



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1380 – BRCA mutation testing to determine eligibility for olaparib maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer

Applicant: AstraZeneca Pty Ltd

Date of MSAC consideration: MSAC 68th Meeting, 24-25 November 2016
MSAC 66th Meeting, 30-31 March 2016

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

The integrated co-dependent application requested:

- Medicare Benefits Schedule (MBS) listing for *BRCA* mutation (*BRCAM*) testing as a co-dependent medical service that is performed to inform the eligibility for maintenance treatment with olaparib in women with *BRCAM* platinum-sensitive relapsed high grade serous ovarian or fallopian tube or primary peritoneal cancer (hereafter named platinum-sensitive relapsed ovarian cancer). 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. Patients are only eligible for treatment with olaparib if they have a confirmed *BRCAM*; and
- Pharmaceutical Benefits Scheme (PBS) Authority required listing of olaparib for the maintenance treatment of women with *BRCAM* platinum-sensitive relapsed ovarian cancer, who are in response (complete or partial) to their most recent platinum-based chemotherapy regimen (e.g. carboplatin or cisplatin).

2. MSAC's advice to the Minister – November 2016 consideration

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.

Summary of consideration and rationale of MSAC's advice - November 2016 consideration

MSAC had previously deferred a decision to list *BRCA* mutation testing on the MBS at its March 2016 meeting. *BRCA* mutation testing identifies a subgroup of patients who will obtain the most benefit from the medicine, olaparib, for the treatment of platinum-sensitive relapsed high grade serous ovarian, fallopian and primary peritoneal cancer. At its March 2016 meeting, MSAC noted that the March 2016 PBAC meeting had deferred its decision on whether olaparib would be listed in the PBS. However, MSAC foreshadowed that, if the PBAC subsequently recommended olaparib for listing in the PBS, it would support the MBS funding of germline *BRCA* mutation testing to determine eligibility for olaparib treatment for women with platinum-sensitive relapsed ovarian cancer.

The applicant acknowledged MSAC's recommendation to limit the test for detection of a germline *BRCA* mutation in selected women with relapsed ovarian cancer with continued sensitivity to platinum-based chemotherapy, and agreed not to request testing for somatic *BRCA* mutations.

Following advice from the PBAC in November 2016 that it had recommended to the Minister that olaparib be listed in the PBS, MSAC confirmed its support for MBS funding of germline *BRCA* mutation testing to determine eligibility for olaparib. MSAC reaffirmed that germline *BRCA* mutation testing identifies a subgroup of women who are most likely to benefit from treatment with olaparib. MSAC noted that the test should only be performed once per lifetime for this purpose. MSAC also reiterated that that pre-test genetic counselling was unnecessary, but that any patient testing positive for a germline *BRCA* mutation should be referred to post-test genetic counselling.

MSAC proposed the following the item descriptor and explanatory note:

Detection of germline BRCA1 or BRCA2 gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Explanatory note:

Patients who are found to have a BRCA1 or BRCA2 mutation should be referred for post-test genetic counselling, as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral.

MSAC's advice to the Minister – March 2016 consideration

After considering the available evidence in relation to safety, clinical effectiveness and cost-effectiveness, MSAC deferred the application for the requested MBS item until such time as the PBAC makes a positive recommendation regarding the corresponding PBS listing of olaparib. MSAC advised that, if PBAC subsequently decides to recommend to the Minister that olaparib be listed on the PBS, then MSAC would support an expedited process of reconsideration. This process would be undertaken to ensure MSAC support for public funding of *BRCA* testing is aligned with the circumstances recommended by PBAC.

MSAC foreshadowed its support to limit the test for detection of a germline *BRCA* mutation in selected women with relapsed ovarian cancer with continued sensitivity to platinum-based chemotherapy. MSAC indicated that, should a heritable *BRCA* mutation be identified, the patient should be referred for post-test genetic counselling, but that pre-test genetic counselling would not be required in order to claim the relevant item/s on the MBS.

Summary of consideration and rationale for MSAC's advice – March 2016 consideration

MSAC noted that the application to list *BRCA* testing in the MBS was part of an integrated co-dependent submission, which also requested that PBAC consider listing olaparib in the PBS for maintenance therapy in women with platinum-sensitive relapsed high grade serous ovarian, fallopian and primary peritoneal cancer (hereafter platinum-sensitive relapsed ovarian cancer). MSAC noted that the PBAC had deferred its decision at the March 2016 meeting about whether olaparib would be listed in the PBS. MSAC also noted that the PBAC had foreshadowed that any recommendation to list would limit PBS-subsidised access to olaparib to patients who have a germline *BRCA* mutation (Class 4 or 5 mutation only [Plon, S. E. *et al.* Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum. Mutat.* **29**, 1282–91 (2008)]).

