAC recalled that it had deferred its decision in March 2023 and foreshadowed that it would support the application 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 also requested that the applicant provide further information on the projected patient numbers, cost of the test, cascade testing costs and other testing requirements.

MSAC noted that high-risk breast cancers such as TNBCs are more likely to occur in younger women and be associated with P/LP variants in g*BRCA1* and g*BRCA2* genes, and that patients with P/LP variants in *BRCA1* and *BRCA2* genes are more likely to respond to treatment with poly-ADP ribose polymerase (PARP) inhibitors such as olaparib. Identifying P/LP variants requires sequencing of the *BRCA1/2* genes, and may also need a technique such as multiplex ligation-dependent probe amplification (MLPA) to identify deletions. 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).

MSAC considered that the proposed testing will address unmet clinical needs for women at high risk of HER2 negative early breast cancer by enabling access to PARP inhibitors. MSAC noted that this population (women with HER2 negative early breast cancer) included women with triple negative breast cancers (TNBC). TNBCs are typically more aggressive and more common among younger women, with a 60% 5-year survival rate and 40% relapse rate.

MSAC noted the proposed fee of $1,200 in the original submission was decreased to $1,000 in the resubmission. However, after stakeholder feedback, the fee was increased back to $1,200. MSAC agreed with the higher fee, because MLPA would sometimes be required. MSAC also considered the proposed MBS item descriptor to be appropriate.

MSAC noted the applicant's proposal to merge all MBS items related to detection of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants. This would cover patients with advanced (FIGO III–IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; metastatic castration-resistant prostate cancer; TNBC; and HR-positive, HER2-negative early breast cancer with at least one of the following high-risk characteristics: (i) tumour histological grading of at least 3; (ii) tumour size of greater than 2 cm; or (iii) one or more axillary lymph node metastases. MSAC considered that one g*BRCA* MBS item would be appropriate.

MSAC noted that prespecifying the risk of inherited cancer predisposition was historically used to decide who should access testing dating from when such testing was very expensive. MSAC agreed with the Department that details of the specific 'high risk' characteristics of breast cancer can be omitted from the proposed new item descriptor as whether a patient is at 'high risk' is based on the expert clinical opinion of the requesting specialist or consultant physician. MSAC further considered that it is appropriate for the eligible population for testing to remain broader than the eligible population for PBS treatment, noting that aligning the two populations may lead to delays in treatment initiation. MSAC noted the clinical management algorithm and the comparator (no testing). Because this test is for g*BRCA* P/LP variants, MSAC considered it appropriate that *BRCA1* and *BRCA2* cascade testing be available for biological relatives of *gBRCA* positive patients.

MSAC noted that no additional safety data were included in the resubmission to support the comparative safety of g*BRCA* testing. MSAC previously considered that adverse events (AEs) resulting from the testing procedure were unlikely, and that the accuracy of contemporary testing and variant curation meant downstream safety concerns resulting from false positive or false negative test results were unlikely. MSAC noted the commentary's observation that the claim of inferior, but manageable, safety for olaparib compared to placebo was supported by the evidence presented. In the OlympiA trial – a randomised controlled trial (RCT) that compared olaparib to placebo in high-risk HER2-negative early breast cancer patients who had g*BRCA* variants and who had received adjuvant or neoadjuvant chemotherapy – patients receiving olaparib had more treatment-related AEs overall (80.8% vs 53.1%).

MSAC also noted that the clinical evidence presented in the PBAC resubmission remained based on the OlympiA trial. No updated data from this trial were provided. However, MSAC previously accepted that g*BRCA* testing was safe and effective. MSAC also noted that the PBAC previously considered that a claim of superior efficacy was supported for olaparib compared with placebo, based on immature invasive disease-free survival data. Although the data presented had not changed since the previous submission (and so remained immature), the claim of superior efficacy was supported by the evidence presented.

MSAC noted that the PBAC resubmission presented a stepped economic evaluation that also remained based on the OlympiA RCT. The economic evaluation was a cost-effectiveness analysis and a cost-utility analysis. The structure of the model was unchanged from that presented previously, which was a semi-Markov model with time varying transition probabilities and a 40-year time horizon in the base case. The incremental cost-effectiveness ratio (ICER) was moderately sensitive to accounting for the difference in the population eligible for testing and that eligible for treatment. MSAC acknowledged that this analysis does not consider the other benefits associated with identifying g*BRCA* variants beyond access to olaparib treatment (such

as increased monitoring for other cancers and preventative actions, e.g. bilateral salpingo-oophorectomy or mastectomy). The resubmission presented an ICER of $35,000 to < $45,000 ($45,000 to < $55,000 per quality-adjusted life year [QALY] at $1,200 per test), which was less than the ICER in the initial submission ($45,000 to < $55,000). MSAC noted that the key driver of the ICER was the time horizon.

MSAC noted the pre-MSAC response justified the ICER by stating that this testing presented an opportunity of a cure in the adjuvant setting for younger HER2-negative, high-risk, early breast cancer patients. Because these patients are younger than the average breast cancer patient, with treatment, they will have the capacity to remain in employment or start employment following treatment, and so can better contribute to society.

MSAC noted that the base case of the financial impact in the resubmission did not consider cascade testing, which MSAC considered inappropriate, though the results of cascade testing were reported in a scenario analysis. The scenario analysis reported that under a $1,200 fee and cascade testing (using a fee of $400), the financial impacts to the MBS ranged from $0 to < $10 million in year 1 to $0 to < $10 million in year 6.

MSAC considered that given the testing population are at a high risk of poor outcomes, g*BRCA1* and g*BRCA2* testing is required to determine eligibility for PARP inhibitors and PBAC had recommended the listing of olaparib, the item descriptor for g*BRCA1* and g*BRCA2* testing as proposed by the Department should be supported without further amendment.

4. Background

MSAC has previously considered g*BRCA* testing to determine eligibility for olaparib for the treatment of HER2− high risk early breast cancer. The original application was considered by MSAC at its March 2023 meeting.

MSAC deferred its decision and foreshadowed that would reconsider if the 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. The specific key matters of concern raised by MSAC and how the resubmission addressed these are presented in Table 1.

Table 1 Summary of key matters of MSAC concern

Component	Matter of concern (1716 PSD March 2023 MSAC Meeting)	How the resubmission addresses it
Proposed item	MSAC noted that expanding MBS item 73295 would be preferable to introducing a new MBS item for this patient population (PSD, p1 and 3)	The resubmission proposed a new item as amending item 73295 may be considered unsuitable, as this item is restricted to those in whom testing of tumour tissue is not feasible.
	MSAC noted that the proposed item could be futureproofed by generalising it to all PARP inhibitors (PSD, p4)	Addressed. The proposed MBS item refers to the drug class rather than specific drug name.
	MSAC noted that the proposed descriptor insufficiently defined the population eligible for testing, noting the application's intent to identify patients that had at least one of the high-risk characteristics (PSD, p3)	Not addressed.
	MSAC noted issues regarding misalignment of the population eligible for testing and that eligible for treatment (PSD, pp3−4)	The proposed timing of the test was unchanged so as to match information available about the tumour at time of diagnosis. The commentary considered that that this remained for MSAC consideration. There may be other benefits following the identification of gBRCA variants that were not captured in this analysis (1411.1 PSD March 2016 MSAC Meeting)
	MSAC considered that a reference to multigene assays did not need to be included in the proposed item descriptor (PSD, p4)	Addressed. The proposed MBS item was modified to remove reference to multigene assays.
Proposed fee	MSAC noted variation in current schedule fees for similar services and that the Dept. was investigating which fee would be more appropriate (PSD, p3)	The resubmission proposed a lower schedule fee ($1,000). However, the commentary noted that Dept. supported a schedule fee of $1,200, based on stakeholder consultation.
Cascade testing	MSAC noted that the proposed clinical management algorithm did not include cascade testing which would be triggered by proposed testing (PSD, p5)	Addressed. The proposed clinical management algorithm included cascade testing.
	The impact on the use of cascade testing was not considered in the financial estimates presented in the submission (PSD, p24).	This was included in a sensitivity analysis only. The commentary considered the justification for including this in a sensitivity analysis only was not clear.
Prevalence of g*BRCA* variants	MSAC noted that the prevalence of g*BRCA* variants assumed was likely an overestimate (PSD, p5)	Addressed. A lower prevalence (5%) was applied in the HR+ population, however the prevalence was unchanged in TNBC, based on advice provided by the PBAC (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting).

