



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1658 – Testing of tumour tissue to determine a positive homologous recombination deficiency (HRD) status in women newly diagnosed with advanced (FIGO stage III-IV) high grade epithelial ovarian, fallopian tube or primary peritoneal cancer for access to PBS olaparib

Applicant: AstraZeneca Pty Limited

Date of MSAC consideration: 28-29 July 2022

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

1. Purpose of application

The integrated codependent application requested:

- Medicare Benefits Schedule (MBS) listing of homologous recombination deficiency (HRD) testing of ovarian tumour tissue (to establish genomic instability and breast cancer gene (*BRCA1/2*) status) to determine eligibility for access to PBS-subsidised olaparib in combination with bevacizumab; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing for olaparib in combination with bevacizumab after a response to first-line platinum-based chemotherapy (with or without bevacizumab) in newly diagnosed advanced high grade epithelial ovarian cancer (HGEOC) patients found to be positive for genomic instability without a pathogenic *BRCA1* or *BRCA2* variant i.e. HRD positive *BRCA* wild type (*BRCAwt*).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of testing ovarian tumour tissue for genomic instability to determine homologous recombination deficiency (HRD) status to define eligibility for treatment of ovarian cancer with olaparib and bevacizumab. MSAC advised that further information is needed to elucidate how to confidently identify ovarian tumour tissue as being homologous recombination deficient. Currently HRD status has not yet been satisfactorily defined by reference to a single test method, scoring algorithm and threshold. MSAC also considered that, across medicines in the same class as olaparib, there is equivocal evidence regarding how well the extent of response to olaparib is predicted by a tumour being classified as HRD positive without a pathogenic variant in the *BRCA1/2* genes.

Consumer summary

This is an application from AstraZeneca Pty Limited requesting MSAC consider Medicare Benefits Schedule (MBS) listing of testing of tumour tissue to detect homologous recombination deficiency (HRD) status in women with newly diagnosed advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. The test would determine whether the person was eligible for a medicine called olaparib in combination with bevacizumab as maintenance therapy, funded under the Pharmaceutical Benefits Scheme (PBS). This was a codependent application with the Pharmaceutical Benefits Advisory Committee.

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

Both somatic and germline variants can cause cancers which are unable to properly repair mistakes in the DNA. One type of repair problem is called HRD. HRD can be caused by a pathogenic variant (mutation) in the genes *BRCA1* or *BRCA2*. This means the body of a person with an HRD positive cancer is less able to repair breaks in the DNA of their cancer cells. For this reason, these HRD positive cancers may be more easily killed by some cancer drugs. In the case of HRD positive ovarian cancer, this may be more likely to respond to treatment with olaparib than ovarian cancer that is HRD negative.

Olaparib is already available on the PBS for people whose ovarian cancer has a pathogenic *BRCA1* or *BRCA2* variant (*BRCAm*).

MSAC noted that there is no accepted definition of HRD, beyond having a cancer which is *BRCAm*. MSAC noted that the HRD test (called Myriad My Choice Plus) used in the main clinical studies of olaparib and similar medicines was not the same test as the one that would be used in Australia. These different tests use different methods to examine whether a tumour is considered HRD positive, and MSAC did not consider the two tests to be equivalent. The way each of the two HRD tests work is also secret (called a "black box" algorithm) and MSAC considered that this lack of transparency was important because it would hinder quality assurance of the test results. MSAC also considered that the evidence is not clear about how well a person whose tumour is HRD positive (but without being *BRCAm*) would respond to olaparib, so the test result might not predict improved clinical outcomes for patients. MSAC advised that consultation was needed with experts in this field to find out more about HRD, the associated tests and their ability to predict how people with ovarian cancer respond to treatment.

MSAC noted that the medicine component of the integrated codependent application was considered by the PBAC in July 2022, and the PBAC did not recommend olaparib in combination with bevacizumab as requested. In doing so, the PBAC also referred questions to MSAC that could not be addressed satisfactorily based on the information available to MSAC.

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

MSAC did not support funding of the test to detect HRD status. MSAC considered that more information is needed, including an internationally agreed clear definition of HRD positive and clear evidence that HRD status can predict how a person will respond to olaparib.

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

MSAC noted that the purpose of the integrated codependent application was to seek Medicare Benefits Schedule (MBS) funding for testing of tumour tissue for the detection of HRD status to determine eligibility for Pharmaceutical Benefits Scheme- (PBS-) funded olaparib in combination with bevacizumab as maintenance therapy for women with newly diagnosed HRD-positive *BRCA*wt (wild type) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (referred to as ovarian cancer for brevity). Olaparib is a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor. The medicine component of this application was considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in July 2022, and the PBAC did not recommend olaparib in combination with bevacizumab for this indication.

MSAC noted that HRD is a concept that is broadly defined as an inability of cells, including tumour cells, to effectively repair double-stranded breaks in its DNA using the homologous repair pathway. MSAC considered that there is no agreed definition of an HRD score that can be used for any HRD test nor a single test that will definitively identify all tumours with HRD. MSAC noted that there are three main approaches to HRD testing: (i) testing for pathogenic variants in genes involved in the homologous recombination repair pathway (such as *BRCA1/2*); (ii) functional assays of homologous repair status, which is currently used in research settings; and (iii) assessment of genomic instability or 'scars', which are mutational signatures that are considered to be due to HRD-related genomic damage. MSAC noted the 2020 recommendations from the European Society for Medical Oncology (ESMO) on predictive biomarker testing for HRD and PARP inhibitor benefit in ovarian cancer, in which ESMO reported that the use of these tests "is limited by a failure to consistently identify a subgroup of patients who derive no benefit from PARP inhibitors in most studies".¹ MSAC considered the lack of an accepted definition of HRD and the failure of HRD tests to consistently identify patients who will derive less or no benefit from PARP inhibitor therapy represented substantial limitations for this application. In particular, MSAC considered that the effects of *BRCA* as the dominant homologous recombination repair (HRR) gene over other HRR genes (as measured by the surrogate of genomic instability) for predicting response with PARP inhibitors in ovarian cancer are inconsistent as the results across the various subgroups differed across the key trials (see Table 1 and Table 17). This is important given the definition of the proposed subgroup to be eligible for olaparib, which is a proposed combination of *BRCA1/2* status and genomic instability status compared to either *BRCA1/2* status or genomic instability status alone. MSAC also noted that the Royal College of Pathologists Australasia had raised similar concerns and it did not support the application.²

