



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1554 – Testing of tumour tissue or blood to detect somatic or germline BRCA1 or BRCA2 gene mutations, in a patient with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (PBAC codependent)***

**Applicant:** AstraZeneca Pty Ltd

**Date of MSAC consideration:** MSAC 77<sup>th</sup> Meeting, 28-29 November 2019

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

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

An application (part of an integrated codependent submission) requesting amendment of existing Medicare Benefits Schedule (MBS) funding to include testing of tumour tissue or blood to detect somatic or germline *BRCA1* or *BRCA2* gene mutations (*BRCAm*), in a patient with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy) was received from AstraZeneca by the Department of Health.

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

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the modification of existing MBS item 73295 and the creation of two new MBS items to fund somatic *BRCA* testing to help identify additional patients as eligible for PBS-subsidised olaparib beyond its existing second-line restriction.

MSAC advised that implementation of this advice would need coordination via the Pharmaceutical Benefits Advisory Committee (PBAC) to change the existing PBS restriction for olaparib.

#### **Consumer summary**

AstraZeneca Australia applied for public funding through the Medicare Benefits Schedule (MBS) for testing of *BRCA* genes for mutations in a sample of tumour tissue (somatic testing). This application was also for testing in women who have just been diagnosed with advanced, high-grade ovarian cancer. Ovarian cancer includes fallopian tube cancer and cancer in the peritoneum (the tissue that lines the cavity of the abdomen).

AstraZeneca markets a drug called olaparib for women with advanced, high-grade ovarian cancer. Olaparib is likely to be more effective for such women if they also have a mutation in their *BRCA1* or *BRCA2* genes. Genetic testing is the only way to find out if someone has a gene mutation. Genetic testing can be done on a blood sample to determine if the mutation is inheritable (germline testing). It can also be done on a sample from the tumour, which can be taken during surgery, to determine if the mutation is present in the tumour (somatic testing).

Olaparib is already listed on the Pharmaceutical Benefits Scheme (PBS) for women with ovarian cancer whose cancer has come back (relapsed) after initial response to treatment. Subsequent treatment after the first treatment that either was not effective or is no longer effective is called second-line treatment. Right now, based on previous MSAC advice, women with ovarian cancer can be tested to see if they have a germline *BRCA* gene mutation, and if they do they can get olaparib as second-line treatment. But this test is currently not funded on the MBS for testing of *BRCA* genes for mutations in a sample from the tumour.

MSAC decided to support the funding of tumour genetic testing for *BRCA* mutations in these women. This decision was informed by newly provided evidence of acceptable test performance and recently established quality assurance for this type of tumour testing.

MSAC noted that, at its November 2019 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) decided not to recommend that the PBS listing of olaparib be extended to include women who have just been diagnosed with ovarian cancer and are responding to initial treatment. MSAC therefore did not provide advice on *BRCA* testing for this population.

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

MSAC supported public funding of testing for *BRCA* mutations in tumour samples from women with ovarian cancer. This is so they can get treated with olaparib as a second-line treatment. MSAC decided this because olaparib should be similarly effective in women with ovarian cancer and a *BRCA* mutation, without having to know whether this mutation was inherited or is present only in the tumour.

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

MSAC noted that this application was part of an integrated codependent submission, and that it requested amendment of the existing MBS funding to include testing of tumour tissue or blood to detect somatic or germline *BRCA1* or *BRCA2* pathogenic variants, in a patient with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy.

MSAC was advised that the November 2019 PBAC meeting had not recommended the extension of the PBS listing of olaparib to include the first-line maintenance treatment of ovarian, fallopian tube or primary peritoneal cancer. As a result, MSAC did not consider the question of considering germline *BRCA* testing in this expanded population (scenario 1 in the submission). Instead, MSAC focussed on the scenario 2 question in the submission of whether to extend MBS funding from only germline *BRCA* testing, to both germline and somatic *BRCA* testing in patients with advanced high-grade epithelial ovarian cancer (HGEOC), but only in the context of the existing PBS listing of olaparib as second-line treatment.

MSAC noted that MBS item 73295 currently only covers germline testing for *BRCA* in the context of olaparib. This item excludes somatic testing. MBS item 73296 is also limited to germline testing for *BRCA* and related genes in the context of predisposition testing.

MSAC accepted the safety profile of tumour *BRCA* testing, noting that, although obtaining a tumour biopsy is associated with adverse events, surgical samples suitable for testing should be collected at the time of diagnosis.

MSAC discussed the evidentiary standard for *BRCA* testing on tumour samples, and considered that most studies included as the evidence base for olaparib and other poly ADP ribose polymerase (PARP) inhibitors would most likely have used Sanger sequencing to determine the *BRCA*m status of study participants. However, most Australian pathology laboratories are now using next-generation sequencing (NGS). NGS is faster, more accurate and more cost-effective than Sanger sequencing. MSAC also agreed with the pre-MSAC response from the applicant, stating that tumour *BRCA* testing services are becoming more widely available, with increasing use of NGS. MSAC accepted that using NGS would pick up marginally more women with *BRCA* mutations than Sanger sequencing, but this would have a negligible effect on the overall estimated budget implications for olaparib.

MSAC considered that the analytical performance data of somatic *BRCA* testing provided in the application formed an acceptable basis to address its previous concerns about somatic *BRCA* testing compared to germline *BRCA* testing. In addition, MSAC accepted that quality assurance was now routinely established for somatic *BRCA* testing, particularly in relation to dealing with potential contaminants and variants of unknown significance.

MSAC noted the clinical need for this test, as women with HGEOC currently have poor outcomes, with more than 70% of women with advanced disease who initially respond to first-line chemotherapy relapsing within 3 years.

MSAC discussed the clinical utility of *BRCA* testing and the response to olaparib. MSAC recalled that it had previously accepted that ovarian cancers with germline *BRCA* mutations are associated with an improved response to PARP inhibitors (such as olaparib) in the second-line setting than ovarian cancers without a *BRCA* mutation. MSAC noted that, in the studies presented, most women had germline *BRCA*m with or without somatic *BRCA*m, rather than somatic *BRCA*m alone. MSAC also considered that the evidence base for the clinical utility of *BRCA* testing for olaparib and other PARP inhibitors was stronger in the second-line setting than in the first-line setting. However, MSAC considered that it was biologically plausible that women with somatic or germline *BRCA*m would each have an improved response to olaparib over women without any *BRCA*m, that is, clinical utility was expected regardless of where the *BRCA* pathogenic variant originated. As a somatic variant may only have “one hit” whereas germline variants have a “double hit”, it is plausible that the predictive effect would be smaller for somatic than germline variants.