Component	Matter of concern (1716 PSD March 2023 MSAC Meeting)	How the resubmission addresses it
Projected patient numbers	MSAC was concerned that the patients eligible for testing, and therefore the financial impact, were underestimated (PSD, p6) as:	
	• Current use of g*BRCA* testing was likely overestimated, particularly in HR+ population (PSD, p27)	Addressed. Lower estimates of g*BRCA* testing uptake in the absence of olaparib listing were assumed in the HR+ population, based on advice provided by the PBAC (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting).
	• Cost-shifting to MBS of current non-MBS funded testing was not considered (PSD, p27)	Not addressed. The commentary considered that the extent of other sources of funding for current testing was unknown. Any shift in testing from these other sources to the MBS had not been accounted for in the estimates presented in the resubmission, and so the cost to the MBS may have been an underestimate.
	• The approach used to estimate the number of tests was inconsistent with the approach used to estimate use of olaparib treatment (PSD, p27)	Addressed. The same epidemiological approach was used to estimate the number of tests and to estimate the use and cost of olaparib treatment.
	• Cost-offsets were not justified as the proposed listing would increase the number of people eligible for g*BRCA* testing (PSD, p27)	The commentary considered that derivation of costs in the resubmission was clearer. No cost-offsets were assumed, however, only additional tests in incident cases were costed.

Source: Constructed during the evaluation.
g*BRCA* = germline *BReast CAncer* gene; HR+ = hormone receptor positive; PARP = poly adenosine diphosphate-ribose polymerase; TNBC = triple negative breast cancer.

5. Prerequisites to implementation of any funding advice

BRCA testing is well established in a number of laboratories in Australia with external quality assurance available through the European Molecular Genetics Quality Network.

At the time of resubmission lodgement, olaparib remained under review by the TGA for g*BRCA* variant HER2− early breast cancer. The PBAC resubmission expected that the Delegate's decision would be made in September 2023.

6. Proposal for public funding

The resubmission proposed a new MBS item for g*BRCA* testing in HER2− high risk early breast cancer (Table 2).

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, 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 one test per lifetime	
Fee: $1,000.00 Benefit: 75% = $750.00 85% = $850.00*	
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).
Source: Table 1 of minor resubmission

This included three changes in the wording of the proposed item relative to that in the previous submission:

- Removing the reference to a high recurrence score from a multigene assay;
- Replacing specified drug name with the name of the relevant drug class; and
- Replacing the explanatory note previously proposed with PN.0.27.

The commentary considered that these changes were consistent with some of the advice provided by MSAC previously (p4, 1716 PSD March 2023 MSAC Meeting). The proposed schedule fee was also reduced to $1,000. The commentary noted that the MSAC PSD noted inconsistencies in the schedule fee for other current BRCA testing items (item 73304, $1,000; and item 73295, $1,200) and that the department was to investigate which fee would be more appropriate (p3, 1716 PSD March 2023 MSAC Meeting). The department supported a schedule fee of $1,200, based on stakeholder consultation feedback indicating this was most appropriate to cover the costs of providing the service

While these changes were consistent with some of the advice previously provided by MSAC, the commentary considered that the following issues remain outstanding in the proposed MBS item descriptor:

- MSAC previously noted that if funding for proposed *gBRCA* testing were approved, either a new item could be introduced, or the existing item 73295 could be amended to include the proposed population (p3, 1716 PSD March 2023 MSAC Meeting). Amending item 73295 was noted to be the preferred option, and suggested amendments to this item were included in the MSAC PSD (Table 1, 1716 PSD March 2023 MSAC Meeting). A new item was proposed in the resubmission on the basis that amendments to item 73295 would not be suitable, as currently, this item is restricted to only those patients in whom testing of tumour tissue is not feasible. The commentary considered that the item descriptor could be reworded such that this requirement applies only to those patients with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (Table 3 and Table 4).

- The population eligible for testing remained insufficiently defined, as it suggested that hormone receptor positive (HR+) HER2− patients would require all specified high-risk characteristics in order to be eligible for testing. MSAC previously noted that the application's intention was to identify patients that had at least one of the high-risk characteristics (p3, 1716 PSD March 2023 MSAC Meeting).
- 85% benefit did not adequately account for the effects of the greatest permissible gap (GPG) on the applicable rebate.

Options proposed in the commentary for the amendment of item 73295 that account for the concern noted in the resubmission regarding the suitability of an amendment, in addition to addressing other concerns noted by the commentary above, are presented in Table 3 and Table 4.

Table 3 MSAC's advice of potential amendment to MBS item descriptor 73295 with proposed rewording to account for concerns noted in the resubmission

	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 in a patient with 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% = $1,106.80*	
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).
Red text denotes changes proposed by MSAC in March 2023. Blue text denotes changes proposed in the commentary to address subsequent concerns raised by the applicant.
Source: Adapted from 1716 PSD Table 1 with proposed commentary additions

As the proposed item intended that different criteria apply depending on the type of cancer a patient has, e.g. advanced epithelial ovarian, fallopian tube or primary peritoneal cancer or early breast cancer; or whether additional criteria are required, the commentary suggested alternate amendments to item 73295 (Table 4) to allow these criteria to be more clearly related to the respective patient populations.

Table 4 Suggested amendments to item 73295 proposed in the commentary

	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
• 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% = $1,106.80*	
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).
Source: Constructed during evaluation for proposed amendments to MBS item 73295 by commentary

7. Population

The population intended for g*BRCA* testing was unchanged from the previous submission (i.e. patients with triple negative early breast cancer [TNBC], or patients with HR+ HER2− early breast cancer with high-risk characteristics). The proposed clinical management algorithm presented in the resubmission was unchanged (Figure 1). Therefore, the commentary noted that this has not been updated to reflect the removal of the reference to a high recurrence score from a multigene assay, nor that the intent of the application for funding was to identify HR+ patients who had at least one of the high-risk characteristics.

Of note, the requested PBS listing for olaparib is for the adjuvant treatment of HER2− early breast cancer in patients with g*BRCA* variants in which:

- there is residual invasive cancer in the breast and/or resected lymph nodes following neoadjuvant chemotherapy; or
- in a patient with triple negative breast cancer who has received adjuvant chemotherapy, there is node positive disease or where the primary tumour is greater than 20 mm; or
- in a patient with HR+ HER2− breast cancer who has received adjuvant chemotherapy, there are 4 or more positive lymph nodes.