MSAC noted that the application was for an MBS item for a validated HRD test that was agnostic to the approach for assessing HRD, including components of genomic scar markers to determine genomic instability. MSAC considered that the proposed fee of \$2,500 (which was not specified in the MBS item descriptor but was used for the economic and financial analysis) was not fully justified and seemed excessive for the costs of conducting the assay and the bioinformatics. MSAC noted the potential for patients to incur further out-of-pocket costs for this testing given that the commercial tests sell for higher prices overseas.

The proposed test for initial implementation – the SOPHiA HRD assay – uses next generation sequencing (NGS) that performs low-pass whole genome sequencing (lpWGS) on tumour samples to generate an aggregated genomic instability result known as the Genomic Integrity Index (GII), focusing on loss of heterozygosity (LOH) and some deletions and some insertions. Using the SOPHiA test, HRD positive is defined as a score greater than zero, and HRD negative is defined as a score less than zero. The GII component of the SOPHiA test is determined using a deep-

¹ Miller *et al.* ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Ann Oncol.* 2020;31(12):1606-1622.

² Feedback provided in March 2021 based on information provided in the [Application 1658 application form](#). A description of the proposed HRD test was not available for public consultation.

learning algorithm (“black box”), and limited information is available on how the score is calculated. MSAC considered that this lack of transparency was an important limitation, as it hinders the establishment of a robust quality assurance program. MSAC noted that the SOPHiA HRD assay also performs targeted sequencing of genes involved in the homologous recombination pathway. MSAC noted the SOPHiA HRD assay was not registered with the United States Food and Drug Administration. MSAC noted that the Australian use of the SOPHiA HRD assay as an in-house test had not yet been accredited by the National Association of Testing Authorities (NATA). MSAC further noted that standards had not yet been set for validating the use of any test to be used as a companion diagnostic for the purposes of regulation by the Therapeutic Goods Administration (TGA), let alone an algorithm-based test like this. The pre-MSAC response advised that NATA accreditation was expected in the third quarter of 2022.

The clinical utility standard assay is the Myriad MyChoice Plus assay, which generates a Genomic Instability Score (GIS) based on an assessment of 54,000 single nucleotide polymorphisms (SNPs). The score is also a measure of genomic instability and is the unweighted sum of LOH, telomeric allelic imbalance (TAI), and large-scale state transitions (LST). Using the Myriad assay, HRD positive was defined as a somatic *BRCA* mutation or a GIS of 42 or higher. The threshold score of 42 was chosen as this represents the 5th percentile of a set of biallelic inactivated *BRCA1/2* tumours from a training set of 1,058 tumour samples, representing 95% sensitivity for *BRCA1/2* pathogenic variants. MSAC queried whether the Myriad assay’s methodology for calculating the GIS had changed as the description of the methods have changed.

The submission sought to demonstrate that the SOPHiA HRD assay’s GII (using a threshold of >0) identified the same group of patients as the Myriad assay’s GIS (using a threshold of ≥ 42). MSAC noted that methods of HRD testing differ in terms of the HRD genes and the types of genomic instability they detect, as well as how the status of HRD genes and genomic instability are scored by the bespoke (often proprietary) algorithms with a threshold that is unique to each algorithm. MSAC noted that these algorithms therefore differ in the types of genomic instability detected. Based on the available methodological data, MSAC considered that SOPHiA HRD assay and the Myriad assay may produce similar assessments on LOH although the two tests used different methods (lpWGS and genome-wide single nucleotide variant testing, respectively). MSAC considered the SOPHiA HRD assay may identify other genomic aberrations such as deletions and duplications. MSAC considered the SOPHiA HRD assay might capture chromosomal inversions depending on their location. As such, MSAC concluded that these different methods may not consistently provide concordant results nor identify similar populations as having genomic instability.

MSAC expressed concerns with setting binary thresholds for HRD positive or negative, as there is no distinct point at which an individual can be classified as either positive or negative; similarly, there is no distinct point at which the codependent treatment will or will not be effective (or will be more or less effective). The threshold used to define HRD positivity to determine eligibility for PARP inhibitors also depends on the test used, and the performance of the tests is intended to improve the more test samples are added to inform their algorithms, thus narrowing the confidence intervals around the performance statistics (assuming that the same basis for defining the threshold is still being applied – an assumption which needs to be verified for dynamic rather than fixed algorithms). MSAC considered whether, as an alternative, the response to platinum-based chemotherapy in itself may be a better biomarker of HRD, but noted that waiting to evaluate the patient’s response to platinum would mean that the sample would not have the highest quality DNA for HRD testing.

MSAC accepted the comparator for tumour HRD testing (i.e. combined *BRCA1/2* testing with genomic instability testing) was tumour *BRCA1/2* testing alone (i.e. MBS item 73301). MSAC noted that, as currently, patients with *BRCAm* tumours would then undergo germline *BRCA1/2* testing, followed by cascade testing for relatives if germline testing is positive. Germline *BRCA* testing (as opposed to HRD testing) would therefore still be required to capture germline variants and for cascade testing.