MSAC considered that the low utilisation of MBS item 73295 suggested that most patients considered potentially suitable for olaparib would already be eligible for germline *BRCA* testing via MBS item 73296 because of their expected >10% risk of having a *BRCA1/2* pathogenic variant. MSAC therefore considered that the number of extra women eligible for testing by including somatic *BRCA* testing would be small. MSAC also noted that somatic *BRCA* testing is likely to detect about 5% more women with *BRCA* pathogenic variants than detected by germline *BRCA* testing alone.

MSAC considered that the order of the testing (e.g. somatic then germline, or germline then somatic) was not important to its advice, and that the order of testing would depend on the

clinical situation. MSAC accepted that women first identified with a somatic *BRCA*m should be followed up with germline testing, and that predictive (cascade) testing should still be offered only to family members of women with confirmed germline *BRCA*m (MBS item 73297). However, this predictive testing should not be offered to family members of women with variants of unknown significance.

MSAC noted the economic evaluation was slightly uncertain as it:

- underestimated the germline *BRCA* tests displaced
- did not include subsequent germline *BRCA* testing (to identify the need for familial testing) after a positive somatic *BRCA* test result; and
- calculated the overall cost to the MBS using 100% of the MBS item fee, rather than applying the 85% or 75% rebate, or a combination of both.

However, MSAC accepted that these uncertainties would not have a large impact on the overall MBS budget, because of the few additional women who would become eligible for this test.

In the absence of sufficient justification, MSAC did not support a larger fee for somatic *BRCA* testing (proposed item XXXXX) than for existing germline *BRCA* testing (MBS items 73295 and 73296).

MSAC noted some issues with the proposed descriptor for item XXXXX, and the applicant's pre-MSAC response suggesting it was amenable to changes to the descriptor. MSAC agreed that an additional item YYYYY be created to identify the need for predictive testing in family members, however, MSAC advised that the fee for this targeted testing item should be similar to those for other existing cascade testing items (i.e. a particular variant is being looked for; the whole gene would not need to be assessed). MSAC also advised that MBS item 73295 also needs to be amended for patients for whom the tumour tissue is not suitable for tumour *BRCA* testing. MSAC affirmed that none of these items should be pathologist determinable. MSAC suggested the following changes (in red).

Category 6 – Pathology services	
MBS item 73295	Group P7 – Genetics
<p>Detection of germline BRCA1 or BRCA2 gene mutations, in a patient <del>advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, platinum sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous epithelial features or a high grade serous epithelial component, and who has responded to subsequent platinum based chemotherapy, for whom testing of tumour tissue is not feasible</del>, requested by a specialist or consultant physician, to germline whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$1200.00 Benefit: 75% = \$900.00 85% = \$1116.60</p>	
MBS item XXXXX	Group P7 – Genetics
<p>A test of tumour tissue from a patient diagnosed with advanced, <del>high-grade or</del> high grade epithelial ovarian, fallopian tube or primary peritoneal cancer requested by a specialist or consultant physician, to determine whether the requirements relating to BRCA status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p><del>Maximum one test per lifetime</del> Once per primary tumour diagnosis</p> <p>Fee: <del>\$redacted</del> \$1200.00 Benefit: 75% = <del>\$redacted</del> \$900.00 85% = <del>\$redacted</del> \$1116.60</p>	
MBS item YYYYY	Group P7 – Genetics
<p><del>Targeted germline mutation testing Characterisation of germline gene mutations</del>, requested by a specialist or consultant physician, <del>for a pathogenic or likely pathogenic mutation (including copy number variants)ion in BRCA1 and or BRCA2 genes in a patient who has had a pathogenic or likely pathogenic mutation identified in one or more of the genes specified above in a patient</del> by tumour testing (MBS item XXXXX).</p> <p><del>Maximum one test per lifetime</del> Once per primary tumour diagnosis</p> <p>Fee: \$400.00 Benefit: 75% = 300.00 85% = \$340.00</p>	
<p><b>Explanatory notes</b></p> <p><del>Patients who are found to have a pathogenic or likely pathogenic variant in BRCA1 or BRCA2 should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist.</del></p>	

MSAC advised that implementation of this advice would need coordination via the PBAC to change the existing PBS restriction for olaparib.

#### 4. Background

MSAC has previously considered tumour *BRCA* testing for access to olaparib for the treatment of advanced high-grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSOC) in the second-line setting. The original application (Application 1380; integrated codependent submission) was considered by MSAC at its March and November 2016 meetings. In brief, the advice to the Minister was: *“Following advice from the Pharmaceutical Benefits Advisory Committee (PBAC) that it had recommended to the Minister that olaparib be listed in the PBS, MSAC supported the MBS funding of germline BRCA mutation testing to determine eligibility for PBS-subsidised olaparib maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer. MSAC advised the test should only be performed once per lifetime for this purpose.”* (PSD, Application 1380, p1).

For Application 1380, the applicant initially requested testing for both germline and tumour tissue, however tumour testing was removed following the recommendation of MSAC that testing should be for germline mutations only (Public Summary Document [PSD], Application 1380, p1). Key issues identified by MSAC were the:

- Difficulty to discern the evidentiary standard: *“In brief, MSAC agreed with the joint ESCs advice that, given the approach to BRCA testing in Study 19 was inadequately presented, it was difficult to discern the evidentiary standard used as the basis for the submission’s claim of codependence with olaparib and thus clinical utility. MSAC noted that the claim of codependence between BRCA testing and olaparib relied on an acceptance that BRCA testing predicted an important variation between women with and without a detected BRCAm with regards to the effectiveness of olaparib, and that this was distinguishable from the prognostic value of BRCA testing. To help establish this, statistical tests of interaction by BRCA status were suggested. While this was done for progression free survival (see above), it was not provided for overall survival”* (PSD, Application 1380, p4).
- Inadequate support for the performance of somatic BRCA testing: *“MSAC considered that testing should be restricted to germline mutation testing, which is already well established within Australian laboratories and has been shown to be accurate (see above). MSAC noted that there was limited evidence regarding the performance of somatic (tumour) mutation testing. In Study 19, somatic testing missed three of the 96 mutations (4%) detected with germline testing. MSAC considered the technique for somatic testing and its diagnostic accuracy is still to be established. Furthermore, evidence from Study 19 in women in whom germline testing was negative and somatic testing was positive was limited to 18 patients”* (PSD, Application 1380, pp4-5).
- Incremental cost of testing: *“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 BRCAm only, argued against support for funding somatic BRCA testing at this stage. MSAC noted that if access to somatic BRCA testing is to be requested in the future, there may be an incremental cost to the MBS because patients without an identified germline BRCAm would need additional tumour testing. As such, MSAC would require a new application before considering the addition of somatic BRCA testing to the MBS”* (PSD, Application 1380, p5).