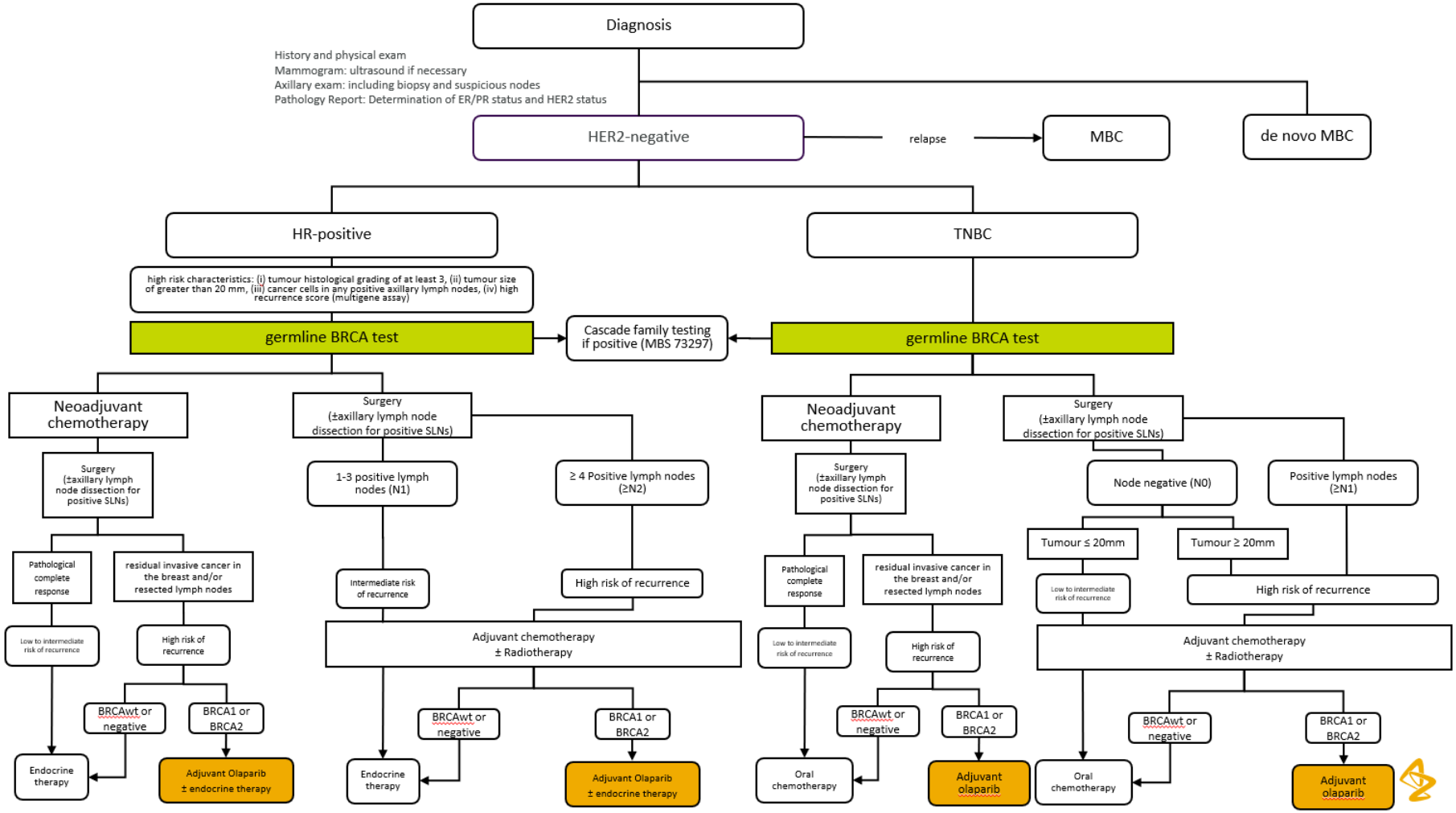
The commentary noted that the proposed population eligible for testing therefore remains broader than the population proposed for olaparib treatment (Figure 1). Concerns were noted by MSAC previously that misalignment of the testing and treatment populations may be a cause for confusion in clinicians and disappointment in patients, despite knowing their g*BRCA* status (pp3−4, 1716 PSD March 2023 MSAC Meeting). The resubmission acknowledged this difference

but noted it matched information available about the tumour at time of diagnosis (and so reduces any risk of delays in olaparib treatment initiation).

The timing of testing remained for MSAC consideration, however the commentary noted that there were other benefits with identifying g*BRCA* variants beyond access to olaparib treatment (such as increased monitoring for other cancers and preventative actions e.g. bilateral salpingo-oophorectomy or mastectomy) (1411.1 PSD March 2016 MSAC Meeting, where g*BRCA* testing was considered cost-effective in patients with >10% risk of having a g*BRCA* variant). As the PBAC has accepted a prevalence of >10% in patients with TNBC (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting), g*BRCA* testing in these patients even in the absence of olaparib treatment is likely to be cost-effective.

The commentary noted that while the financial implications analysis presented in the PBAC resubmission did take into account this misalignment between the testing and treated population, the economic analysis did not (and so assumed that all patients identified with g*BRCA* variants would receive olaparib treatment).

Figure 1 Proposed clinical treatment algorithm



Source: Figure 1.3, p21 of the PBAC resubmission.
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; PR = progesterone receptor; SLN = sentinel lymph node biopsy; TNBC = triple negative breast cancer

8. Comparator

The nominated comparator was unchanged in the resubmission and remained 'no test' and 'watch and wait'. The MSAC Executive previously considered that no testing would be a comparator (p11, 1716 PSD March 2023 MSAC Meeting) and the PBAC previously accepted watch and wait as the main appropriate comparator for olaparib (paragraph 7.4, Olaparib PSD March 2023 PBAC Meeting).

9. Summary of public consultation input

All consultation feedback received on the resubmission indicated support for the application. For the summary of the consultation feedback from the previous submission refer to 1716 PSD March 2023 MSAC Meeting, pp11–12.

10. Characteristics of the evidence base

The clinical evidence presented in the PBAC resubmission remained based on the OlympiA trial. This was a randomised controlled trial which compared olaparib to placebo in high-risk HER2– early breast cancer patients who have g*BRCA* variants and who had received adjuvant or neoadjuvant chemotherapy. No updated data from this trial were provided. The key features of the trial 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 vs. placebo						
OlympiA	1836 (1830 women and 6 men)	R, DB, PC, MC 3.5 years	*Low*	HER2 negative, g*BRCA* variant, early breast cancer [a] previously treated with chemotherapy.	Primary outcome: IDFS. Secondary outcomes: OS, DDFS, FACIT-Fatigue, EORTC QLQ-C30, safety.	IDFS EORTC QLQ-C30

Source: Figure 2.3, p45, Table 2.6, pp47-48, Table 2.8 pp50-54, Table 2.15, pp66-67, Table 2.11, p59 of the PBAC resubmission.
g*BRCA* = germline *BReast CAncer* gene, DB = double blind; DDFS = distant disease-free survival; EORTC = European Organisation for the Research and Treatment of Cancer; FACIT = functional assessment of chronic illness therapy; HER2 = human epidermal growth factor receptor 2; IDFS = invasive disease-free survival; MC = multi-centre; N = number of patients; OS = overall survival; PC = placebo controlled; QLQ-C30 = quality of life questionnaire core 30; R = randomised.
[a] Patients could be positive or negative for hormone receptors. This was a stratification factor during randomisation.

11. Comparative safety

Test

No additional safety data were presented in the resubmission to support the comparative safety of g*BRCA* testing. The commentary noted that previously it was noted that 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).

Drug

No additional safety data were presented in the PBAC resubmission to support the comparative safety of olaparib. However the commentary considered, as described below in 'Clinical claim', the claim of comparative safety was updated from the claim in the previous submission of non-inferior safety based on the previous PBAC consideration of this evidence (paragraph 7.7, Olaparib PSD March 2023 PBAC Meeting).

12. Comparative effectiveness

Comparative analytical performance

No additional data were presented in the resubmission to support the comparative analytical performance of g*BRCA* testing. The commentary noted previously, MSAC expected high testing concordance between next generation sequencing and the Sanger sequencing method used in the clinical trials (p3, 1716 PSD March 2023 MSAC Meeting).

Drug

No additional data were presented in the PBAC resubmission to support the comparative effectiveness of olaparib. Refer to 1716 PSD March 2023 MSAC Meeting, pp15–18, for a summary of the results from the OlympiA trial. The commentary noted that PBAC previously considered that while a claim of superior efficacy was supported for olaparib compared with placebo, this was based on immature invasive disease-free survival (IDFS) data (paragraph 7.6, Olaparib PSD, March 2023 PBAC Meeting). IDFS was noted to be a composite endpoint and although a clinically relevant measure by itself, its relationship to overall survival (OS) and its minimally clinically important difference are not known in this population (paragraph 6.45, Olaparib PSD March 2023 PBAC Meeting). The PBAC also noted that while the OS data were immature, the OlympiA trial would require a significantly longer duration of follow-up for the OS data to reach maturity (paragraph 7.6, Olaparib PSD, March 2023 PBAC Meeting).

Clinical claim

The clinical claim presented in the resubmission was that in patients with HER2− high-risk early breast cancer with confirmed g*BRCA* variants who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (with anthracyclines and/or taxane):

- olaparib has superior comparative efficacy (IDFS, distant disease-free survival [DDFS], OS) relative to placebo; and
- olaparib has an inferior yet manageable safety profile compared to placebo.