MSAC accepted the proposed clinical management algorithm and noted the proposed MBS item descriptor. MSAC noted the submission presented parallel testing of tumour *BRCA1/2* status and genomic instability as the preferred testing approach. MSAC agreed that parallel testing with a single combined test is preferred as it would be more efficient use of the sample for the pathology laboratory workflow, would more likely use the fresh tissue which gives the best genetic test results and would report both results faster than sequential testing. MSAC considered the logistics of sequential testing would be complex. MSAC noted that consumers had expressed concerns that HRD testing and olaparib treatment were widely available in other countries. MSAC advised that HRD testing was not widely used in in the European Union, highlighting that the ESMO recommendations were not supportive of HRD testing, however it has some use in the UK and widest use in the USA. MSAC noted that clinicians might request the Myriad MyChoice CDx assay performed overseas, however access could depend on funding decisions by local authorities or individual patients.

The submission presented a validation study conducted by the ■■■ (■■■) to demonstrate the comparative analytical performance between the SOPHiA HRD assay and the Myriad MyChoice CDx assay. MSAC considered the tests were not fully concordant. The applicant's pre-MSAC response stated that the tests had overall percentage agreement of 91%, and 100% when only samples less than 3 years old were assessed. MSAC noted that the study was not performed prospectively, rather the validation study sourced archival samples that had previously been tested using the Myriad MyChoice CDx assay. MSAC considered that a limitation of this approach was that it was uncertain whether the samples used for each test were derived from the same part of the tumour. MSAC considered fresh samples would be preferred for testing as formalin-fixed paraffin-embedded (FFPE) degrades sample quality by the fixing processing and by prolonged storage. MSAC advised that a more robust approach would be required, with adequate statistical power by identifying enough ovarian tumour samples that are tested with both the SOPHiA HRD assay and the Myriad MyChoice CDx assay in parallel (without knowledge of either result). This would enable an assessment of the comparative analytical performance without questions arising about the quality and comparability of the samples. MSAC also advised that HRD testing should not be limited to a single provider as this would provide better patient access given the expected volume of testing and back-up options in the event that problems arise in a single laboratory.

MSAC advised that the concept of the clinical utility standard (in this case assay, algorithm and threshold) remains relevant as a basis for judging whether to allow other test options to be used within the scope of a broad MBS item descriptor. However, in the context of this application, more fundamental concerns regarding the different definitions of genomic instability (in this case assay, algorithm and threshold) in the context of different definitions of HRD status needed clearer resolution as a prerequisite to accepting this concept for this purpose. In addition, MSAC anticipated that a means to reconcile across the different clinical utility standards used across different PARP inhibitor trials would need to be determined to future-proof the proposed MBS item for HRD testing.

MSAC noted the PBAC had sought its advice on the proportion of patients who are HRD-positive *BRCAwt*. MSAC advised that approximately 25% of people with advanced ovarian cancer would be HRD-positive *BRCAwt* in addition to the 25% of this population who would be *BRCAm*. These estimates are broadly consistent with the results of the validation study, although the prevalence of HRD-positive may vary with choice of assay and threshold of genomic instability.

MSAC noted that there is high unmet clinical need for effective, well-tolerated treatments for advanced ovarian cancer. MSAC noted longitudinal studies presented to assess the submission's claims that HRD status, including with different combinations of *BRCA* status predict response to PARP inhibitors as summarised in Table 1 below.

Table 1 Trials assessing HRD status as effect modifier of PARP inhibitor effect

Trial PARP inhibitor	HRD assay	PFS HR (95% CI)		Risk of bias
		HRD+	HRD-	
PAOLA-1 2019 Olaparib N=806	Myriad myChoice Threshold ≥42 (≥33 also reported)	<i>BRC</i> Awt/m (n=387) 0.33 (0.25, 0.45) <i>BRC</i> Awt (n=152) 0.43 (0.28, 0.66)	<i>BRC</i> Awt/m HRD- (n=277) 1.00 (0.75, 1.35) <i>BRC</i> Awt/m HRD-/unknown (n=419) 0.92 (0.72, 1.17) <i>BRC</i> Awt HRD- ?	ITT-based risk of bias assessed to be low. But risk of bias in HRD subgroups may be high in PAOLA-1 and Coleman 2017: HRD subgroups in PAOLA-1 were considered exploratory and were not included in the statistical analysis plan.
Coleman 2019 Veliparib N=1140	Myriad myChoice Threshold ≥33	<i>BRC</i> Awt/m 0.58 (0.44, 0.76)	0.81 (0.60, 1.09)	
Gonzalez-Martin 2019 Niraparib N=733	Myriad myChoice Threshold ≥42	<i>BRC</i> Awt/m 0.40, (0.27, 0.62) <i>BRC</i> Awt 0.50, (0.31, 0.83)	0.68 (0.40, 0.94)	
Coleman 2017 Rucaparib N=564	Foundation Medicine Threshold ≥16%	<i>BRC</i> Awt/m 0.32 (0.24, 0.42) <i>BRC</i> Awt 0.44 (0.29, 0.66)	<i>BRC</i> Awt/m HRD- 0.58 (0.40, 0.85)	

*BRC*Am = breast cancer gene mutation; *BRC*Awt = breast cancer gene wild type; HR = hazard ratio; HRD = homologous recombination deficiency; ITT = intention-to-treat; PARP = poly adenosine diphosphate-ribose polymerase; PFS, progression-free survival

MSAC noted that the majority of studies provided in the application used the Myriad assay, although some studies used different thresholds for HRD positivity. MSAC considered that there was uncertainty about whether the treatment effect is predicted by the combination of *BRC*A1/2 status and genomic instability, compared with either *BRC*A1/2 status or genomic instability alone. MSAC noted that response to platinum-based chemotherapy itself is a predictor of response to PARP inhibitors.