MSAC considered the application's claim that *BRCA* mutation testing identifies the subgroup of women who will obtain the most benefit from treatment with olaparib. This claim of clinical utility was considered to be biologically plausible, because the *BRCA1* and *BRCA2* mutations (hereafter *BRCAM*) can be used as a surrogate for identifying tumour cells without a functional homologous recombination repair pathway, a mechanism through which cells repair double stranded breaks in DNA. Treatment with olaparib inhibits the function of a complementary DNA repair system, the base excision repair pathway in which PARP enzymes repair single stranded breaks in DNA. As olaparib inhibits PARP enzyme function, *BRCAM* tumour cells treated with olaparib will be unable to repair DNA using either the homologous recombination repair pathway or the base excision repair pathway, thereby compounding DNA damage and leading to cell death.

MSAC noted that the evidence to support this clinical utility of testing for *BRCAM* in women with platinum-sensitive relapsed ovarian cancer relied upon a single study, Study 19. In this randomised controlled trial, 265 relapsed ovarian cancer women who had partially or completely responded to the preceding platinum-containing chemotherapy regimen were randomised to olaparib or placebo. *BRCA* status was not established prior to enrolment in the trial, but was collected from case report forms after local germline testing or determined retrospectively via analysis of blood (germline testing) or tumour (somatic testing) samples collected at baseline. *BRCAM* status was determined for 254 (96%) of these patients and 136 (54%) had a mutation.

A subgroup analysis of Study 19 after a median of 37 months follow-up separated the results of the women with a *BRCAM* from the women without a detected *BRCAM*. MSAC noted that among the women with a *BRCAM* (n = 136), there was a significant improvement in progression free survival (PFS) between those using olaparib and those using placebo, 11.2 months vs 4.3 months (HR 0.18, 95% CI 0.10 to 0.31).

A statistical interaction test performed for *BRCA* status by treatment group was statistically significant (p=0.03) suggesting that having a *BRCAM* is predictive of a better PFS response to olaparib. When analysed within each treatment group, the women who took olaparib and had a *BRCAM* had a median PFS of 11.2 months vs. 7.4 months in those women taking olaparib

who did not have a *BRCAM*. Among the placebo group, women with a *BRCAM* had a median PFS of 4.3 months vs 5.5 months in women without a *BRCAM*.

MSAC noted that there was also a smaller, but statistically significant, improvement in PFS among women (n = 118) in whom a *BRCAM* was not detected and who took olaparib versus those taking placebo (median PFS of 7.4 months vs. 5.5 months, respectively [HR 0.54, 95% CI 0.34 to 0.85]).

After a median of 37 months follow-up, an interim analysis of overall survival found no significant difference between women with a *BRCAM* who were taking olaparib compared with those with a *BRCAM* who were taking placebo (HR 0.73, 95% CI 0.45 to 1.17). However, once patients stopped taking study medicines, investigators were able to administer olaparib (or another investigational PARP inhibitor) to any study participant, regardless of whether they were originally in the placebo or olaparib study arm. As a result, 23% of the placebo group were prescribed olaparib post-study, and this may have contaminated the overall survival results. A post-hoc analysis which excluded trial sites that allowed crossover treatment reported a significant improvement in overall survival among women with a *BRCAM* who were using olaparib compared with women with a *BRCAM* using placebo (HR 0.52, 95% CI 0.28 to 0.97). MSAC noted that no statistical interaction test was presented for *BRCA* status by treatment group for overall survival, but that unpublished longer follow-up results for the *BRCAM* subgroup were supportive of an olaparib effect on overall survival.

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 co-dependence with olaparib and thus clinical utility. MSAC noted that the claim of co-dependence 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.

Both germline and somatic testing were used to establish *BRCA* status in Study 19. To establish the diagnostic accuracy of *BRCA* testing, the submission identified 11 published diagnostic accuracy studies. All involved germline testing which correctly identified 100% of individuals with a *BRCAM* (true positives) and 95.9% to 100% of individuals who did not have a *BRCAM* (true negatives). None of the 11 studies used DNA extracted from tumour samples to determine *BRCA* status.