Germline *BRCA1* or *BRCA2* testing to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed HGSOc was listed on the MBS (Item 73295) alongside PBS listings for olaparib (Items 11034R and 11050N) since 1 February 2017. Subsequently, germline gene mutation testing, including *BRCA1* and *BRCA2* testing, at diagnosis of ovarian cancer in patients at >10% risk of having a pathogenic gene mutation, became available on the MBS from November 2017 (Item 73296).

## **5. Prerequisites to implementation of any funding advice**

There are at least ten molecular pathology laboratories that currently perform tumour *BRCA* testing and germline *BRCA* testing in Australia using in-house developed next generation sequencing (NGS) testing methods.

To obtain National Association of Testing Authorities (NATA) accreditation to offer medical genetic testing services, including *BRCA* testing, pathology laboratories must participate in an external quality assurance programme (QAP). The Australian laboratories performing tumour *BRCA* testing have enrolled in a QAP that has been conducted for the last 2-3 years. The European Molecular Quality Network (EMQN) has conducted the QAP, which has been administered by the Royal College of Pathologists of Australasia Quality Assurance Programs Pty Limited (RCPAQAP).

The currently available in-house-developed tumour *BRCA* tests have not yet been approved by the Therapeutic Goods Administration (TGA). The submission indicated that at least four laboratories had submitted their tests to the TGA and are awaiting approval. These include: Department of Molecular Pathology, Peter McCallum Cancer Centre, Melbourne; Hunter Area Pathology Service (HAPS) Pathology North, Newcastle; Genomics Diagnostics; and Genomics for Life, Brisbane.

#### *Pre-MSAC response*

The applicant stated that the four laboratories listed in the integrated codependent submission who have developed and validated their own in-house methods for tumour testing to detect somatic *BRCA1/2* mutation have now had their test accredited by the NATA and notification provided to the TGA.

## 6. Proposal for public funding

The submission proposed two scenarios for MBS listing of the proposed testing:

- In Scenario 1, the current MBS item 73295 would be amended to permit its use for the proposed listing of olaparib in the first-line maintenance setting (Table 1)
- In Scenario 2, a new MBS item would be required to permit tumour *BRCA* testing in patients with newly diagnosed advanced high-grade epithelial ovarian cancer (HGEOC), and this scenario would also require an amendment to MBS item 73295 for patients for whom the tumour tissue is not suitable for tumour *BRCA* testing (Table 1 and Table 2).

**Table 1 Proposed amended MBS item 73295 (Scenario 1 and Scenario 2)**

Category 6 – Pathology Services	
MBS item 73295	Group P7 – Genetics
Detection of germline <i>BRCA1</i> or <i>BRCA2</i> gene mutations, in a patient with ovarian, fallopian tube or primary peritoneal cancer with high grade epithelial features or a high grade epithelial component, for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Maximum one test per lifetime	
Fee: \$1,200.00 Benefit: 75% = \$900.00 85% = \$1,116.60	

Source: Table ES5, pV of the submission.

**Table 2 Proposed new MBS item (Scenario 2)**

Category 6 – Pathology Services	
MBS item XXXXX	Group P7 – Genetics
A test of tumour tissue from a patient diagnosed with advanced, high-grade or high grade epithelial ovarian, fallopian tube or primary peritoneal cancer requested by a specialist or consultant physician, to determine whether the requirements relating to <i>BRCA</i> status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Maximum one test per lifetime	
Fee: \$redacted Benefit: 75% = \$redacted 85% = \$ redacted	

Source: Table ES6, pV of the submission.

The Commentary noted that all patients diagnosed with advanced HGEOC have a greater than 10% risk of having a *gBRCAm* (prevalence rate is 20–23% in the Australian population). Thus, these patients would all be eligible for testing under the current MBS item 73296, making MBS item 73295 redundant in Scenario 1. The Commentary stated that there should also be a restriction preventing testing under MBS item 73295 if testing has already been undertaken using MBS item 72396 for both scenarios. However, the pre-ESC response stated that not all patients would be eligible for germline testing under MBS item 73296, as a quantitative algorithm is required.

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

Three letters of support were received by the Department of Health, plus one supportive feedback from a specialist.

The specialist feedback addressed the fact that if this intervention is approved for MBS funding it would also provide access to the women who cannot financially afford to pay for the test.

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

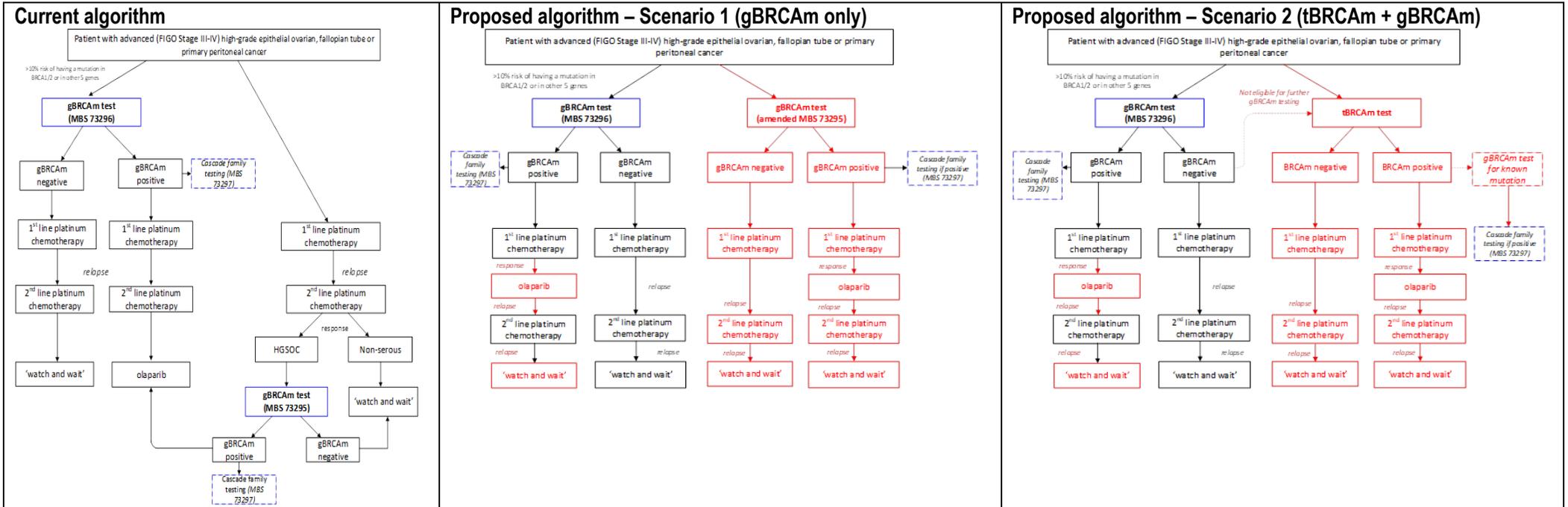
The current treatment algorithm for advanced HGEOC and the proposed clinical management algorithm for Scenario 1 and Scenario 2 are illustrated in Figure 1.