MSAC noted data on comparative clinical effectiveness from the PAOLA-1 trial, which showed improved progression-free survival (PFS) but no improvement in overall survival (OS) in the ITT population, the HRD-positive subgroup and the HRD-positive *BRC*Awt subgroup. MSAC considered that data demonstrating an improvement in OS would be ideal, however considered that this is unlikely to be available in the near future due to long post-progression survival.

MSAC noted the economic evaluation, which was a cost-utility analysis. MSAC noted that the uncertainty relating to the analytic performance of the SOPHiA test compared with the Myriad test also flowed through to the economic model. MSAC noted the applicant's pre-MSAC response, which acknowledged that costs and outcomes associated with inconclusive test results were omitted from the initial analysis. The applicant stated that, although 17% of samples in the PAOLA-1 trial were inconclusive, the [redacted] study found that 10–13% of samples were inconclusive, and this would be expected to decrease over time with education and awareness about extracting adequate tumour tissue.

MSAC noted the financial implications, with two utilisation scenarios. In the base case, the total cost to the MBS was estimated at \$1,470,612 in year 1, and the total cost to the PBS and MBS was estimated at \$10 million to < \$20 million in year 1.

Overall, MSAC considered that the current evidence was not sufficient to ascertain the clinical validity of HRD tests broadly for predicting benefits of PARP inhibitors in patients with these cancers, especially when removing *BRC*Am as the basis for defining the cancer as being HRD-positive. MSAC considered that this was necessary to enable a tradename-agnostic HRD test listing on the MBS including to enable a benchmarking HRD test and threshold and thus comparison across different HRD test and threshold options. MSAC considered that further biological and clinical rationale was required to elucidate which aspects of HRD may predict response to olaparib and other PARP inhibitors. With respect to the clinical utility standard, MSAC queried the relative importance of LOH, TAI and LST in predicting response to olaparib. MSAC noted the results of Takaya (2020) which reported that a GIS threshold of ≥63 for identifying

HRD in ovarian cancer, however, this group was also enriched with *BRCA1/2* variants. There was uncertainty about whether the treatment effect is predicted by the combination of *BRCA1/2* status and genomic instability compared with either *BRCA1/2* status or genomic instability alone. MSAC requested the Department to contact Australian and overseas experts on HRD to seek their expert advice on the possible roles of the HRD biomarker and the means by which it is detected by testing in order for MSAC to better judge whether it has been sufficiently established for the purpose requested and by the means proposed. MSAC noted that most HRD assays assessing genomic instability have underlying proprietary multifactorial algorithms. MSAC considered the MBS fees for tests based on proprietary multifactorial algorithms should include a separate justification for the pathology laboratory component of the fee and the algorithm component of the fee. MSAC considered that it could not yet advise the PBAC on the equivalence or validation of the SOPHiA assay versus the clinical utility standard due to the lack of an established definition of HRD. MSAC considered that it could not yet advise the PBAC on the threshold that should be used to define HRD positivity for determining eligibility for PARP inhibitor eligibility, including olaparib. *MSAC considered that the threshold would need to be specific to each HRD test assessing genomic instability and so any tradename agnostic MBS item for HRD testing would need to be linked with an accepted clinical utility standard threshold against which other HRD test options should be validated.*

MSAC considered that a resubmission would particularly need to:

- Provide a definition of HRD which can be applied confidently in clinical practice
- Provide a basis to define and ideally harmonise test thresholds of HRD positivity for different proprietary tests that can confidently distinguish clinically meaningful variation in the treatment effect of PARP inhibitors in ovarian cancer
- Provide a basis to demonstrate how the different definitions in this threshold of HRD positivity affects the ability to distinguish treatment effect variation, specifically definitions based on being (a) *BRCAM* or (b) *BRCAwt* and HRD positive (e.g. algorithm-based genomic instability positive)
- Provide a basis to demonstrate that the different test options that might become available in Australia have sufficient concordance to confidently distinguish clinically meaningful variation in the treatment effect of PARP inhibitors in patients who have *BRCAwt* ovarian cancer
- Provide the preferred method of reporting HRD results and specify whether the results of underlying genetic mutations (beyond *BRCA* status) will be included in reports and how interpretation will be considered in the light of discordance (eg *BRCAwt* but HRD positive).
- Provide a justification for the proposed fee, with separate justifications for the assay component of the fee and the algorithm component of the fee.

MSAC noted that the PBAC had nominated the early re-entry pathway for this application; however, MSAC considered that the consultation required to resolve these issues would require evaluation, including by its ESC, which would prevent MSAC reconsideration at its November 2022 meeting.

4. Background

MSAC has not previously considered this combination of HRD testing to allow access to treatment for ovarian cancer or for any other indication.

In February 2017 olaparib was first listed on the PBS (Items 11034R and 11050N) as maintenance treatment for patients with platinum sensitive, relapsed high grade ovarian, fallopian tube or primary peritoneal cancer who have a germline *BRCA1/2* gene mutation

(codependent MSAC/PBAC Application 1380). The detection of germline *BRCA1/2* gene mutations (MBS Item 73295) in patients with platinum sensitive, relapsed high grade serous ovarian cancer (HGSOC) or HGEOC was listed on the MBS to determine eligibility for PBS treatment with olaparib.