The commentary noted no specific concerns were raised by MSAC previously on the comparative claims of safety and effectiveness of g*BRCA* testing compared to no testing in the population proposed.

The PBAC previously considered that a claim of superior efficacy was supported for olaparib compared with placebo, based on immature IDFS data (paragraph 7.6, Olaparib PSD, March 2023 PBAC Meeting). While the data presented did not change since the previous submission (and so remains immature), this claim remains supported by the evidence presented.

The commentary considered that the claim of inferior, but manageable safety for olaparib compared to placebo was supported by the presented evidence as patients receiving olaparib in

the OlympiA trial had more treatment-related adverse events (AEs) overall (80.8% vs 53.1%), more AEs of grade 3 or higher (24.5% vs 11.3%), and more AEs requiring dose reduction (23.4% vs. 3.7%), interruption (31.4% vs. 11.0%), or discontinuation (10.8% vs 4.6%). This was consistent with concerns noted by the PBAC previously (paragraph 7.7, Olaparib PSD March 2023 PBAC Meeting). The commentary further noted that the safety profile of olaparib in the OlympiA trial aligned with what was already established for olaparib in the indications for which it has received PBAC and TGA approval.

13. Economic evaluation

Model overview and summary of changes related to testing

The PBAC resubmission presented a stepped economic evaluation which remained based on the OlympiA randomised controlled trial. The type of economic evaluation presented was a cost-effectiveness analysis and a cost-utility analysis. The structure of the model was unchanged from that presented previously, namely a semi-Markov model with time varying transition probabilities and a 40-year time horizon in the base case. The cost of testing remained front-loaded into the model.

A comparison of parameters related to testing used in the previous and current submission is presented in Table 6.

Table 6 A comparison of testing parameters used in the previous vs current submission's economic model

	Previous submission	Current submission
Prevalence of g*BRCA* variants		
• TNBC	13.25%	13.25%
• HR+	13.25%	5.0%
Proportion of patients with high-risk characteristics		
• TNBC	100%	100%
• HR+	49.0%	49.0%
Uptake of g*BRCA* testing before olaparib listing		
• TNBC	74.0%	74.0%
• HR+	74.0%	20.0%
Uptake of g*BRCA* testing following olaparib listing	**redacted**%	**redacted** %
Proportion of patients that are TNBC	12.1%	15.0%
Performance of g*BRCA* testing	100% sensitivity 100% specificity	100% sensitivity 100% specificity
Cost of g*BRCA* testing	$1,200	$1,000
Proportion of patients tested who have a high risk of recurrence (and so eligible for olaparib treatment)	100.0%	100.0%

Source: Constructed during the evaluation.
g*BRCA* = germline *BReast CAncer* gene; HR+ = hormone receptor positive; TNBC = triple negative breast cancer.

The prevalence of g*BRCA* variants in HR+ patients tested was reduced from what was assumed previously. The commentary considered this was reasonable, as MSAC previously considered the prevalence applied was overestimated (p5, 1716 PSD March 2023 MSAC Meeting). The estimate applied was 5.0%, based on advice provided by the PBAC (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting). The commentary noted that this was consistent with other published

literature (Tung et al. 2016[1] reported that 15 of 301 [5.0%] patients with HR+ HER2− breast cancer had g*BRCA* variants). The prevalence applied in TNBC patients was unchanged. The commentary considered this was consistent with PBAC advice (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting).

Uptake of current g*BRCA* testing was reduced from that assumed previously in HR+ patients. The commentary considered this was reasonable, as current testing is available only for a subset of people with breast cancer (p5, 1716 PSD March 2023 MSAC Meeting). The estimate applied was 20%, based on advice provided by the PBAC (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting). Uptake of testing in TNBC patients was unchanged, based on previous PBAC advice (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting).

Uptake following olaparib listing was unchanged in the economic model presented in the resubmission (**redacted**%). The commentary noted this was higher than estimates anticipated by the PBAC previously (85% in TNBC and 30% in HR+ HER2− breast cancer; paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting), and also higher than that applied in the estimated financial impact (up to 90%). The PBAC resubmission stated that the value applied would be that once the "steady state" had been reached. The commentary considered that this remained for MSAC and PBAC consideration, noting that there are benefits aside from accessing olaparib treatment associated with the identification of g*BRCA* variants (described in 'Population') which may affect uptake of testing if available.

All patients tested and were found to have g*BRCA* variants were assumed to have a high-risk of recurrence meeting the eligibility criteria for olaparib treatment. The commentary considered that this was not reasonable as the population eligible for testing is broader than the population eligible for treatment. Further, this was not consistent with the approach adopted in the estimates of the financial implications, where a proportion of patients found with g*BRCA* variants following testing did not meet subsequent criteria for treatment.

As described earlier, the resubmission proposed a reduction to the MBS fee for g*BRCA* testing (from $1,200 to $1,000). The commentary considered that as the Department supported a schedule fee of $1,200, based on stakeholder consultation feedback, the alternate analyses presented in the Commentary on the PBAC resubmission (Table 9) adopted this higher fee.

Results of the economic analysis

The results of stepped economic evaluation are presented in Table 7. The commentary considered analyses in Step 1 of the PBAC resubmission underestimated the extent of testing in the comparator arm of the model (20%, compared to 53% weighted across the TNBC and HER2− HR+ populations). Furthermore, these analyses reflected the cost of testing in the tested population, however all other costs and outcomes estimated in this step reflected those of the treated population. These were corrected in the Commentary on the PBAC resubmission. The cost per recurrence avoided in the trial-based analysis was also calculated.

The results of Steps 2 and 3 in the PBAC resubmission were presented across the tested population. The commentary considered as these estimates reflected a dilution in the incremental costs and outcomes in those treated with olaparib across those who uptake testing, the Commentary on the PBAC resubmission presented these steps for the treated rather than tested population. An additional step was presented in Table 7 reflecting the resubmission's base case across the tested population (where it was be observed that while there is no change

[1] Tung N et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. *J Clin Oncol*. 2016 May 1;34(13):1460-8.

in the ICER, the incremental costs and outcomes reflected approximately 7.1% of those estimated in the treated population).

Table 7 Results of the stepped economic analysis

Step and component	Olaparib	Placebo	Increment
Step 1: Trial-based analysis, including test cost, olaparib cost and cost for treatment of AEs, over 79 months (duration of follow-up of IDFS in the OlympiA trial) (costs and outcomes reflect the treated population)[a]			
Costs	**redacted**	$1,046	**redacted**
Revised [b]	**redacted**	*$8,328*	**redacted**
Invasive disease-free years gained	5.71	5.24	0.47
Recurrence-free rate (per modelled data)	*78%*	*70%*	*7%*
Incremental cost/invasive disease-free year gained			**redacted** [1]
Revised [b]			**redacted** [2]
2Incremental cost/recurrence avoided [b, c]			**redacted** [3]
Step 2: Modelled analysis (LYs)[d], as above plus costs for genetic counselling, disease monitoring, subsequent therapies, and terminal care, with time horizon extended to 40 years			
Costs	**redacted**	$34,051	**redacted**
LYs	14.22	13.19	1.03
Incremental cost/LY gained			**redacted**[4]
Step 3: Modelled analysis (QALYs)[d], as above incorporating utility values			
Costs	**redacted**	$34,051	**redacted**
QALYs	12.27	11.36	0.91
Incremental cost/QALY gained			**redacted** [4]
Step 4: Modelled analysis, as above reflecting the tested population			
Costs	**redacted**	**$19,776**	**redacted**
QALYs	12.94	12.87	0.065
Incremental cost/QALY gained			**redacted** [4]
Results of modelled economic evaluation in the March 2023 PBAC submission			
Costs	**redacted**	$37,929	**redacted**
QALYs	12.36	11.32	1.04
Incremental cost/QALY gained			**redacted** [5]