In Scenario 1, all patients receive a germline *BRCA* test, requiring a blood sample, at diagnosis of advanced HGEOC. The Commentary suggested that, in current clinical practice, all patients diagnosed with advanced HGEOC would be eligible for testing at diagnosis under MBS item 73296. However this required clarification as it is unclear whether primary peritoneal and fallopian tube cancers are covered by this item.

In Scenario 2, all patients initially receive a tumour *BRCA* test, requiring either fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tumour tissue. Those who have a positive tumour *BRCA* test result then receive a germline *BRCA* test. If the tumour *BRCA* test fails due to inadequate tumour tissue, the patient would receive a germline *BRCA* test instead, requiring a blood sample to be taken.

Testing, in both scenarios, would occur at diagnosis of advanced HGEOC. The patients would undergo surgical debulking and first-line platinum-based chemotherapy. The tumour tissue removed during surgery (stored as either fresh-frozen or FFPE) would most likely be used for the tumour *BRCA* test. The test result would then be available by the time first-line chemotherapy has been completed and it has been determined whether or not the patient has responded to treatment. If the patient has responded and a *gBRCA* mutation (Scenario 1) identified, the patient would be eligible to receive olaparib maintenance therapy. In Scenario 1, *sBRCAm* patients are not identified and would not receive olaparib. In Scenario 2, both *gBRCAm* and *sBRCAm* patients would be identified and both would receive olaparib.

In current clinical practice, patients with ovarian cancer and a greater than 10% risk of having a *gBRCAm* are eligible for germline *BRCA* testing at diagnosis under MBS item 72396. As 20-23% of all patients diagnosed with HGEOC will have a *gBRCAm*, such patients with epithelial ovarian cancer are eligible for testing at diagnosis as per Scenario 1. This is also reflected in quantitative algorithms such as the Manchester Score which score an epithelial cancer at 10-15 depending on patient age at diagnosis and grade. Currently 70% of HGEOC patients are being tested under MBS item 72396, with 30% being tested after response to second-line platinum-based chemotherapy under MBS item 72395.



**Figure 1 Current vs proposed clinical management algorithms**

Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline *BRCA1* or *BRCA2* mutation; tBRCAm = tumour (somatic) *BRCA1* or *BRCA2* mutation

## 9. Comparator

### *For Scenario 1*

According to the PICO confirmation ratified by PASC, the comparators for germline *BRCA* testing at diagnosis of advanced HGEOC in Scenario 1 would be no testing for non-serous HGEOC and germline *BRCA* testing following response to second-line platinum therapy for serous HGEOC. It is unclear whether all of these patients are covered by MBS item 73296 (see above).

### *For Scenario 2*

The comparator for tumour *BRCA* testing, according to the PICO confirmation ratified by PASC, would be current practice, which is germline *BRCA* testing for those eligible under MBS item 73296 and second-line germline *BRCA* testing for those eligible under MBS item 73295.

The comparator for codependent olaparib maintenance therapy following a response to first-line platinum-based chemotherapy is watch and wait for both scenarios. If *gBRCAm* patients relapse they would receive second-line platinum-based chemotherapy followed by olaparib maintenance therapy in those who responded to treatment. In patients without a *gBRCAm*, regardless of *sBRCAm* status, olaparib maintenance therapy is not currently an option.

## 10. Comparative safety

### *Adverse events from testing*

The submission did not discuss the safety of tumour *BRCA* testing. The Commentary outlined two safety issues:

#### Rebiopsy

In Scenario 1, if the germline test fails, a repeat test using the pre-prepared DNA should be sufficient. No additional blood samples should be required, thus no safety issues would be associated with repeat testing.

In Scenario 2, patients with inadequate tissue sample or poor quality DNA may need a rebiopsy to have a tumour *BRCA* test. Although adverse events from a rebiopsy are rare, an alternative to a rebiopsy would be a germline *BRCA* test. The submission suggested germline *BRCA* testing as an alternate test for those patients whose tumour NGS *BRCA* test fails. As this test uses a blood sample there would be negligible adverse events associated with this test. The number of patients with *sBRCAm* who would forgo olaparib maintenance therapy due to retesting using a germline *BRCA* test would be minimal.

#### Psychological harms

There are potential psychological harms associated with tumour NGS *BRCA* testing. Patients who have a tumour with a *BRCAm* or variant of unknown significance (*VUS*) could potentially have an increased level of worry and anxiety. They may be concerned about their own risk of developing new cancers, e.g. in the breast, or of family members (especially siblings or their children) being susceptible to cancer.

Thus, it may be important that these (*BRCAm* and possibly *VUS*) patients be referred to a family cancer clinic or genetic counsellor for further evaluation and/or germline *BRCA* testing and, if positive, appropriate cascade testing of family members, as presented in the proposed clinical management algorithm.

### *Adverse events from changes in management*

The submission did not present any evidence that diagnosis of a *BRCAM* would lead to a change in management. However, the Commentary stated there was some evidence to suggest that patients with *BRCAM* will have a greater response to olaparib maintenance therapy than those with *BRCA* wildtype (*BRCAwT*).

The Commentary stated that the safety data presented for Study 19 suggests that the side effects from taking olaparib would not differ between patients with and without a *BRCAM* (somatic or germline).

Thus, the Commentary stated that false positive patients would experience the same level of side effects as true positive patients, but may receive a reduced benefit from olaparib. This may be acceptable, as false positive patients are not forgoing any potentially beneficial treatment while receiving olaparib maintenance therapy.

The Commentary stated that false negative patients would forgo olaparib maintenance therapy for “watch and wait”. They would be monitored to detect disease progression. These patients may progress quicker than true positive patients receiving olaparib, but are still more likely to respond to second-line platinum-based chemotherapy than true negative patients.

The Commentary stated that the effects on overall survival (OS) for both false positive and false negative patients are yet to be determined. The immature data from SOLO1 does not show an OS benefit for any *BRCAM* patients receiving olaparib compared with those receiving placebo.

However, the Commentary stated it should be noted that there are likely to be few false positive or false negative patients as Sanger sequencing and NGS are generally accepted as highly accurate “gold standard” tests.

## **11. Comparative effectiveness**

The submission presented a linked evidence approach, with supporting evidence as summarised in Table 3.