MSAC did not identify any significant safety issues around *BRCA* testing. While MSAC recommended that the patients in whom a heritable *BRCA* mutation was identified be referred for post-test genetic counselling, pre-test genetic counselling was not considered to be mandatory as *BRCA* testing was being used for diagnostic purposes and would be arranged by a specialist for the benefit of the individual patient. MSAC noted that identification of a *BRCAM* has implications for a patient's family, but considered that this consequence of testing was outside the scope of the application.

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.

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.

MSAC considered it was appropriate to perform germline *BRCA* testing once a woman had subsequently responded to platinum-based chemotherapy following an initial relapse. It was considered that testing at relapse before subsequent platinum sensitivity was known would result in unnecessary testing. This is because some relapsed patients would not meet the eligibility criteria for treatment with olaparib because their tumour was platinum resistant.

MSAC noted that there are ongoing studies into the use of olaparib in women with *BRCAm* platinum-sensitive relapsed ovarian cancer that should provide further relevant information once they are concluded.

The economic model was driven by treatment with olaparib rather than *BRCA* testing. Sensitivity analyses which varied the prevalence of *BRCAm* within the patient population, or varied the sensitivity and specificity of *BRCA* testing, had little impact upon cost-effectiveness. Similarly, reducing the number of *BRCA* tests carried out by 31%, to account for women who already know their *BRCA* status from previous testing, did not influence cost-effectiveness.

The model presented was consistent with testing at the time of relapse, before response to platinum-based chemotherapy was established. MSAC reiterated its preference for testing to be conducted after response to platinum-based chemotherapy was known. This would be likely result in fewer tests being conducted and as a result, the application could also overestimate costs to the MBS.

Over a five year period, it was estimated that net cost to the MBS for *BRCA* testing would be approximately \$redacted million. The highest MBS costs - around \$redacted million - would be incurred in years one and two falling to approximately \$redacted in year five as the prevalent pool of women with platinum-sensitive relapsed ovarian cancer falls as they access treatment.

MSAC foreshadowed the following item descriptor and notes, noting that this does not include the PBAC requirement for Class4/5 mutation (which would be a matter for the PBS restriction rather than the MBS item descriptor), and there is potential for PBAC to make other recommendations which may affect the associated MBS item descriptor for *BRCA* testing when PBAC further considers olaparib:

Detection of germline BRCA1 or BRCA2 gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme are fulfilled.

Note: The test must be requested by a medical specialist responsible for the patient's care.

Note: The benefit is limited to one test per patient.

Note: Patients who are found to have a BRCA1 or BRCA2 mutation should be referred for post-test genetic counselling, as there may be implications for other family members.

3. Background

There are no current arrangements for public reimbursement for BRCAm testing on the MBS.

4. Prerequisites to implementation of any funding advice

All current providers use in-house developed BRCA testing methods (as opposed to commercial test kits). Laboratories that deal with in-house diagnostic tests, such as the BRCA test, are to provide the TGA with a declaration of conformity (DoC) that the in-house methods comply with essential principles by 30 June 2017. Any commercial test kits for BRCA mutation testing would require a submission to the TGA for listing on the Australian Register of Therapeutic Goods (ARTG).

5. Proposal for public funding

Applicant-proposed MBS listing

Category 6 PATHOLOGY SERVICES
Detection of <i>BRCA1</i> and <i>BRCA2</i> gene mutations, in a patient diagnosed with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme are fulfilled.
Note: Patients who are found to have <i>BRCA1</i> or <i>BRCA2</i> mutation should be referred for post-test genetic counselling, as there may be implications for other family members.
Fee: \$redacted

The submission-based assessment report deviated from the Final Protocol agreed by the Protocol Advisory Sub-Committee (PASC), to include tumour mutation testing in addition to germline testing. Whilst germline BRCA mutation testing is well established, somatic BRCA mutation testing is still undergoing validation.

Testing is done by a variety of methods, but will most likely be by next-generation sequencing and multiplex ligation-dependent probe amplification in the future in order to pick up the wide variety of mutations that affect BRCA1 or BRCA2.

Currently, the wording of the test restriction does not include that one test applies per patient in a lifetime nor whether the test could include germline or tumour line approaches. One test per patient in a lifetime would be appropriate for germline BRCA testing, but not for somatic (tumour) BRCA testing, as patients may develop subsequent tumours with different biomarker/mutation profiles.

6. Summary of public consultation feedback/consumer issues

Consumers considered that the co-dependent pairing of BRCA testing and olaparib addresses a current unmet clinical need. However, consumers expressed concern about equity of access to the laboratories accredited to perform BRCA testing and associated genetic counselling and

about the lack of clarity over the need for tumour *BRCA* testing as well as germline *BRCA* testing.