Source: Table compiled during the evaluation, based on Table 3.45 to Table 3.47, p258 of the PBAC resubmission, the "OlympiA Economic Evaluation" workbook included with the PBAC resubmission; and the March 2023 submission to the PBAC.
AEs = adverse events; g*BRCA* = germline *BReast CAncer* gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; LYs = life years; QALYs = quality-adjusted life years.
Blue shading indicates results presented in the previous submission.
[a] All outcomes and costs, except the cost of testing, reflect the comparison of olaparib versus placebo treatment in patients with g*BRCA* variants. Test costs in the trial-based analysis were estimated by multiplying the unit cost (*i.e.* $1,000) with the testing rate in the proposed scenario (**redacted**%) for the olaparib arm and with the testing rate in the HR+ HER2- patients in the current scenario (20%) for the placebo arm. *This inappropriately reflects the cost of testing across the population eligible for testing – not the cost of testing required to find one patient with a gBRCA variant who is eligible for treatment.*
[b] *Analyses were revised to apply the cost of testing required to identify one treated patient and to correct for an underestimation in the extent of testing across HER2− HR+ (20% uptake) and TNBC (74% uptake) patients in the comparator arm (weighted extent of current testing should be approximately 53%).*
[c] *Additional analysis performed during the evaluation.*
[d] Modelled costs and outcomes are for the 'treated' population and so do not include patients without g*BRCA* mutations. This has been done so that the costs and outcomes relate to a full course of olaparib *vs.* a full course of placebo per patient (which is not intuitive from the absolute and incremental costs and outcomes in the analysis of the 'tested' population).
[1] *$75,000 to < $95,000*
[2] *$95,000 to < $115,000*
[3] *$555,000 to < $655,000*
[4] $35,000 to < $45,000
[5] $45,000 to < $55,000

The disaggregated results of the economic evaluation in terms of health care outcomes and costs in the treated population are summarised in Table 8.

Table 8 Disaggregated costs and outcomes, treated population (discounted)

Resource item	Olaparib	Placebo	Increment	% of increment
Costs				
g*BRCA* testing costs	**redacted**	$8,605	**redacted**	16.4%
Olaparib	**redacted**	$0	**redacted**	94.7%
Subsequent anticancer treatment	**redacted**	$9,370	**redacted**	−6.4%
Non-mBC health state	**redacted**	$455	**redacted**	−0.6%
mBC health state	**redacted**	$8,915	**redacted**	−5.8%
Surgery/radiotherapy post-recurrence	**redacted**	$1,382	**redacted**	−0.8%
Non-mBC health state	**redacted**	$375	**redacted**	−0.2%
mBC health state	**redacted**	$1,006	**redacted**	−0.7%
Adverse events	**redacted**	$846	**redacted**	0.4%
Disease monitoring	**redacted**	$4,984	**redacted**	−0.7%
Terminal care	**redacted**	$8,866	**redacted**	−3.7%
Total	**redacted**	**$34,051**	**redacted**	**100.0%**
Outcomes				
IDFS QALYs	11.78	10.76	1.03	112.7%
Non-mBC QALYs	0.29	0.33	−0.04	−4.7%
Early-onset mBC QALYs	0.06	0.13	−0.07	−8.0%
Late-onset mBC QALYs	0.14	0.14	0.00	−0.1%
Total QALYs	**12.27**	**11.36**	**0.91**	**100.0%**

Source: Table generated during the evaluation, based on the "OlympiA Economic Evaluation" Excel workbook included with the PBAC resubmission.
g*BRCA* = germline *BReast CAncer* gene; IDFS = invasive disease-free survival; mBC = metastatic breast cancer recurrence; non mBC = non-metastatic breast cancer recurrence; QALYs = quality-adjusted life years.

The commentary noted that incremental costs were driven by the cost of olaparib treatment and g*BRCA* testing (which included both the cost of testing and genetic counselling), offset by a reduction in cost of subsequent anticancer treatment and terminal care. It is noted that only additional g*BRCA* testing costs due to the listing of olaparib were included in the resubmission. The incremental life years and quality-adjusted life years (QALYs) gained were predominantly accrued in the invasive disease-free survival health state, with a reduction in time spent with early-onset metastatic and non-metastatic disease.

The commentary on the MSAC minor submission noted that the commentary on the PBAC resubmission proposed an alternate base case (Table 9) based on previous PBAC advice (paragraph 7.11, Olaparib PSD March 2023 PBAC Meeting) and additional economic issues identified during the evaluation. This resulted in a substantially higher incremental cost-effectiveness ratio (ICER) than what the PBAC had previously considered to be cost-effective in this setting $55,000 to < $75,000 /QALY gained vs. $35,000/QALY gained, paragraph 7.12, Olaparib PSD March 2023 PBAC Meeting).

Table 9 Stepwise multivariate sensitivity analyses to generate the alternate base case in the Commentary on the PBAC resubmission

Description of change	Base case value	Alternative value	ICER (cumulative)	Change in ICER
Resubmission base case		–	**redacted** [1]	**redacted** %
Observed data truncation point	48 months	60 months	**redacted** [2]	**redacted** %
Proportion of recurrences that are non-metastatic vs. metastatic	Treatment-specific: Olaparib: 25.0% vs. 75.0% Placebo: 23.2% vs. 76.8%	Equal across arms: 23.9 vs. 76.1% in both arms	**redacted** [2]	**redacted** %
Increase background mortality for g*BRCA* mutated patients to account for other cancer deaths	1.61	2	**redacted** [2]	**redacted** %
Treatment rate in the mBC setting	80%	70%	**redacted** [2]	**redacted** %
Adjustment for increased PARP use for non-mBC and mBC	Included	Removed	**redacted** [2]	**redacted** %
Treatment duration of sacituzumab govitecan treatment	6.6 months	5.6 months, taking to account dose interruptions	**redacted** [2]	**redacted** %
g*BRCA* testing unit cost	$1,000	$1,200	**redacted** [2]	**redacted** %
Echocardiography	Included in the mBC health state	Removed	**redacted** [2]	**redacted** %
Model time horizon	40 years	30 years	**redacted** [2]	**redacted** %

Source: Analyses performed during the evaluation.
g*BRCA* = germline Breast Cancer gene; ICER = incremental cost-effectiveness ratio; mBC = metastatic breast cancer recurrence; non-mBC = non-metastatic breast cancer recurrence; PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase.
[1] *$35,000 to < $45,000*
[2] *$55,000 to < $75,000*

Additional sensitivity analyses based on the alternate base case presented in the Commentary on the PBAC resubmission are presented in Table 10.

Table 10 Sensitivity analyses (PBAC Commentary alternate base case)

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
PBAC Commentary alternate base case	**redacted**	**0.61**	**redacted** [1]	–
Time horizon (base case: 30 years)				
40 years	**redacted**	0.67	**redacted** [1]	**redacted** %
Observed data truncation point (base case: 60 months)				
54 months	**redacted**	0.74	**redacted** [1]	**redacted** %
Increased background mortality multiplier (base case: 2)				
1.61	**redacted**	0.622	**redacted** [1]	**redacted** %
Discount rate (base case: 5%)				
0%	**redacted**	1.18	**redacted** [2]	**redacted** %
3.5%	**redacted**	0.73	**redacted** [1]	**redacted** %
Assumption of reduced recurrence rate in the olaparib arm (base case: Years 5-10: 1% per year; Year 10+: 0%)				
Delayed by 1 year, i.e. Years 6-11: 1% per year; Year 11+: 0%)	**redacted**	0.47	**redacted** [3]	**redacted** %
g*BRCA* testing cost (base case: $1,200; To estimate the number needed to be tested to identify one patient treated with olaparib, it was assumed that 100% patients who undergo g*BRCA* testing and are tested positive for g*BRCA* variants would receive olaparib therapy)				
Unit cost of $1,000	**redacted**	0.61	**redacted** [1]	**redacted** %
Assuming 50% of patients tested positive for g*BRCA* would be eligible for olaparib [a]	**redacted**	0.61	**redacted** [3]	**redacted** %
Treatment duration of olaparib (base case: 9.7 months)				
10.27 months (based on trial TTD)	**redacted**	0.61	**redacted** [1]	**redacted** %

Source: Analyses performed during the evaluation.
g*BRCA* = germline Breast Cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; TTD = time-to-treatment discontinuation; TNBC = triple negative breast cancer.
[a] Tested assuming similar estimates as per previous PBAC recommendations (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting) on the financial impact analysis (40% of TNBC patients tested eligible for testing and 51% of HR+, HER2− patients tested eligible for treatment). This effectively doubles the incremental cost for g*BRCA* testing between the two arms.
[1] *$55,000 to < $75,000*
[2] *$35,000 to < $45,000*
[3] *$75,000 to < $95,000*

The commentary noted that while the ICER was moderately sensitive to accounting for the difference in the population eligible for testing, and that eligible for treatment, it is acknowledged that this analysis does not take into account the other benefits associated with identifying g*BRCA* variants beyond access to olaparib treatment (such as increased monitoring for other cancers and preventative actions e.g. bilateral salpingo-oophorectomy or mastectomy) (1411.1 PSD March 2016 MSAC Meeting).