Testing of tumour tissue to detect *BRCA* (germline and somatic) mutation was MBS listed in August 2020 (73301) and the PBS listing of olaparib in germline *BRCA1/2* mutation(s) (*BRCAm*) platinum sensitive recurrent HGSOC or HGEOC was extended to include somatic *BRCA* mutated patients.

In November 2020 olaparib was PBS listed for patients newly diagnosed with *BRCAm* advanced HGEOC. Most recently, olaparib was recommended for patients with *BRCAm* metastatic castration resistant prostate cancer (November 2021).

5. Prerequisites to implementation of any funding advice

The proposed combination HRD test is not registered in Australia, although there are Australian laboratories that currently offer MBS-funded *BRCA* pathogenic variant tests.

The submission (p41) reported that the [REDACTED] is currently establishing a HRD test to be performed locally based on the SOPHiA Genetics assay (referred to as the SOPHiA assay herein). The sponsor stated that this HRD assay will be TGA notified as a Class 3 in-house in vitro diagnostic (IVD) following the completion of local validation, including a concordance study with the commercial Myriad myChoice® CDx assay.

The pre-ESC response advised that completion of all requirements for NATA accreditation has been delayed and will likely be at the end of the third quarter of 2022. As advised in the submission (dated February 2022), the sponsor anticipates that the [REDACTED] will notify the TGA on receipt of accreditation from NATA. The submission initially reported that NATA accreditation and TGA notification is expected to be complete prior to the PBAC and MSAC's consideration of the submission in July.

6. Proposal for public funding

Table 2 Proposed MBS item

Category 6 – Pathology Services	
MBS item XXXXX	Group P7 - Genetics
A test of tumour tissue from a patient with advanced (FIGO III-IV), high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, requested by a specialist or consultant physician, to detect homologous recombination deficiency (HRD), including <i>BRCA1</i> or <i>BRCA2</i> pathogenic or likely pathogenic gene variants to determine patient eligibility to access olaparib with or without bevacizumab under the Pharmaceutical Benefits Scheme (PBS).	
Once per primary tumour diagnosis	
Fee: \$2,500 (TO BE CONFIRMED)	

Source: Table 1.9, p43 of the submission

The commentary considered the proposed MBS item was not entirely aligned with the proposed PBS listing. The proposed PBS listing requests use in patients with high grade stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer and not in patients with high-grade serous ovarian cancer. However as serous cancer is a subtype of epithelial cancer this was unlikely to be an issue in practice.

The proposed MBS item descriptor is identical to the descriptor detailed in the [Ratified PICO Confirmation](#).

The proposed clinical management algorithm included HRD testing for all patients after diagnosis of HGEOC, thereby establishing both *BRCA* variant status and genomic instability status. The commentary considered that HRD testing is a broad concept that encompasses different methods of defining HRD, rather than being a specific test. The different methods of HRD testing differ in terms of the HRR genes and the types of genomic instability they detect as well as how the presence of HRR and genomic instability is scored by the bespoke (often proprietary) algorithms with a threshold that is unique to each algorithm in order to provide a binary result (i.e. HRD positive or negative). As such, these different methods may not provide identical results or identify identical populations. For example, Mills 2020³ examined whether different genomic instability aggregated results are equivalent and reported that the correlation between the “Myriad myChoice HRD” test and loss of heterozygosity (LOH) was 0.864 and between the “Myriad myChoice HRD” test and % LOH was 0.845.

The SOPHiA assay (the proposed test for implementation) is a next generation sequencing (NGS) based test that performs Low-pass Whole Genome Sequencing (lpWGS). The analytical algorithm processes the lpWGS data via a deep-learning algorithm capable of quantifying genomic integrity. This provides a genomic instability result known as a Genomic Integrity Index (GII). The GII measures the amount of genomic scarring as determined by the algorithm. Anything above a threshold of “0” is considered HRD-positive and anything below “0” is considered HRD-negative. The ADAR contends that the SOPHiA assay’s GII demonstrated very strong agreement with the clinical utility standard (Myriad MyChoice HRD plus assay using the GIS score of 42).

The SOPHiA assay also performs targeted sequencing of *BRCA1*, *BRCA2*, as well as 26 other genes involved in HRR or linked to HRD. The commentary highlighted that the eviQ guidelines recommend germline testing in for some non-*BRCA* genes if they are identified in solid tumours.⁴ These include *BRIP1*, *PALB2*, *RAD51C*, and *RAD51D*. Other genes have more complex guidance regarding the clinical utility of germline testing (*ATM*, *CHEC2* and *TP53*) where the guidance for germline testing varies depending factors specific to each patient such as family history, the specific variant, and age of diagnosis.

The ESCs noted that the SOPHiA HRD assay appeared to be different to the HRD tests considered by PASC.

The submission proposed that the medical service for the requested HRD test should replace MBS item 73301 that is currently used to determine eligibility relating to *BRCA* status for access to olaparib in patients with advanced ovarian cancer. The commentary considered that patients who only require *BRCA* testing (i.e. *BRCAM* patients who are eligible for olaparib under the current PBS-listed ovarian cancer indications) would be required to undergo fuller HRD testing and could incur additional out of pocket expenses associated with the fuller HRD test for no additional benefit and potentially have higher risks of misclassification and thus receive suboptimal treatment. The requested PBS restriction for olaparib plus bevacizumab excludes treatment in *BRCAM* patients.