7. Proposed intervention's place in clinical management

The submission presented evidence that approximately 23% of Australian women newly diagnosed with high-grade serous ovarian, fallopian tube or primary peritoneal cancer are positive for a *BRCA* mutation. Of the women with a *BRCA* mutation, germline mutations might account for 84% and an additional 16% are only identified in the tumour (Study 19). The prevalence of *BRCAM* is greatest among patients who are classified 'platinum-sensitive'; that is, those patients who have responded to platinum-based therapies such as carboplatin. In Study 19, this was estimated at 54% of the randomised participants.

The submission assumed within the proposed clinical management algorithm that germline and tumour *BRCAM* testing would be the same, and that no retesting would be required. However, evidence suggested that there could be discordance between *BRCA* mutation status in the germline and tumour (i.e. 18/111 = 16% of *BRCA* mutations were present only in the tumour i.e. were somatic, not heritable, mutations). This might mean that archived resected tumour material or additional biopsies might occasionally be required to determine eligibility for treatment with olaparib, with associated potential harm associated with such biopsies. Once tumour testing for *BRCAM* is established, a reasonable strategy could be to first test tumour material, thereby identifying both germline and somatic *BRCAM*; in patients with a mutation in the tumour, subsequent testing of blood would be required to identify those with germline mutations as this would have consequences for cascade testing of family members.

The main concern for MSAC was the claim that one next-generation sequencing *BRCAM* test (germline or tumour) would correctly identify all olaparib-eligible platinum-sensitive resistant ovarian cancer patients, given the limited evidence available regarding the performance of tumour testing and the response to olaparib in patients with somatic *BRCAM*.

8. Comparator

The submission nominated 'no *BRCA* testing' as the appropriate main comparator for *BRCAM* testing in this setting. The nomination of the main test comparator was appropriate. However, for patients who have already had a *BRCA* test through familial cancer risk centres, which the submission estimated at 31%, the appropriate comparator would be the '*BRCA* test already performed'.

The submission's approach (Table 1) was to link the:

- prognostic evidence of *BRCAM* in patients with platinum-sensitive relapsed ovarian cancer;
- diagnostic performance (sensitivity and specificity) of next-generation sequencing versus Sanger sequencing for germline *BRCAM* testing in a broad patient population, that allowed for any type of cancer; and
- comparative efficacy of germline and tumour *BRCAM* testing in patients with platinum-sensitive relapsed ovarian cancer in Study 19.

Table 1: Evidence for the test performance

Prognostic evidence	Study 19. Comparison of placebo arms of <i>BRCAm</i> vs. <i>BRCAw</i> t/unknown	☒	k=1	n=107
Test accuracy	Comparison of Sanger vs. NGS (broad patient population, including any type of cancer).	☒	k=11	n=8,410
Test concordance	Comparison of germline vs. tumour (<i>BRCAm</i> , PSR ovarian cancer)	☒	k=1	n=265

Source: compiled during evaluation

BRCAm = *BRCA1* or *BRCA2* mutation; *BRCAw*t = *BRCA* wildtype; NGS = next-generation sequencing; PSR = platinum-sensitive relapsed; k = number of studies; n = number of study participants

9. Comparative safety

The submission did not provide safety information for the diagnostic test. MSAC accepted that there are no safety issues for germline testing.

There was concern for potential harms if additional biopsies for tumour *BRCAm* testing were required to determine eligibility for treatment with olaparib.

10. Comparative effectiveness

Prognostic evidence

Although patients with *BRCAm* who respond to platinum-based chemotherapy generally have a better prognosis than for patients without an identified *BRCAm*, the submission stated that there was no evidence of a prognostic impact associated with *BRCAm* compared with patients who lack *BRCAm*, in the population of patients with platinum-sensitive relapsed ovarian cancer. As such, it presented a comparison of the placebo groups of Study 19, which recruited women with platinum-sensitive relapsed ovarian cancer to demonstrate the prognostic effect associated with biomarker status.

The submission stated that similar findings were observed across placebo patients with or without a *BRCA* mutation for both overall survival and intermediate clinical endpoints. Only limited baseline characteristics were available for those patients in whom there was no *BRCAm* identified or whose *BRCA* status was unknown, and therefore it was difficult to interpret these results.

Comparative analytical performance

Table 2 summarises the diagnostic accuracy of germline *BRCAm* next-generation sequencing versus the reference standard Sanger sequencing.