The commentary noted that PBAC previously considered that olaparib (following g*BRCA* testing at a cost of $1,200) could be considered cost-effective with changes to the economic model and price reduction to achieve an ICER of $35,000/QALY. While this recommended ICER was higher

than other decisions in the adjuvant therapy setting ($30,000/QALY) (para 7.9, nivolumab PSD, July 2022 PBAC meeting), MSAC may wish to consider whether this adequately accounted for the costs and benefits resulting from cascade testing not captured in the analysis. The economic evaluation included in the resubmission (with reduced test cost of $1,000), however did not incorporate all of the changes suggested by the PBAC and presented a higher ICER ($35,000 to <$45,000). Increasing the cost of g*BRCA* testing from $1,000 (assumed in the current base case) to $1,200 in isolation from the other changes listed in Table 9 results in an ICER of $45,000 to <$55,000 per QALY which is less than 3% higher than the current resubmission base case. Addressing the outstanding concerns (and other matters identified during the evaluation) increased the ICER to $55,000 to < $75,000/QALY and $55,000 to < $75,000/QALY (as per Table 9) , assuming test costs of $1,000 and $1,200, respectively.

14. Financial/budgetary impacts

The epidemiological approach used previously to estimate the changes in use and cost to the MBS and PBS resulting from the proposed listing of g*BRCA* testing for access to olaparib treatment in high-risk HER2− early breast cancer was updated. In general, the commentary noted that the approach was consistent with the previous submission, with updates to the epidemiological estimates used, based on advice provided by the PBAC.

A summary of the data sources and parameter values used to estimate the utilisation and financial implications of g*BRCA* testing in the resubmission are summarised in Table 11.

Table 11 Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Value applied and source	Comment
Incident cases of breast cancer	Increasing from 21,729 in Year 1 to 24,173 by Year 6 based on AIHW breast cancer incidence projections for all persons, 2022−2031[a]	The commentary noted that source was unchanged from the previous submission, though estimates were updated to reflect 2024−29 (compared to 2023−28, previously)
Proportion of patients at Stage I-III at diagnosis	95.1% based on AIHW breast cancer incidence by stage data, 2011, adjusted for patients with unknown disease stage [b]	The commentary considered this change was consistent with PBAC advice [c]
Proportion of patients with TNBC (eligible for testing)	15.0% based on Cancer Council Australia, accepted by the PBAC previously (Table 16, atezolizumab PSD, March 2021 PBAC meeting)	The commentary considered this change was consistent with PBAC advice [c]
Proportion of TNBC that is high risk (eligible for treatment with olaparib)	Assumed to be 80.0%, as previous PBAC advice (40%)[c] was considered to be an underestimate, due to unknown *BRCA* status in the study cited, and a higher risk of recurrence could be expected in g*BRCA* patients (due to poor prognosis)	The commentary considered this may not have been reasonable given that previous studies[d] suggested that response with neoadjuvant chemotherapy may have been higher in those with g*BRCA* variants. The commentary considered this was inconsistent with the economic model which assumed all TNBC patients tested found with g*BRCA* variants would meet the criteria for olaparib treatment.
Proportion with HR+ HER2− breast cancer	69.3% (Stuart-Harris et al. 2019) [e]	The commentary noted this was unchanged.

Parameter	Value applied and source	Comment
Proportion of HR+ HER2− breast cancer that is high risk (eligible for treatment with olaparib)	39.2% assuming 49.0% of patients have high-risk characteristics eligible for testing (based on the proportion that use (neo)adjuvant therapy reported in Patiniott et.al. 2019[f]) (unchanged from the previous submission), and that of these, 80% do not respond to treatment (as assumed for TNBC)	The commentary noted the PBAC considered that 25% would be more appropriate. [c] The commentary considered this was inconsistent with the economic model which assumed all HR+ HER2− breast cancer patients eligible for testing (i.e. 49%) found with g*BRCA* variants would meet the criteria for olaparib treatment.
g*BRCA* testing before olaparib listing	TNBC: 74.0% HR+ HER2−: 20.0%	The commentary considered this was consistent with PBAC advice [c]
g*BRCA* testing after olaparib listing		
• TNBC	74.0% in Year 1 to 90.0% from Year 3. Year 1−2 estimates were as advised by the PBAC[c]. In Year 3+, a higher rate was applied as PBAC advice was considered an underestimate.	The commentary considered the basis for the claimed underestimate in Year 3+ was not clear.
• HR+ HER2−	Assumed to increase from 50.0% in Year 1 to 90.0% from Year 4 as estimates advised by the PBAC[c] were considered an underestimate based on high testing uptake in advanced ovarian and prostate cancer following olaparib listing.	The commentary considered tt was unclear whether use of testing for treatment in the advanced setting would be indicative of use of testing for treatment in the early (adjuvant) setting.
Proportion with g*BRCA* variants		
• TNBC	13.25% based average of Armstrong et al. (2019)[g], Wong-Brown et al. (2015)[h] and IPSOS commissioned data (Att. 1 to the resubmission)	The commentary considered this was consistent with PBAC advice [c]
• HR+ HER2−	5.0% based on PBAC advice [c]	The commentary considered this was consistent with PBAC advice.
Cost of g*BRCA* testing	$1,000 as per the proposed MBS item.	The commentary noted the Department supported a schedule fee of $1,200, based on stakeholder consultation feedback.
Number of relatives tested	1.8 per incident case identified with g*BRCA* variants, based on the Departmental Overview on the previous submission.	The commentary considered while the number of relatives tested per patient is reasonable, this does not reflect the incremental number of relatives tested due to the listing of olaparib.
Cost per relative tested (included in sensitivity analysis only)	$1,000 as per the proposed MBS item.	The commentary did not consider the assumption to be appropriate as MBS item 73297 has a Schedule Fee of $400

Source: Constructed during the evaluation from Table 4.3, pp267−8 of the PBAC resubmission.
g*BRCA* = germline *BReast CAncer* gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.
Blue shading indicates estimates that were unchanged from the previous submission.

[a] Australian Institute of Health Welfare. Cancer in Australia 2021. Canberra: AIHW 2021. Cancer series no. 133. Cat. no. CAN 144.
[b] Australian Institute of Health Welfare. Cancer in Australia 2019. Canberra: AIHW 2019. Cancer series no. 119. Cat. no. CAN 123.
[c] Paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting.
[d] Desai NV, Zakalik D, Somerfield MR, Tung NM. Q and A: A New Standard of Care for Germline *BRCA1* and/or *BRCA2* Mutation Carriers With Early-Stage Breast Cancer. JCO Oncol Pract. 2022 Jun;18(6):427-9.
[e] Stuart-Harris R, Dahlstrom JE, Gupta R, Zhang Y, Craft P, Shadbolt B. Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015. The Breast. 2019 2019/04/01/;44:153-9.
[f] Patiniott PD, Wong GYM, Lam YH, Fosh B. Neoadjuvant chemotherapy rates for breast cancer in Australia—"are we there yet?". Annals of Breast Surgery. 2019;3.
[g] Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of *BRCA* mutation in breast cancer. Clin Epidemiol. 2019;11:543-61.
[h] Wong-Brown MW, Meldrum CJ, Carpenter JE, Clarke CL, Narod SA, Jakubowska A, et al. Prevalence of *BRCA1* and *BRCA2* germline mutations in patients with triple-negative breast cancer. Breast cancer research and treatment. 2015;150(1):71-80.