PASC (ratified PICO confirmation, p16) considered that, should the proposed test replace the current MBS item for testing for *BRCA1/2* pathogenic variant status in tumour samples (MBS item 73301), it would also be important to demonstrate that the proposed test, which tests for HRD status and *BRCA1/2* pathogenic variant status, has the same or very similar concordance

³ Mills et al. [Comparison of genomic instability \(GI\) scores for predicting PARP activity in ovarian cancer \(confex.com\) https://sco.confex.com/sco/2020/meetingapp.cgi/Paper/15650](https://sco.confex.com/sco/2020/meetingapp.cgi/Paper/15650)

⁴ eviQ Cancer Treatments Online, Considerations for germline testing for variants identified in solid tumours (2022). Available from: <https://www.eviq.org.au/cancer-genetics/resources/4056-considerations-for-germline-testing-for-ovaria#gene-table>

and discordance for *BRCA1/2* as the current MBS tests. In particular, it should be demonstrated that the new test would identify the same patients that respond to olaparib monotherapy as the current tests for MBS item 73301. However, no concordance or validation of the SOPHiA assay to the nominated comparator (current testing for *BRCA1/2* pathogenic variant status) was presented by the submission.

An MBS fee was not proposed as part of the item descriptor, however a fee of \$2,500 was used in the economic model and financial estimates. A justification was not provided for this fee, so it is not clear whether it is higher than would be needed once economies of scale occur or there may be any out-of-pocket costs if it is too low. The applicant is requested to confirm that the proposed test can be performed for a fee of \$2,500.

The cost of the *BRCA* test (MBS item 73301) is currently listed as \$1,200. MSAC previously advised (p1, Application No. 1618 MSAC PSD, MSAC meeting November 2021) that the fee for MBS items to test for pathogenic variants in only the *BRCA1* and *BRCA2* genes should be reduced from \$1,200 to \$1,000 as the cost of this testing has decreased. Therefore, the cost of fuller HRD testing (based on the inputs used in the economic evaluation) is estimated to be \$1,500 more than *BRCA* testing.

The commentary queried whether [REDACTED] would have the capacity to process the number of tests estimated in the first and subsequent years following the listing. The pre-ESC response stated that [REDACTED] perform approximately 80% of tumour *BRCA* tests. The ESCs considered [REDACTED] may be able to meet national demand for testing.

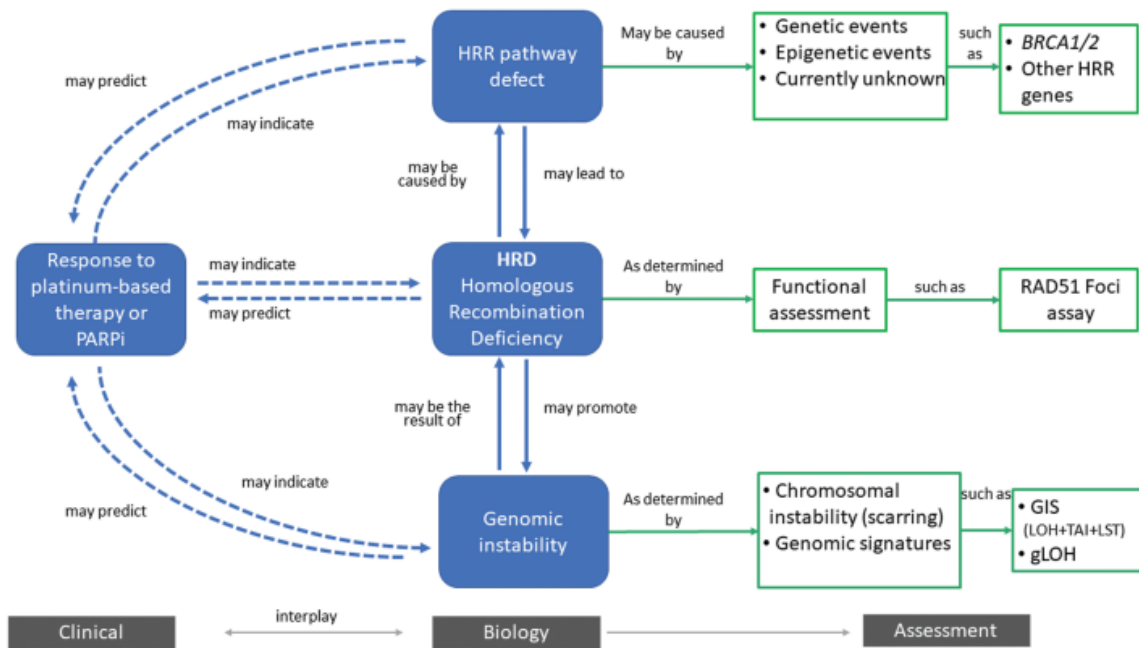
7. Population

The proposed MBS item descriptor is intended to allow testing of tumour tissue from patients with HGEOC and would provide HRD status (both *BRCA* and genomic instability result in parallel), with the base case presented by the submission assuming that testing occurs upfront following diagnosis of advanced HGEOC. The HRD testing will determine whether patients are eligible to receive treatment with olaparib (plus bevacizumab) for patients with advanced ovarian cancer who are both HRD positive and *BRCAwt* (referred to as HRD positive *BRCAwt* herein) under the proposed PBS listing.

HRD is a phenotype that is characterised by the inability of a cell to effectively repair DNA double-strand breaks using the homologous recombination repair (HRR) pathway. Alterations in these genes have been deemed “causes” of HRD (e.g. genetic events and epigenetic events). This can result in an impaired HRR pathway, which can be assessed by probing the genome for evidence of genomic instability (e.g. chromosomal instability and other genomic signatures). Loss-of-function genes involved in this pathway can sensitise tumours to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapy, which target the destruction of cancer cells by working in concert with HRD through synthetic lethality (Stewart 2022⁵). Refer to Figure 1 below for an overview of HRD.