**Table 3 Summary of the linked evidence approach**

	Type of evidence supplied	Extent of evidence supplied
Accuracy and performance of the test (analytical validity)	Level III-2 diagnostic accuracy evidence: a comparison with reference standard that does not meet the criteria required for level II (blinded reference standard among consecutive patients) or level III-1 (blinded reference standard among non-consecutive patients)	<input checked="" type="checkbox"/> k=11, n=2,151
Prognostic evidence	Level I prognostic evidence: SR of level II evidence Level II prospective cohort study	<input checked="" type="checkbox"/> k=1 SR, n=18,396 <input checked="" type="checkbox"/> k=2 cohort, n=702
Clinical utility of the test		
Predictive effect (treatment effect variation)	Four randomised, controlled trials comparing PARP inhibitor maintenance therapy to placebo in the second-line setting	<input checked="" type="checkbox"/> k=4, n=1,138
Change in management	Evidence to show that biomarker determination guides decisions about treatment with the medicine	<input type="checkbox"/> k=0, n=0
Treatment effect (enriched)	Single randomised controlled trial of olaparib vs placebo in patients that are test positive in both arms	<input checked="" type="checkbox"/> k=1, n=391

SR = systematic review

k=number of studies, n=number of patients.

Source: Constructed during evaluation.

### Prognostic evidence

The submission included a recent systematic review and meta-analysis by Xu et al. (2017) that determined the effect of *BRCAm* on the survival outcomes of women with ovarian cancer in 18,396 patients and a cohort study from The Cancer Genome Atlas (TCGA) that analysed the progression-free survival (PFS) and OS outcomes of 467 patients within the ovarian cancer (Lai et al. 2019). This study included a subgroup analysis of patients with *gBRCAm* compared with *sBRCAm*. The Commentary concluded from these data that women with ovarian cancer and a *BRCAm*, regardless whether it is somatic or germline in origin, have a better prognosis, with longer PFS and OS after surgery and platinum-based chemotherapy, compared to women who have ovarian cancers with *BRCAt*.

### Predictive evidence

There was no direct predictive evidence available in the first-line setting.

### Response to olaparib maintenance therapy compared with placebo in the second-line setting

#### *HGSOC patients with sBRCAm versus those with gBRCAm*

The outcomes from the four studies that reported on the PFS (and OS) for patients receiving olaparib maintenance therapy compared to placebo in patients with either a germline or a somatic *BRCAm* are summarised in Table 4.

**Table 4 Summary of the included evidence**

Trial	N	Design	Patient population	Outcomes: <i>sBRCAm</i> HR (95% CI)	Outcomes: <i>gBRCAm</i> HR (95% CI)
Study 19	113 20 <i>sBRCAm</i>	R, DB, MC	Patients with platinum-sensitive HGSOC	<b>PFS:</b> 0.23 (0.04, 1.12) <b>OS:</b> 0.15 (0.02, 0.88)	<b>PFS:</b> 0.17 (0.09, 0.34) <b>OS:</b> 0.62 (0.34, 1.12)
SOLO2	286 <i>gBRCAm</i>	R, DB, MC	Patients with platinum-sensitive HGEOC	-	<b>PFS:</b> 0.33 (0.24, 0.44)
NOVA	553 47 <i>sBRCAm</i>	R, DB, MC	Patients with platinum-sensitive HGEOC	<b>PFS:</b> 0.27 (0.08, 0.90)	<b>PFS:</b> 0.27 (0.17, 0.41)
ARIEL3	186 56 <i>sBRCAm</i>	R, DB, MC	Patients with platinum-sensitive HGEOC	<b>PFS:</b> 0.23 (0.10, 0.54)	<b>PFS:</b> 0.25 (0.16, 0.39)
Meta-analysis	1,138 123 <i>sBRCAm</i>	Included Study 19, NOVA, ARIEL3, SOLO2		<b>PFS:</b> 0.24 (0.13, 0.46)	<b>PFS:</b> 0.27 (0.09, 0.33)

*BRCA* = breast cancer gene 1 and 2; DB=double blind; *gBRCAm* = germline *BRCA* pathological or likely pathological variant; CI = confidence interval; HGEOC = high grade epithelial ovarian cancer; HGSOC = high grade serous ovarian cancer; HR = hazard ratio; MC = multicentre; OS = overall survival; PFS = progression-free survival; R = randomised; *sBRCAm* = somatic *BRCA* pathological or likely pathological variant; **bold** = statistically significant

Source: Table 2-28, Figures 2-25 and 2-26 in section 2.2.D.11.3 of the submission.

#### *HGSOC patients with BRCAm versus those with BRCAt*

The Commentary noted that, of the studies reporting on response to olaparib maintenance therapy in *sBRCAm* compared to *gBRCAm*, two also reported on the response in *BRCAm* compared with *BRCAt* (Table 5).

**Table 5 Summary of the included evidence**

Trial	N	Design/ duration	Patient population	Outcomes: <i>BRCAm</i> HR (95% CI)	Outcomes: <i>BRCawt</i> HR (95% CI)
Study 19	265	R, DB, MC	Patients with platinum-sensitive HGSOC	<b>PFS:</b> 0.18 (0.10, 0.31) <b>OS:</b> 0.62 (0.41, 0.94)	<b>PFS:</b> 0.54 (0.34, 0.85) <b>OS:</b> 0.83 (0.55, 1.24)
NOVA	553	R, DB, MC	Patients with platinum-sensitive HGEOC	<b>PFS:</b> 0.27 (0.17, 0.41)	<b>PFS:</b> 0.58 (0.36, 0.92)

*BRCA* = breast cancer gene 1 and 2; *BRCAm* = *BRCA* pathological or likely pathological variant; *BRCawt* = *BRCA* wild type; CI = confidence interval; DB=double blind; HR = hazard ratio; MC = multicentre; OS=overall survival; PFS=progression-free survival; R=randomised  
Source: Constructed during the evaluation.

### Comparative analytical performance

The Commentary presented the results of concordance of tumour NGS *BRCA* testing with germline *BRCA* testing in Table 6.