Table 2: Summary of the diagnostic accuracy of germline *BRCAM* testing (NGS)

Study ID	Sensitivity	Specificity	PPV	NPV	Concordance
Breast/ovarian ca					
Trujilano 2015	100% ^a	99.9% ^b	91.2% ^c	100% ^d	—
Ruiz 2014	100%	99.9%	—	—	—
Breast ca					
D'Argenio 2015	100%	100%	100%	100%	—
Dacheva 2015	100%	95.9%	92.5%	100%	—
Any ca					
Judkins 2015	LL 95% CI: > 99.9%	LL 95% CI: > 99.9%	—	—	100%
Included familial risk					
Castera 2014	100%	98.2%	—	—	—
Chong 2014	100%	99.9%	—	—	—
Feliubadalo 2013	100%	100%	—	—	—
Lincoln 2015	100% ^e	100% ^f	—	—	100%
Strom 2014	—	—	—	—	96.7%
Illumina MiSeq	100%	99.4% to 100%	—	—	Failure: 2.8%
Ion Torrent PGM	100%	96.2% to 96.7%	—	—	Failure: 16.7%
Unclear patient pop					
Costa 2013	100%	97%	—	—	—

Source: Table BT.6, pp144-145; BT.8, p146 of the submission

BRCAM = *BRCA1* or *BRCA2* mutation; CI = confidence interval; LL = lower limit; NGS = next-generation sequencing; NPV = negative predictive value; PPV = positive predictive value; ca = cancer; pop = population

^a (95% CI: 99.7 to 100)

^b (95% CI for *BRCA1m*, 99.9% to 100.0%); (95% CI for *BRCA2m*: 99.9% to 100.0%)

^c (95% CI: 89.7% to 92.6%)

^d (95% CI: 100% to 100%)

^e (95% CI for sequencing: 99.7% to 100.0%); (95% CI for copy number alterations: 91.8% to 100.0%)

^f (95% CI for sequencing: 99.9% to 100.0%); (95% CI for copy number alterations: 99.9% to 100.0%)

The submission concluded that next-generation sequencing germline *BRCAM* testing was:

- 100% sensitive (true positives) and so unlikely to produce a false negative;
- 96% to 100% specific (true negatives) and therefore 0% to 4.1% likely to produce a false positive;
- reproducible with 100% reliability; and
- clinically valid at predicting the *BRCAM* condition (positive predictive value > 91.2%).

This was appropriate; however, these results were limited by the heterogeneity of the study characteristics and in particular the applicability of the broader patient population used. Test reliability (27%) was only recorded for three studies and for the germline *BRCAM* method. The submission provided no evidence for the diagnostic accuracy of tumour *BRCAM* testing methods.

At baseline of Study 19, only 98 patients knew their *BRCAM* status. Therefore, to improve the statistical power:

- retrospective germline *BRCAM* testing was performed using Sanger sequencing (Myriad Genetics); and
- retrospective tumour *BRCAM* testing was performed using next-generation sequencing (Foundation Medicine).

MSAC agreed with the joint ESCs that the approach to *BRCA* testing in Study 19 was inadequately presented, so it was difficult to discern the evidentiary standard used as the basis for the submission's claim of co-dependence with olaparib and thus clinical utility.

In total, *BRCAM* status was collected for 254/265 patients (95.8%). The concordance between germline and tumour *BRCAM* testing in Study 19 is summarised in Table 3.

Table 3: Summary of concordance of germline and tumour *BRCAm* testing

		Tumour <i>BRCAm</i> status (n)				Total
		Mutant	Wild-type	Unknown	Missing	
Germline <i>BRCAm</i> Status (n)	Mutant	71 (27%) ^a	3 (1%) ^a	0	22 (8%) ^a	96 (36%)
	Wild-type	18 (7%) ^a	65 (25%) ^b	4 (2%) ^b	23 (9%) ^b	110 (42%)
	Unknown/VUS	0 (0%)	0 (0%)	4 (2%) ^b	0 (0%)	4 (2%)
	Missing	22 (8%) ^a	18 (7%) ^b	4 (2%) ^b	11 (4%)	55 (21%)
Total		111 (42%)	86 (32%)	12 (5%)	56 (21%)	265 (100%)

Source: Table BT.9, pp148-149 of the submission; and Table 1, p854 of Ledermann (2014)

BRCAm = *BRCA1* or *BRCA2* mutation; VUS = variant of uncertain significance

^a 136 patients were found to have a germline *BRCAm* and/or tumour *BRCAm*, and were included in the *BRCAm* data set.