⁵ <https://academic.oup.com/oncolo/article/27/3/167/6515681>

Figure 1 Overview of homologous recombination deficiency (HRD)



BRCA = breast cancer gene; GIS = Genomic Instability Score; gLOH = genomic patterns of loss of heterozygosity; HRD = homologous recombination deficiency; PARPi = poly (ADP-ribose) polymerase inhibitors
 Source: Stewart 2022, Figure 2

A key current challenge to measuring HRD is that there is no standardized method to define, measure, and report HR status using diagnostics in the clinical setting (Stewart 2022).

HRD positive status was defined in the submission as having either tumour *BRCA*m or a GIS greater than a predefined threshold (≥ 42 for the Myriad myChoice HRD plus and Myriad myChoice CDx). This was based on the applicant's definition and is consistent with the definitions used to define subgroups in PAOLA-1. Given this relationship, GIS positivity implies HRD positivity, and they are therefore used interchangeably at times. The commentary noted that the term 'HRD positive' has been used in the commentary to allow consistency as it has previously been used by the PBAC (e.g. niraparib PSD, PBAC Meeting March 2021) and by the sponsor in the requested restrictions. However, the term 'GIS threshold' has been used in the commentary rather than 'HRD threshold' when describing specific threshold criteria to reflect more accurately what was being tested.

The submission proposed that testing of tumours to identify HRD (*BRCA* and GI) status should occur once per primary tumour diagnosis, as part of routine diagnostic work-up for women with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Tumour tissue for HRD testing would be collected during diagnostic biopsy or cytoreductive surgery. The submission (p21) stated that HRD testing includes two components (*BRCA* and GI) which occur in parallel and enables conservation of tumour tissue, however HRD testing could be more accurately described as providing two outputs (GI positivity status and *BRCA* status).

The submission noted that testing at diagnosis rather than after response to first-line platinum-based chemotherapy avoids treatment delay and ensures the most efficient testing sequence of tumour tissue testing. The commentary considered that this also leads to unnecessary testing and increases the total cost of testing as patients who do not respond to platinum-based chemotherapy would not have been eligible for maintenance therapy with olaparib irrespective of HRD or *BRCA* status. The ESCs noted that parallel testing was generally less costly than

sequential testing approaches requested by PASC and could be the preferred approach to testing.

PASC requested the submission explore the following testing scenarios:

- Population 1: HRD testing (*BRCA* and genomic instability in parallel, reports both status) occurs upfront at diagnosis of advanced HGEOC (Base case; proposed patient population).
- Population 2: Tumour *BRCA* testing occurs upfront at diagnosis of advanced HGEOC, whereby patients returning a negative *BRCA* result will be tested for genomic instability status soon after.
- Population 3: Patients with advanced HGEOC who have received bevacizumab as part of initial treatment with first-line platinum-based chemotherapy will be tested to identify genomic instability status. Patients who have not received bevacizumab as part of initial first-line platinum-based chemotherapy will be tested for tumour *BRCA* at diagnosis. Those patients determined to receive bevacizumab will be tested for genomic instability status during their treatment with first-line platinum plus bevacizumab chemotherapy.

The submission further divided this into two subpopulations:

- Population 3a: Patients treated with bevacizumab alongside platinum-based chemotherapy will undergo HRD testing at diagnosis. Patients who do not receive bevacizumab alongside platinum-based chemotherapy will undergo *BRCA* testing; and
- Population 3b: All patients undergo *BRCA* testing at diagnosis, and patients who were *BRCA*wt and treated with bevacizumab alongside platinum-based chemotherapy will undergo HRD testing.

Populations 3a and 3b presuppose that only patients treated with bevacizumab alongside their platinum-based chemotherapy would receive olaparib plus bevacizumab, which is consistent with the enrolment criteria in PAOLA-1.

The submission noted that the methods used to prepare tumour tissue samples for HRD testing are similar to those used for current *BRCA* testing alone and that in order to perform HRD testing, a sufficient quantity of tumour cells is required to ensure that an adequate amount of tumour DNA is extracted for analysis. Thus tumour biopsy samples are the most suitable, commonly available and preferred type. The submission stated that it is necessary to ensure adequate tissue material is obtained when carrying out HRD testing, provided this poses no additional risk to the patient, but did not include details of how much tissue is collected during these procedures and if there would be adequate tissue available for retesting if the initial HRD testing failed to obtain a result. The pre-ESC response stated that the ■ validation is being repeated using 100 ng input DNA due to the high number of inconclusive results when using 50 ng input DNA (as per manufacturer recommendation). The ESCs noted the pre-ESC response reported the proportion of samples with a $\geq 30\%$ tumour purity as a quality metric for the SOPHiA HRD assay. The ESCs queried whether this meant that some samples will not be suitable for testing or if microdissection is needed to enable testing.

The commentary considered that it may not be reasonable or equitable to exclude *BRCA*m patients from treatment with olaparib plus bevacizumab as the PAOLA-1 data found that all patients with HRD positive tumours were benefited by treatment with olaparib plus bevacizumab (progression-free survival (PFS) HR = 0.38, 95% CI 0.29, 0.50).

8. Comparator

Currently tumour *BRCA* testing is MBS funded under MBS item 73301 upon diagnosis of advanced ovarian cancer. This test was nominated by the submission as the main comparator to the proposed test as the submission proposed that the HRD test will replace the existing tumour *BRCA* test, given that the HRD test will provide both *BRCA* and genomic instability status.

The ratified PICO confirmation (p21) detailed that PASC considered that, as proposed by the applicant, the current testing for *BRCA1/2* pathogenic variants (MBS item 73301) is an appropriate comparator for the proposed HRD test that would also test for *BRCA1/2* pathogenic variants in a parallel (rather than a sequential) manner. As such, PASC accepted the intention for MBS item 73301 to be completely replaced by the new item corresponding to the proposed HRD test.