**Table 6 Concordance of tumour NGS *BRCA* testing with germline *BRCA* testing**

Study	Concordance tumour vs germline <i>BRCA</i> testing	Concordance of g <i>BRCA</i> results only for tumour vs germline testing
	<b>Tumour NGS vs germline NGS</b>	
Chao et al 2016	7/12 (58.3%) positive concordance	7/7 (100%) positive concordance
de Jonge et al 2018	49/54 (90.7%) overall concordance 6/11 (54.5%) positive concordance 43/48 (89.6%) negative concordance	49/49 (100%) overall concordance 6/6 (100%) positive concordance 43/43 (100%) negative concordance
Enyedi et al 2016	9/10 (90%) overall concordance 3/4 (75%) positive concordance 6/7 (85.7%) negative concordance	9/9 (100%) overall concordance 3/3 (100%) positive concordance 6/6 (100%) negative concordance
Mafficini et al 2016	10/13 (76.9%) positive concordance	10/10 (100%) positive concordance
Pennington et al 2014	286/306 (93.5%) overall concordance 63/83 (75.9%) positive concordance 223/243 (91.8%) negative concordance	286/286 (100%) overall concordance 63/63 (100%) positive concordance 223/223 (100%) negative concordance
Zhao et al 2017	48/50 (96%) overall concordance 12/14 (85.7%) positive concordance 36/38 (94.7%) negative concordance	48/48 (100%) overall concordance 12/12 (100%) positive concordance 36/36 (100%) negative concordance
	<b>Tumour NGS vs germline Sanger sequencing</b>	
Koczkowska et al 2016	18/22 (81.8%) positive concordance	18/18 (100%) positive concordance
	<b>Tumour NGS vs germline Myriad</b>	
AstraZeneca 2018	323/341 (94.7%) positive concordance	323/323 (100%) positive concordance
Dougherty et al 2017	137/154 (89.0%) overall concordance 71/74 (95.9%) positive concordance 66/80 (82.5%) negative concordance	71/74 (95.9%) positive concordance 3 discordant results due to large insertions or deletions not detectable by the NGS used nor by Sanger sequencing
	<b>Tumour Myriad vs germline Myriad</b>	
Hennessy et al 2010	17/28 (60.7%) positive concordance	-

*BRCA* = breast cancer gene 1 and 2; EOC = epithelial ovarian, fallopian tube or primary peritoneal cancer; HGSOE = high-grade serous ovarian, fallopian tube or primary peritoneal cancer; NGS = next generation sequencing; SOC = serous ovarian, fallopian tube or primary peritoneal cancer

Source: Constructed during the evaluation.

### Prevalence

As NGS is a highly accurate methodology, the diagnostic yield of the tumour NGS *BRCA* test is likely to be equivalent to the prevalence of germline plus somatic variants in HGSOE. A somatic *BRCAm* was identified in 20.4–27.7% of patients with HGSOE in four included accuracy studies.

### *Change in management in practice*

The submission provided no direct evidence to determine whether the tumour *BRCA* test results guides changes in treatment decisions in the clinical setting.

However, given that olaparib is a new treatment in the first-line setting, and germline *BRCA* testing is already available, clinicians are very likely to use the test result to guide the use of olaparib maintenance therapy after response to first-line platinum-based chemotherapy as there are no other treatments available.

### *Clinical utility of the test in the second-line setting*

The Commentary stated that there is currently no evidence for the effectiveness of olaparib in the first-line setting in an unselected or *BRCAwt* population. However, as noted above, the predictive evidence for second-line treatment indicates that olaparib may confer some benefit (at least in terms of PFS) in *BRCAwt* patients in the second-line setting compared with no treatment. There is still a treatment effect variation associated with *BRCAm* in the second-line setting. However, the test may not be necessary as patients who respond to platinum-based chemotherapy, an eligibility criterion for second-line treatment, appear likely to respond to olaparib. Regulatory agencies have removed reference to *BRCAm* in the indication for second-line olaparib in HGEOC, and the National Comprehensive Cancer Network (NCCN) Ovarian Guidelines (2019) only require that patients are in response to platinum-based chemotherapy.

### *Clinical effectiveness*

The clinical effectiveness evidence was provided by the SOLO1 randomised trial. SOLO1 enrolled patients with *gBRCAm* advanced HGEOC who responded to first-line platinum-based chemotherapy (only two patients had *sBRCAm*). These patients were randomised to receive either olaparib maintenance therapy or placebo for a period of 2 years or until progression.

### **Clinical claim**

The overall clinical claim provided in the submission is that olaparib maintenance treatment following response to platinum-based chemotherapy in a patient with *BRCAm* (germline or somatic) is superior in terms of efficacy, with a manageable safety and tolerability profile compared to placebo.

## **12. Economic evaluation**

The submission presented cost-effectiveness and cost-utility analyses, measuring outcomes in terms of life-years gained and quality-adjusted life years (QALYs) gained, respectively, consistent with the submission's clinical claim of superior effectiveness and manageable (but inferior) safety. The economic evaluation involved a decision tree for the testing phase followed by partitioned survival analysis for the treatment phase. Outcomes were modelled for time horizon of 25 years (versus the 41 months median follow-up in the SOLO1 trial), and utility weights from SOLO1 and Havrilesky et al (2009) were applied. The results from the two testing scenarios are provided in Table 7, which includes the Commentary's re-specified model values.

**Table 7 ICERs and considerations of various BRCA testing and olaparib funding scenarios (from the Commentary)**

	<b>Proposed PBAC funded first-line maintenance olaparib</b>
No MSAC funded test	Not modelled and inadequate clinical evidence available to estimate
MSAC funded test: Restricted to germline mutation testing only	Submission estimated ICER: \$redacted/QALY (or \$redacted/LY) <i>Evaluation re-specified model: \$redacted/QALY (or \$redacted/LY)</i>
MSAC funded test: Proposed tumour testing (identifying germline and somatic mutations)	Submission estimated ICER: \$redacted/QALY (or \$redacted/LY) <i>Evaluation re-specified model: \$redacted/QALY (or \$redacted/LY)</i>

<sup>a</sup> Base-case was respecified during the evaluation by adjusting OS curves in patients with a *BRCAm* to be the same across both olaparib and placebo arms after 41 months, utility values for PFS2 and PD sourced from Study 19, corrected modelled cost of olaparib, including downstream germline testing costs in the tumour positives and prevalence of *gBRCAm* as 20.3%

*BRCAm* = *BRCA1* or *BRAC2* mutation; ICER= incremental cost-effectiveness ratio; LY = life year; MSAC = Medical Services Advisory Committee; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = progressive disease; PFS2 = progression-free survival after the first progression; QALY = quality-adjusted life year

Source: Constructed during the evaluation based on results presented in Section 3A.8 of the submission.

There was considerable uncertainty regarding the submission-estimated ICERs due to:

- There being no unadjusted OS benefit demonstrated from the SOLO1 trial. A substantial survival gain is generated in the modelled economic evaluation.
- The use of (predominantly extrapolated) PFS2 SOLO1 as a direct predictor of OS by applying Australian Ovarian Cancer Study Registry mortality data to modelled PFS2 curves to model long term OS rather than extrapolate from the OS results of the trial. This generated significantly different OS curves. However, no clinical evidence was provided to support translation of the second progression to OS and so the divergent modelled OS curves were not supported by the clinical trial results and were highly favourable to the intervention.
- The use of selected utility values from the literature for PFS2 and PD, which are low relative to PFS1 and which favours the intervention
- Under-estimating the cost of testing per patient.

The Commentary’s re-specified base cases accounted for the above issues. ESC considered that these should be considered the preferred base cases.