^b 118 patients were found to be *BRCA* wild type or *BRCA* unknown

Table 4 presents an estimate of the sensitivity and specificity of Study 19, disregarding the missing data (conducted during evaluation). The joint ESCs considered that the usefulness of these calculations was reduced by the fact that 108/265 (41%) study participants had either “unknown” or “missing” status for either germline or tumour testing.

Table 4: Summary of concordance of germline and tumour *BRCAm* testing

N		Either germline or tumour line		Sensitivity	Specificity
		Positive	Negative		
Predicted germline <i>BRCAm</i>	Positive	96	0	84%	100%
	Negative	18	96	—	—
Predicted tumour <i>BRCAm</i>	Positive	111	0	97%	100%
	Negative	3	95	—	—

Source: compiled during evaluation

BRCAm = *BRCA1* or *BRCA2* mutation

Note that patients with missing values for the predicted test were excluded from the calculations.

In the economic evaluation, the submission assumed 100% sensitivity and 100% specificity for (germline or tumour line) *BRCAm* testing in the baseline model. This might not be appropriate, as described below, due to:

- uncertainty with the applicability of the germline test from different populations to the proposed population;
- the lack of information on the specificity and sensitivity of tumour line testing;
- the additional identification of *BRCA* mutations using tumour line testing in Study 19; and
- the potential need for additional biopsies for retesting of tumour line.

MSAC noted the joint ESCs advice that sequencing testing is more complex than simple antibody testing, requiring the development of pathology expertise. For example, an important parameter for analytical test performance (both analytical validity and analytical reliability) is the “read depth”, measured as the number of reads of the sequencing results to be confident in the conclusions drawn. It also involves interacting with software used for alignment of sequences, and judging what constitutes a mutation versus a polymorphism of unknown significance. This complexity raises questions for MSAC over whether consistent and reproducible standards for this type of testing are established and assessable. This is particularly a concern in relation to sequencing of tumour DNA, which is far less standardised than testing for germline mutations. In addition, unlike testing for germline mutations, sequencing of tumour DNA may need to be performed more than once in a patient’s lifetime.

Prevalence

The submission stated that, as the patients enrolled in Study 19 were representative of the proposed population for *BRCAm* testing and olaparib in Australia, the estimate of 136/254 =

53.5% prevalence was appropriate. This estimate is appropriate for patients who receive both germline and tumour *BRCA* testing. If patients only receive germline *BRCA* testing, the estimate of prevalence could be lower. This was investigated in the financial estimates.

Clinical claim and therapeutic relativity

The submission stated that there was strong evidence of the *BRCA* test to support diagnostic accuracy, reliability and clinical validity.

The claim that the next-generation sequencing based *BRCA* test would correctly identify all platinum-sensitive resistant ovarian cancer patients might not be valid because of:

- the uncertainty with the applicability of the germline test from different study populations to the proposed population;
- the lack of information on tumour *BRCA* testing in Australia (i.e., extraction of tumour sample), and test-retest reliability for tumour testing. Therefore it was unknown what the specificity and sensitivity of tumour line testing would be;
- the additional identification of *BRCA* mutations using tumour line testing in Study 19. This might indicate that more than one test per patient might be required, that is, a patient with a negative germline *BRCA* test might also be provided with tumour *BRCA* testing; and
- the potential need for additional biopsies for re-testing of tumour line, with its associated harm. This retesting might be due as 16% of *BRCA* mutations occur alone in the tumour, separate of the germline. Another reason might be due to an insufficient tumour sample or DNA degradation of archived tumour samples.

Claim of co-dependence

The submission claimed the co-dependent technologies ‘*BRCA* testing and olaparib’ to be superior to ‘No *BRCA* testing and standard follow-up care’.

The submission did not provide a detailed comparison of these two scenarios, rather it focussed on the comparison of the effectiveness of olaparib in patients with *BRCA*. The claim of co-dependence between the technologies of *BRCA* testing and olaparib relies on an acceptance that *BRCA* testing predicts an important variation between *BRCA* and non-*BRCA* patients in the effectiveness of olaparib, and that this is distinguishable from the prognostic value of *BRCA* testing. This claim might not be reasonable in the Australian setting as the key issues were:

- The sensitivity and specificity of the tumour *BRCA* testing might be lower than 100% in the Australian setting:
 - If the specificity would be less than 100%, olaparib treatment might be less effective with regards to progression-free survival, as the efficacy was lower in patients with non-*BRCA* /unknown.
 - If the sensitivity would be less than 100%, fewer patients with *BRCA* would be treated, reducing the potential efficacy of the ‘*BRCA* testing and olaparib’ co-dependent technology.
- MSAC noted the joint ESCs advice that, although the initial Study 19 results provided by the submission did not show that olaparib treatment resulted in significant overall survival in the ITT population or the prespecified *BRCA* or non-*BRCA*/unknown subgroups, the Pre-Sub-Committee Response (Table 1) provided updated survival data from Study 19 which showed statistically significant improvements in overall survival in the *BRCA* subgroups.
- MSAC noted the joint ESCs advice that an informative way to help establish the claim of co-dependence between *BRCA* testing and olaparib would be to present statistical tests of interaction for the treatment effect variations on (a) progression-free survival

and (b) updated overall survival hazard ratios across the *BRCAM* and non-*BRCAM*/unknown subgroups from Study 19.

11. Economic evaluation

Test cost per patient

The proposed fee for the *BRCA* test (either germline or tumour) was \$**redacted** per test based on commercial *BRCA* testing. For the economic model and financial estimates, the submission used the weighted average fee of \$**redacted**, to account for 31% of women estimated to already be tested. The requested fee is 3-fold higher than the fees for other MBS-listed genetic tests.

MSAC noted that the joint ESCs considered the comparison to other MBS-listed genetic tests was not appropriate, given the relatively higher complexity and greater scope of testing required for *BRCA1* and *BRCA2* testing. The proposed fee in this submission may only reflect the costs of consumables and reagents rather than for providing the service overall (for example including the direct laboratory costs and the costs associated with interpreting the findings and report writing).

12. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the expected financial impact of *BRCA* testing and olaparib, over a five year period (Table 5).

Table 5: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use <i>BRCA</i> test					
Eligible population ^a	redacted	redacted	redacted	redacted	redacted
Number of <i>BRCA</i> tests (90% uptake)	redacted	redacted	redacted	redacted	redacted
Estimated extent of use, olaparib					
Eligible population ^b	redacted	redacted	redacted	redacted	redacted
Uptake of olaparib	75%	80%	85%	90%	90%
Number treated	redacted	redacted	redacted	redacted	redacted
Scripts (1 pack per script)	redacted	redacted	redacted	redacted	redacted
Estimated net cost to PBS/RPBS/ MBS					
Net cost to MBS (\$1,139 per test)	\$ redacted				
Net cost to PBS/RPBS	\$ redacted				
Estimated total net cost					
Total net cost to Government	\$ redacted				

Source: Table E.11- E.13 pp223-224; Table E.18. p293 of the submission

BRCAM = *BRCA1* or *BRCA2* mutation; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PSR = platinum-sensitive relapsed; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a PSR ovarian cancer

^b *BRCAM* PSR ovarian cancer

The submission estimated that if *BRCA* testing and olaparib were both listed, the net cost to the MBS would be approximately \$**redacted** million dollars over the first five years.

13. Key issues from ESC for MSAC

Clinical issues:

- The joint ESCs advised that pooling of sensitivity and specificity data is questionable, given that next generation sequencing for somatic mutations is not a standard or uniform test, there is variation about such parameters as the read depth and the software used for alignment of sequences, and judgement is needed about what

constitutes a mutation versus a polymorphism of unknown significance. Hence consideration about the experience and competence of the pathology laboratory must also be taken into account;

- The submission requested both germline and tumour testing for the assessment of the *BRCA* mutation (*BRCAM*: either *BRCA1* or *BRCA2* mutation). There is discordance between *BRCAM* status in the germline and tumour. In the key clinical trial, Study 19, the germline test identified fewer *BRCA* mutations (96/210; 45.7%) than the tumour test (111/209; 53.1%), with a concordance of 140/165 (84.8%). The marginal value or practical implications of adding germline testing to tumour testing (or tumour testing to germline testing) were not assessed;
- Tumour *BRCA* mutations are not stable overtime. The submission did not address the consequences of this in terms of the timing of the test or how recent the tumour sample should be;
- The submission did not provide details on extraction of the tumour sample, and test-retest reliability for tumour testing. Therefore, the estimated sensitivity of 100% and specificity of 100% for *BRCA* mutation testing of tumour tissue might be invalid;
- There might be potential harms if additional biopsies for *BRCA* mutation tumour testing would be required to determine eligibility for treatment with olaparib;
- The joint ESCs noted that the evidence for using olaparib in patients who have acquired a tumour *BRCA* mutation, but not a germline *BRCA* mutation, was based on a small sample size (eighteen Study 19 participants, of whom eight received olaparib). Given that adding tumour *BRCA* mutation testing to germline *BRCA* mutation testing adds complexity and cost, but has unproven additional validity or diagnostic performance, the joint ESCs advised that MSAC consider limiting any support for MBS funding to germline mutation testing only; and
- The joint ESCs advised that an informative way to help establish the co-dependency claim between *BRCA* testing and olaparib (and thus the clinical utility of *BRCA* testing in this context) would be to present statistical tests of interaction for the treatment effect variations on (a) progression-free survival and (b) updated overall survival hazard ratios across the *BRCAM* and non-*BRCAM*/unknown subgroups from Study 19.