The financial implications to the MBS resulting from the proposed listing of g*BRCA* testing for access to olaparib in high-risk HER2− early breast cancer presented in the resubmission are summarised in Table 12. The commentary presented revised estimates assuming a $1,200 schedule fee, with the rebate payable accounting for the GPG.

As some testing is assumed to occur currently in the absence of olaparib listing, the resubmission estimated the incremental number of tests performed, based on current estimates of testing that were not assumed to change over the projected period. This was assumed to be 74% in patients with TNBC, and 20% in patients with HR+ HER2− breast cancer, based on PBAC advice (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting). While the extent of background testing in the absence of an olaparib listing was considered reasonable by the commentary, as only the cost of incremental testing had been included in the analysis, it was noted that this approach implicitly assumed that the background level of testing is all currently funded by the MBS, which may not be reasonable. While it may be reasonable to consider that some of this testing is funded by the MBS (under item 73296), States and Territories and patients may also be paying for these tests. The commentary noted that the extent of other sources of funding for the background level of testing is unknown, though any shift in testing from these other sources to the MBS had not been accounted for in the estimates presented in the resubmission, and so the cost to the MBS may be an underestimate.

However, the commentary further noted that the impact of this may be limited due to a possible overestimation of the extent of testing uptake following olaparib listing, as higher rates were applied (increasing to 90% in both TNBC and HR+ HER2− breast cancer) than those previously anticipated by the PBAC (85% in TNBC and 30% in HR+ HER2− breast cancer) (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting).

The resubmission maintained that 49.0% of HR+ HER2− patients would have high-risk characteristics eligible for testing (i.e. tumour histology grade ≥3; tumour size ≥20 mm; or any positive lymph nodes). The PBAC previously considered that 25.0% would be a more appropriate estimate of the proportion at high-risk in the HR+ population (paragraph 7.14, Olaparib PSD March 2023 PBAC Meeting). However, the commentary considered that this advice may apply to the overall proportion of patients with both high-risk characteristics and a high-risk of recurrence that would be eligible for olaparib treatment (i.e. who also have residual invasive cancer following neoadjuvant chemotherapy, or ≥4 positive lymph nodes). As testing is proposed in a population broader than that eligible for olaparib treatment, using a two-step approach to determine first the number of patients with high-risk characteristics eligible for testing, and then of these, the proportion of which also have a high-risk of recurrence may be reasonable. The commentary considered that the study[2] used to inform this estimate may be a reasonable approximation of the proportion of incident early breast cancer in Australia that would have high-risk characteristics eligible for testing.

[2] Patiniott PD, Wong GYM, Lam YH, Fosh B. Neoadjuvant chemotherapy rates for breast cancer in Australia—"are we there yet?". Annals of Breast Surgery. 2019;3

Table 12 Estimated change in the use and cost to the MBS of g*BRCA* testing in incident cancer cases

		2024	2025	2026	2027	2028	2029
A	Breast cancer incidence	**redacted**[1]	**redacted** [1]	**redacted** [1]	**redacted** [1]	**redacted** [1]	**redacted** [1]
B	No. patients at stage I-III at diagnosis (adjusted) (A × 95.1%)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
	TNBC						
C	No. diagnosed with TNBC (B × 15.0%)	**redacted** [2]	**redacted**[2]	**redacted**[2]	**redacted** [2]	**redacted** [2]	**redacted**[2]
D	No. TNBC patients tested in absence of olaparib listing (C × 74.0%)	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]
E	Uptake of g*BRCA* testing in TNBC patients (following olaparib listing)	**redacted** %	**redacted** %	**redacted** %	**redacted** %	**redacted** %	**redacted** %
F	No. TNBC patients tested (following olaparib listing) (C × E)	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]
G	No. TNBC patients with g*BRCA* variants (F × 13.3%)	**redacted** [3]	**redacted** [3]	**redacted** [3]	**redacted** [3]	**redacted** [3]	**redacted** [3]
	HR+ HER2- breast cancer						
H	No. with HR+ HER2− breast cancer (B × 69.3%)	**redacted** [4]	**redacted** [4]	**redacted** [4]	**redacted** [4]	**redacted** [4]	**redacted** [4]
I	No. patients on (neo)adjuvant chemotherapy (H × 49.0%)	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]
J	No. HR+ HER2− patients tested in absence of olaparib listing (I × 20.0%)	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]
K	Uptake of g*BRCA* testing in HR+ HER2− patients (following olaparib listing)	**redacted** %	**redacted** %	**redacted** %	**redacted** %	**redacted** %	**redacted** %
L	No. HR+ HER2− patients tested (following olaparib listing) (I × K)	**redacted** [2]	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]
M	No. HR+ HER2− patients with g*BRCA* variants (L × 5.0%)	**redacted** [3]	**redacted** [3]	**redacted** [3]	**redacted** [3]	**redacted** [3]	**redacted** [3]
N	Total no. patients tested following olaparib listing (F + L)	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [5]	**redacted** [4]
O	Total no. patients tested in absence of olaparib listing (D + J)	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [2]
P	**Change in use of testing due to listing of olaparib (N – O)**	**redacted** [2]	**redacted** [2]	**redacted** [2]	**redacted** [5]	**redacted** [5]	**redacted** [5]
	Cost of incremental testing to the MBS (P × $850.00)	**redacted** [6]	**redacted** [6]	**redacted** [6]	**redacted** [6]	**redacted** [6]	**redacted** [6]
	Revised (P × $1,106.80)	**redacted** [6]	**redacted** [6]	**redacted** [6]	**redacted** [6]	**redacted** [6]	**redacted** [6]

Source: Constructed during the evaluation from Table 4.32, p291; Table 4.33, p292 and Table 4.37, pp294−5 of the PBAC resubmission and from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file.
Note: Analyses are presented for each calendar year.
g*BRCA* = germline *BReast CAncer* gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.
[1] *20,000 to < 30,000*
[2] *500 to < 5,000*
[3] < 500
[4] 10,000 to < 20,000
[5] 5000 to < 10,000
[6] $0 to < $10 million

The resubmission estimated an additional 500 to < 5,000 to 5,000 to < 10,000 tests per year following the listing of olaparib. The cost to the MBS per additional test applied was $850. This was based on the proposed schedule fee of $1,000 with an 85% rebate applied. The commentary noted that MSAC PSD noted inconsistencies in the schedule fee for other current *BRCA* testing items (item 73304, $1,000; and item 73295, $1,200) and that the department was to investigate which fee would be more appropriate (p3, 1716 PSD March 2023 MSAC Meeting). The department supported a schedule fee of $1,200, based on stakeholder consultation feedback indicating this was most appropriate to cover the costs of providing the service. The department also supported conducting a sensitivity analysis using a schedule fee of $1,000, given there are some similar services funded on the MBS with a fee of $1,000.

While it was reasonable that the resubmission assumed the 85% rebate, the commentary considered that the implications of the GPG were not considered. This would result in the rebate payable by the MBS increasing to the difference between the schedule fee and the GPG.

The MSAC noted previously that proposed testing would trigger cascade testing in biological relatives of patients found to carry g*BRCA* variants using MBS item 73297 (p5, 1716 PSD March 2023 MSAC Meeting). Changes in the use and cost of cascade testing to the MBS were included in the resubmission as a sensitivity analysis only. The commentary considered that this was not reasonable nor well justified. In this sensitivity analysis, the resubmission assumed that for each patient identified with g*BRCA* variants following the listing of olaparib, 1.8 relatives would take up cascade testing at an assumed cost of $850 per test. While the number of relatives tested per patient was reasonable, the commentary considered that this approach reflected the cost of the total number of relatives tested due to the listing of olaparib rather than the incremental number of relatives tested. The commentary considered that this was not reasonable given that cascade testing can currently be accessed under MBS item 73297 which also has a lower rebated fee (85% rebate: $340).