#### *ICERs by germline and somatic subgroups*

The germline *BRCAm* subgroup respecified model predicted a very high ICER (\$redacted/QALY), suggesting a relatively small incremental benefit associated with moving from second- to first-line testing. The somatic *BRCA* subgroup respecified base case (\$redacted/QALY) was driven by benefit gained through access to treatment; however, this model was based on indirect evidence.

#### *Pre-MSAC response*

The applicant presented results for the revised base case model in which utilities are taken from the NICE review (PFS2: 0.63; PD: 0.34), and the prevalence of *gBRCAm* is 20.3% (Table 8).

**Table 8 Applicant's revised base-case**

	Proposed scenario 1 (available to first-line gBRCAm patients only)			Proposed scenario 2 (available to all first-line BRCAm patients (g+s))		
	Proposed scenario	Current scenario	Incremental	Proposed scenario	Current scenario	Incremental
Discounted costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Discounted QALYs	redacted	redacted	redacted	redacted	redacted	redacted
ICER	\$redacted			\$redacted		

BRCA = breast cancer gene 1 and 2; gBRCAm = germline BRCA pathological or likely pathological variant; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; sBRCAm = somatic BRCA pathological or likely pathological variant

Source: Calculated for the pre-MSAC response

### 13. Financial/budgetary impacts

The predicted use and cost to the Commonwealth of extended BRCA testing under requested Scenario 2, and associated with the listing of olaparib on the PBS for the first-line maintenance treatment of a patient newly diagnosed with advanced HGEOC, was estimated using an epidemiological approach over six full calendar years from 2021 (Year 1) to 2026 (Year 6) [Table 9; as presented in the Commentary]. The submission's financial estimates were uncertain as: they under-estimated the gBRCA tests displaced; did not include subsequent gBRCA testing (for familial testing) required following a positive tumour BRCA test result; and calculated cost to MBS using 100% MBS item fee rather than applying 85% or 75% MBS rebate or combination of both. The Commentary noted that the methodology used in the financial model was particularly complex (e.g. different approaches to costs vs. cost offsets) making it difficult to amend the financial model to incorporate alternative data or assumptions.

**Table 9 The estimated financial implications to the MBS of tumour BRCA testing**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use and financial implications of tumour BRCA testing</b>						
Number of patients tested with tumour BRCA test	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients tested with germline BRCA test <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the MBS less copayments	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
<b>Estimated reduction in the extent of the use and financial implications of germline BRCA testing</b>						
Number of patients no longer receiving germline testing	redacted	redacted	redacted	redacted	redacted	redacted
Saving to MBS less copayments <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
<b>Net financial implications</b>						
Net cost to MBS	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

<sup>a</sup>MBS item 73296 (>10% risk) or 73295 (proposed to be amended to permit use for first-line olaparib).

<sup>b</sup>Re-calculated during the evaluation to account for a higher proportion of patients receiving a germline test at baseline.

Source: Table 4-28 and Table 4.29, p334 of the submission.

## 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Discerning the evidentiary standard for sBRCA testing <sup>a</sup>	This remained uncertain, as the submission provided limited information on the evidentiary standard (defined as the detailed description of the test(s) as performed in the study/ies provided as evidence to the support the claim of clinical utility or predictive value) for somatic BRCA testing.
Evidence for analytical validity of sBRCA testing using tumour samples <sup>a</sup>	The diagnostic performance of somatic BRCA testing was established to have high sensitivity and specificity taken from indirect evidence. However, ESC was concerned with missing data from 55/253 samples in Dougherty et al. 2017 (Study 19) which informed the concordance of tumour next generation sequencing (NGS) vs. germline Sanger sequencing.
Evidence of clinical utility in patients with only a somatic mutation <sup>a</sup>	This remained uncertain, as it was unclear if patients with sBRCAm in the absence of gBRCAm were included in the meta-analysis of several PARP inhibitors in the second-line setting. In addition, ESC noted that the key comparative trial (SOLO1) for PBAC consideration in the requested maintenance setting identified only two patients from this subgroup.
MBS items and descriptors	The wording of item descriptor for MBS item 73296 needs clarification regarding coverage of fallopian tube/primary peritoneal cancer. The tumour BRCA testing fee could be revisited due to the overlap with MBS item 72860. The descriptors should include clear definitions of test scope (eg somatic testing should specify sequence and copy number variants, subsequent germline confirmatory testing as needed should be targeted, and the germline sample should be tested in parallel with the original somatic sample to reduce false negatives). The 'once per lifetime' restriction for somatic testing may be inappropriate.
Somatic variants of unknown significance (VUSs)	ESC suggested that these not be eligible for confirmatory germline testing unless they are formally reclassified by the testing laboratory as 'likely pathogenic' or 'pathogenic'.
In-house-developed tumour BRCA tests	The test from one pathology laboratory is already included on the Australian Register of Therapeutic Goods, with tests from three others under consideration by the TGA. Evidence for the analytical sensitivity and specificity of somatic BRCA testing has strengthened since the last submission.
Codependence – test versus no test	Codependence is unclear. ESC noted (uncertain) evidence of effectiveness of olaparib in BRCA wildtype (wt) patients in the second-line setting; however, any broadening of population would reduce incremental effectiveness and increase the ICER (at a given price).
Should Scenario 1 (germline only) or 2 (germline + somatic) be considered?	This also depends on the recommended PBS listing. Scenario 2 would have wider coverage. However, the ICERs were noted to be high and uncertain: <ul style="list-style-type: none"> <li>• Scenario 1, Commentary's respecified ICER: \$redacted /QALY</li> <li>• Scenario 2, Commentary's respecified ICER: \$redacted /QALY.</li> <li>• Further sensitivity analysis post PBAC ESC reducing the time horizon from 25 to 10 years further increased the ICER to \$redacted /QALY in the respecified base case for scenario 2.</li> <li>• Use Commentary's respecified base case as the new base case</li> </ul>
Unjustified modelled separation of OS curves	The overall survival (OS) results are immature for the requested use of olaparib as first-line maintenance therapy and more mature data are required to establish any OS gain. Progression-free survival (PFS) results are mature, although the PFS results are not as clinically relevant.
Subgroup somatic only versus germline only	The ICER for somatic only (\$redacted) is much lower than the ICER for germline only (\$redacted), but: <ul style="list-style-type: none"> <li>• the ICERs are uncertain</li> <li>• the subgroups need further analysis.</li> </ul>
Uncertain financial estimates	The submission underestimated gBRCA tests displaced (due to reduced second-line testing); did not account for gBRCA testing (for familial testing) subsequent to a positive sBRCA test result; and calculated estimates using MBS fee rather than MBS rebate. In addition, ESC noted the complex methodology used in the financial model (e.g. different approaches to costs vs. cost offsets) and considered that any future resubmission should involve a simplified financial analysis.