Economic/financial issues:

- The proposed fee for *BRCAM* testing was based on commercial *BRCA* testing in a different clinical setting, which might not be appropriate;
- The costs and health outcomes of cascade testing of family members resulting from germline *BRCA* testing have not been considered; and
- The timing of the *BRCAM* test is consistent with the proposed clinical management algorithm, where patients are tested before response to platinum-based chemotherapy has been verified, but inconsistent with the proposed restriction for olaparib, where patients are tested after response to platinum-based chemotherapy. However, using this scenario for the base case provides an upward estimate for the financial estimates.

Other issues:

- The sensitivity and specificity of the tumour testing might be lower than 100% in the Australian setting:
 - If the specificity would be less than 100%, olaparib treatment might be less effective with regards to progression-free survival, as the efficacy was lower in patients with non-*BRCAM*/unknown; and
 - If the sensitivity would be less than 100%, fewer patients with *BRCAM* would be treated, reducing the potential efficacy of the ‘*BRCA* testing and olaparib’ co-dependent technology.

14. Other significant factors

Table 6 presents the scenarios for MBS and PBS listing presented in the submission and in the Protocol ratified by the Protocol Advisory Sub-Committee of MSAC.

Table 6: Scenarios presented in the submission and Protocol

Scenario	Biomarker for testing	Disease subgroup	Time of testing	Time of treatment	Analysis presented in submission
Submission					
Submission base case (Scenario 1)	Germline and tumour	<i>BRC</i> Am PSR ovarian cancer	At relapse after first course of platinum-based chemotherapy	Within 8 weeks of completing second course of platinum-based chemotherapy	Yes
Submission alternative (Scenario 2)	Germline and tumour	<i>BRC</i> Am PSR ovarian cancer	After response to second course of platinum-based chemotherapy	Within 8 weeks of completing second course of platinum-based chemotherapy	No
Protocol					
Protocol base case (Scenario 1)	Germline	<i>BRC</i> Am PSR ovarian cancer	At relapse after first course of platinum-based chemotherapy	Within 8 weeks of completing second course of platinum-based chemotherapy	Yes
Protocol alternative (Scenario 2)	Germline	<i>BRC</i> Am PSR ovarian cancer	After response to second course of platinum-based chemotherapy	Within 8 weeks of completing second course of platinum-based chemotherapy	No

Source: compiled during evaluation

*BRC*Am = *BRCA1* or *BRCA2* mutation; PSR = platinum-sensitive relapsed

The submission explained the advantage of Scenario 1 was that it provided a longer window for the turnaround of *BRC*Am test results, and therefore promoted timely treatment with olaparib. However, given the expected increase in next-generation sequencing technology, which is known to improve turnaround time, and the eight-week window allowed before maintenance treatment with olaparib is required, Scenario 2 represents the PBS-aligned setting, where *BRC*Am testing is done after response to platinum-based chemotherapy has been verified.

The joint ESCs noted that the prevalence of a *BRCA* mutation in serous epithelial ovarian cancer is 16%, which suggests that having platinum-sensitive relapsed ovarian cancer selects an enriched population for *BRCA* testing. This has consequences for when to conduct *BRCA* testing: rather than testing all patients with ovarian cancer, it may be more efficient to determine which of these patients remains platinum-sensitive after a relapse following earlier platinum-based therapy, and then test only this subset, as is proposed in the item descriptor. However, there are no Australian data on which to estimate the potential improvement in efficiency. Depending on how long it takes to determine platinum sensitivity, and whether tumour *BRCA* testing is to be conducted as well as germline *BRCA* testing, this may involve retrieval of archived resected tumour material or even additional biopsies.

The joint ESCs considered that Scenario 2 would be more appropriate, noting that this would optimise the efficiency of *BRCA* testing. The proposed clinical management algorithm, economic model and financial estimates used Scenario 1.

15. Applicant's comments on MSAC's Public Summary Document

The applicant had no comments.

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at:
www.msac.gov.au.