The estimated number of cascade tests and cost to the MBS for cascade testing as estimated in the resubmission is presented in Table 13. The commentary presented revised estimates, based on the incremental number of relatives tested and cost of testing based on MBS item 73297, in Table 14.

Table 13 Estimated change in use and cost of cascade testing

	2024	2025	2026	2027	2028	2029
No. patients identified with g*BRCA* variants following olaparib listing (Row G + Row M, Table 12)	**redacted**[1]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
No. cascade tests (1.8 per patient with g*BRCA* variants identified)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
Cost of cascade testing to the MBS ($850.00 per relative tested)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
Revised ($340.00 per relative tested)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]

Source: Constructed during the evaluation from Table 4.34, p293; Table 4.35, pp293–4 and Table 4.38, p295 of the PBAC resubmission and from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file.
Note: Analyses are presented for each calendar year.
g*BRCA* = germline *BReast CAncer* gene.
[1] < 500
[2] 500 to < 5,000
[3] $0 to < $10 million

Table 14 Estimated change in use and cost of incremental cascade testing

		2024	2025	2026	2027	2028	2029
A	No. TNBC patients tested without olaparib listing (Row D, Table 12)	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1
B	No. TNBC patients who would have been identified with g*BRCA* variants (A × 13.3%)	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2
C	No. HR+ HER2− patients tested without olaparib listing (Row J, Table 12)	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1
D	No. HR+ HER2− patients who would have been identified with g*BRCA* variants (C × 5.0%)	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2
E	Total no. patients identified with g*BRCA* variants without olaparib listing (B + D)	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2
F	No. patients identified with g*BRCA* variants following olaparib listing (Row G + Row M, Table 12)	**redacted** 2	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1
G	Additional patients with g*BRCA* variants identified following olaparib listing (F – E)	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2	**redacted** 2
H	No. additional cascade tests (G × 1.8)	**redacted** 2	**redacted** 2	**redacted** 1	**redacted** 1	**redacted** 1	**redacted** 1
	Cost of additional cascade testing to the MBS (H × $340.00)	**redacted** 3	**redacted** 3	**redacted** 3	**redacted** 3	**redacted** 3	**redacted** 3

Source: Constructed during the evaluation from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file included in the resubmission.
Note: Analyses are presented for each calendar year.
g*BRCA* = germline *BReast CAncer* gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.
[1] 500 to < 5,000
[2] < 500
[3] $0 to < $10 million

The net cost to the MBS is estimated in Table 15.

Table 15 Net changes to the MBS

	2024	2025	2026	2027	2028	2029
Cost to the MBS of testing additional incident cases	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Revised [a]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Cost to the MBS of additional cascade testing	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Revised [b]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Net cost to the MBS [c]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
Revised	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]

Source: Table 4.37, pp294−5 of the PBAC resubmission and from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file.
Note: Analyses are presented for each calendar year.
[a] Revised to assume a schedule fee of $1,200 per test in incident patients, with 85% rebate applied what accounted for the greatest permissible gap.
[b] Revised to include the cost of incremental cascade testing only due to the listing of olaparib, and to assume a schedule fee of $400 per relative tested (based on MBS item 73297)
[c] The base case net cost to the MBS estimated in the resubmission did not include the impact on cascade testing.
[1] $0 to < $10 million

The commentary presented the impact of using testing uptake estimates as advised previously by the PBAC in Table 16. This resulted in a substantially lower estimate of the incremental number of tests performed due to the listing of olaparib, and therefore, lower cost impact to the MBS. However, these costs do not account for any shift in testing of incident cases from other funding sources to the MBS (and so this may underestimate the cost to the MBS).

Table 16 Estimated change in the use and cost to the MBS due to the listing of olaparib (using PBAC specified estimates on uptake of g*BRCA* testing following olaparib listing)

		2024	2025	2026	2027	2028	2029
	TNBC						
A	No. diagnosed with TNBC (Row C, Table 12)	**redacted**[1]	**redacted**	**redacted**	**redacted** [1]	**redacted** [1]	**redacted** [1]
B	No. TNBC patients tested without olaparib listing (Row D, Table 12)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
C	No. TNBC patients identified with g*BRCA* variants without olaparib listing (B × 13.3%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
D	*Uptake of testing in TNBC patients (following olaparib listing)*	**redacted** *%*	**redacted** *%*	**redacted** *%*	**redacted** *%*	**redacted** *%*	**redacted** *%*
E	No. TNBC patients tested (following olaparib listing) (A × D)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
F	No. TNBC patients identified with g*BRCA* variants following olaparib listing (E × 13.3%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
	HR+ HER2- breast cancer						
G	No. HR+ HER2− patients with high-risk characteristics (Row I, Table 12)	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]	**redacted**[3]
H	No. HR+ HER2− patients tested without olaparib listing (Row J, Table 12)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
I	No. HR+ HER2− patients identified with g*BRCA* variants in the absence of olaparib listing (H × 5.0%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
J	*Uptake of testing in HR+ HER2− patients (following olaparib listing)*	**redacted** *%*	**redacted** *%*	**redacted** *%*	**redacted** *%*	**redacted** *%*	**redacted** *%*
K	No. HR+ HER2− patients tested (following olaparib listing) (G × J)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
L	No. HR+ HER2− patients identified with g*BRCA* variants following olaparib listing (K × 5.0%)	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]	**redacted**[2]
M	Total no. patients tested following olaparib listing (E + K)	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[3]	**redacted**[3]	**redacted**[3]

		2024	2025	2026	2027	2028	2029
N	Total no. patients tested without olaparib listing (B + H)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
O	**Change in use of testing due to listing of olaparib (M – N)**	redacted[2]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
P	***Cost of incremental testing to the MBS (O × $1,106.80)***	redacted [4]	redacted [4]	redacted [4]	redacted [4]	redacted [4]	redacted [4]
Q	*Additional patients with gBRCA variants identified following olaparib listing (F – C) + (L – I)*	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
R	*No. additional cascade tests (Q × 1.8)*	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
S	***Cost of additional cascade testing to the MBS (R × $340.00)***	redacted [4]	redacted [4]	redacted [4]	redacted [4]	redacted [4]	redacted [4]
	Net cost to the MBS (P + S)	redacted [4]	redacted [4]	redacted [4]	redacted [4]	redacted [4]	redacted [4]

Source: Constructed during the evaluation from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file using estimates advised by the PBAC (paragraph 7.14, olaparib PSD, March 2023 PBAC meeting).
Note: Analyses are presented for each calendar year.
g*BRCA* = germline *BReast CAncer* gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple negative breast cancer.
[1] 500 to < 5000
[2] < 500
[3] 5,000 to < 10,000
[4] $0 to < $10 million

No sensitivity analyses were presented in the resubmission, as the main source of uncertainty had been identified in the previous submission and were considered to be addressed. *The commentary considered that this was not reasonable as the resubmission had not adhered to all of the recommendations made by the PBAC previously regarding gBRCA testing uptake and the proportion of patients considered to have a high risk of recurrence.*

Additional analyses were conducted during the evaluation exploring the effect of decreasing the schedule fee and testing only those patients who would otherwise meet the criteria for olaparib treatment (Table 17). These have only been explored using the resubmission's estimates of uptake of g*BRCA* testing, as the commentary considered that estimates advised by the PBAC may have limited applicability in the narrower population.

Table 17 Sensitivity analyses conducted during the evaluation

	2024	2025	2026	2027	2028	2029
Net cost to the MBS (revised)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Schedule fee, $1,000	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Testing only in patients who have a high-risk of recurrence (i.e. at time of treatment)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]

Source: Constructed during the evaluation from the 'Att_4.1_OlympiA UCM_AZ Resubmission_FINAL.xlsx' file included in the resubmission.
Note: Analyses are presented for each calendar year.
[1] $0 to < $10 million

The commentary considered that while restricting testing to better align with the population eligible for treatment does reduce the financial impact to the MBS, this may be associated with delays in the initiation of olaparib treatment and other foregone benefits resulting from the identification of g*BRCA* variants.

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