## ESC discussion

ESC noted the two scenarios under consideration. ESC noted that Scenario 2, which covers both somatic (tumour) and germline *BRCA* mutations, would depend on MSAC's acceptance of the basis provided to reverse its previous advice. ESC noted that somatic *BRCA* testing has implications for patients and possibly their relatives since they would then need to have germline *BRCA* testing (which was not accounted for in the submission).

ESC noted the descriptor for MBS item 73296, which relates to breast and ovarian cancer. ESC confirmed the assumption that 'ovarian' cancer should include fallopian cancer and primary peritoneal cancer, as it is assumed that patients with fallopian and peritoneal cancer would respond the same as for ovarian cancer. ESC recommended changing the item descriptor for MBS item 73296 to reflect these assumptions.

ESC considered that the genetic testing methods required clarification. Currently, proposed MBS item XXXXX states 'requirements relating to *BRCA* status' and does not specify the scope of testing. ESC considered that the type of test, such as including copy number variation testing, should be stipulated in the MBS item descriptor. ESC considered that the Commentary included some misconceptions regarding genetic testing methods – for example, Multiplex Ligation-dependent Probe Amplification (MLPA) cannot detect indels and gene rearrangements.

In addition, the sequence of tests is an issue for Scenario 2. ESC considered that it might be practical to perform somatic testing first, as this would detect all mutations and provide access to the drug, then germline and cascade testing could be performed as necessary. If this is the case, then the wording of the somatic testing item would need to be as prescriptive as the existing germline items as to the scope of testing (ie sequencing and copy number variation) as this may be the only *BRCA1* and *BRCA2* test that the patient may have. ESC also considered that the downstream germline test to confirm a somatic variant should be targeted and involve testing the original somatic sample in parallel, as is best practice for predictive testing, to avoid the potential for false negative results.

ESC considered that the restriction of 'once per lifetime testing' for somatic testing was unnecessary. Although the requirement for additional testing would be rare, it may be inappropriate to restrict the test on once per lifetime. 'Once per primary malignancy' might be more appropriate.

ESC also considered that the cost for this tumour test (**\$redacted**) may be too high, as this likely includes costs for sample retrieval, but there is a separate MBS item (72860) for sample retrieval that can be claimed if the retrieving and testing laboratories are different.

ESC noted the immature overall survival (OS) results from SOLO1. Although the progression-free survival (PFS) results look promising, ESC queried the clinical acceptability of extrapolating from these PFS results; the PFS gain was only associated with a grade of 3 out of 5 on the European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale version 1.

ESC also noted the lack of data for *BRCA* testing compared with no testing. SOLO1 did not include *BRCAwt* patients, so the olaparib treatment effect variation by *BRCA* status cannot be determined from this trial. Thus, ESC raised concerns regarding the codependency claim in this application based on SOLO1, an important point that the applicant has not addressed.

Previously, MSAC queried the reliability of somatic *BRCA* testing (Application 1380), but somatic *BRCA* testing is now shown to have high analytical sensitivity and specificity, from indirect evidence. However, ESC was concerned with missing data from 55/253 samples (the causes of failure are described for only 44 samples) in Dougherty et al. 2017 (Study 19) which informed the concordance of tumour NGS vs. germline Sanger sequencing and was the basis of MSAC's previous consideration of somatic *BRCA* testing. In addition, ESC considered that there remained uncertainty associated with the identification of the evidentiary standard<sup>1</sup> for somatic *BRCA* testing as the submission provided limited information on this.

ESC also noted that the evidence to support the clinical utility of the tumour *BRCA* test was based on a meta-analysis of several PARP inhibitors in the second-line setting, suggesting similar effectiveness in those with somatic *BRCA* mutation (*sBRCAm*) and germline *BRCA* mutation (*gBRCAm*). However, it was unclear if the patients identified with a *sBRCAm* in the absence of a *gBRCAm*. Therefore, ESC considered there remained insufficient evidence of clinical utility in patients with only a somatic *BRCA* mutation. In addition, ESC noted that the key comparative trial (SOLO1) for PBAC consideration in the requested maintenance setting identified only 2 patients from this subgroup (those with *sBRCAm* in the absence of *gBRCAm*).

ESC noted the Commentary re-specified the base case by adjusting the OS curves in *BRCAm* positives to be the same across both olaparib and placebo arms after 41 months, utility values for progression-free survival after the first progression (PFS2) and progressive disease (PD) sourced from Study 19, corrected modelled cost of olaparib, including downstream germline testing costs in the tumour positives and prevalence of *gBRCAm* as 20.3%. This increased the incremental cost-effectiveness ratio's (ICERs) to \$redacted /quality-adjusted life year (QALY) for Scenario 1 and \$redacted /QALY for Scenario 2. ESC advised that the Commentary base case should be preferred over the submission base case. ESC noted further sensitivity analysis post PBAC ESC reducing the time horizon from 25 to 10 years further increased the ICER to \$redacted /QALY for Scenario 2.

ESC considered that the ICERs were high and remained uncertain even with the Commentary re-specifications. Scenario 1 has more evidence but higher ICERs; the ICERs for Scenario 2 are lower but are based on less evidence.

ESC considered that the financial estimates were uncertain, due to underestimated *gBRCA* tests displaced (due to reduced second-line testing); did not account for *gBRCA* testing (for familial testing) subsequent to a positive *sBRCA* test result; and calculated estimates using MBS fees rather than MBS rebates. In addition, ESC noted the complex methodology used in the financial model (e.g. different approaches used for costs and cost off-sets) and considered that any future resubmission should involve a simplified financial analysis.

ESC noted that the TGA has changed the indication for olaparib for patients with ovarian cancer which has relapsed, so that access to olaparib does not depend on *BRCA* status after second-line platinum chemotherapy. This affects the 'watch and wait' group, as these patients could gain access to olaparib beyond the PBS without genetic testing; thus, the potential benefits would likely reduce and the ICERs would likely increase.

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<sup>1</sup> Defined as the detailed description of the test(s) as performed in the study/ies provided as evidence to the support the claim of clinical utility or predictive value.

ESC noted the variants of unknown significance (VUSs) that could be identified in tumour testing in Scenario 2 should not be eligible for confirmatory germline testing unless formally reclassified by the testing laboratory as ‘likely pathogenic’ or ‘pathogenic’.

ESC noted that, since lodgement of the submission, one pathology laboratory has now received TGA approval for its in-house-developed tumour *BRCA* test, and considered that access to the testing should not be of concern if supported by MSAC.

ESC noted that consultation feedback was limited but supportive. One organisation noted that the testing is complex and should only be performed by laboratories with demonstrated experience of germline and somatic testing.

#### **15. Other significant factors**

Nil.

#### **16. Applicant’s 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](#)