PASC (ratified PICO confirmation, p16) also considered that, should the proposed test replace the current MBS item for testing for *BRCA1/2* pathogenic variant status in tumour samples (MBS item 73301), it would also be important to demonstrate that the proposed test, which tests for HRD status and *BRCA1/2* pathogenic variant status, has the same or very similar concordance and discordance for as the current MBS tests. In particular, it should be demonstrated that the new test would identify the same patients that respond to olaparib monotherapy as the current tests for MBS item 73301. However, it is noted that no concordance or validation of the SOPHiA assay to the nominated comparator (current testing for *BRCA1/2* pathogenic variant status using NGS) was presented by the submission.

The submission referenced several different Myriad HRD tests in the submission but did not confirm the equivalence of the tests. The clinical utility standard, as per the definition in the MSAC Guidelines, is the Myriad myChoice HRD plus test – the test used in the PAOLA-1 trial (based on the protocol and CSR). The references to the Myriad tests used are summarised in Table 3.

Table 3 Nomenclature around Myriad test used to determine HRD in various studies

Study	Myriad Test used
PAOLA 1	Myriad myChoice HRD plus (CSR) Myriad myChoice CDx PLUS (myChoice CDx PLUS technical document and Table 2.33 of submission)
■■ validation	Myriad myChoice CDx
FDA 2019	Myriad myChoice CDx
Hodgson 2018	"The reported results are based on a research assay performed at Myriad Genetics and not upon the commercially available test"
Coleman 2019	"Myriad myChoice HRD CDx assay" – submission (p75 and 91) claimed this was the myChoice CDx
Gonzalez-Martin 2019	"Myriad myChoice HRD test" as nominated in supplement to Gonzalez-Martin 2019, but the myChoice CDx PLUS technical document implies test was conducted using myChoice CDx

HRD = homologous recombination deficiency; ■■

Source: constructed during evaluation

The commentary considered that it was not clear on how the different Myriad MyChoice HRD tests differed with respect to determining the GIS. However, both tests were likely testing for similar signs of genomic instability based on the fact that both tests used the same scoring threshold of ≥ 42 to determine GIS positivity. Some concordance information between the Myriad

myChoice HRD plus assay and the Myriad myChoice CDx assay was identified in the Myriad myChoice CDx PLUS technical specification document.⁶

9. Summary of public consultation input

Consultation input was received from seven organisations, five from pathology service providers, two medical organisations, and one from a consumer group. The organisations that submitted input were:

- Royal College of Pathologists Australasia (RCPA)
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- Queensland Genomics (Queensland Cancer Clinical Network and Queensland Cancer Genomics Steering Committee)
- Australian Genomics
- Omico (Australian Genomic Cancer Medicine Centre)
- Myriad Genetics Australia and Myriad Genetics International
- Ovarian Cancer Australia

The consumer groups were supportive of the application. The remaining consultation feedback was mixed. Some supported the proposed intervention. Others raised concerns that:

- Several approaches to testing HRD with the original application not clearly specifying the type of HRD test. The other measures include:
 - pathogenic variants in somatic HRD genes;
 - pathogenic variants in non-*BRCA1/2* germline HRD genes;
 - evaluation of a genomic scar; or
 - a combination of the above.
- An MBS item should not be funded for a test or an analyte that is not clearly defined.
- The proposed service should be compared to the clinical utility standard.
- Tumour HRD testing should occur at the same time as *BRCA1/2* testing to limit the need to use and access tissue, however, the result is only needed after response to initial chemotherapy has been established.
- The clinical utility of HRD tests needs to be established.
- There is a preference to add reflex testing of germline HRD genes.

10. Characteristics of the evidence base

The submission presented a linked evidence approach to support the contention that patients with HGEOC whose tumours are HRD positive *BRCAwt* who respond to first line chemotherapy (with or without concurrent bevacizumab) will derive benefit from maintenance treatment with olaparib plus bevacizumab.

A randomised controlled trial of olaparib plus bevacizumab versus bevacizumab alone as maintenance therapy after response to chemotherapy and bevacizumab (PAOLA-1) was presented in the submission in which all randomised patients were stratified based on tumour

⁶<https://myriad-library.s3.amazonaws.com/technical-specifications/myChoice+CDx+Plus+Technical+Specifications.pdf> , Accessed 11 May 2022

BRCA status, with GIS status subsequently determined post randomisation (where possible) using the Myriad myChoice® HRD Plus assay. A direct evidence approach could not be used as the method used to test HRD status (and *BRCA* status) in the clinical trial was different to the proposed test to be used in Australia (which will be carried out at the [REDACTED] using a test by SOPHiA Genetics). Instead, the evidence presented included:

- Validation of the SOPHiA assay against the Myriad myChoice CDx assay in detection of *BRCA* and genomic instability as well as detection of HRD status;
- Accuracy and performance of Myriad myChoice CDx and Myriad myChoice HRD plus assays compared to NGS and the Foundation Medicine T5 panel in detection of *BRCA* and genomic instability as well as detection of HRD status; and
- Longitudinal performance of the Myriad myChoice CDx and Myriad myChoice HRD Plus assays, considering the response of PARP inhibitors in HRD positive and HRD positive *BRCA*wt patients compared to HRD negative patients.

Table 4 Summary of the linked evidence approach

Assessment	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (cross-sectional accuracy)	The [REDACTED] validation study aimed to evaluate concordance between the Myriad myChoice CDx assay and the [REDACTED] test based on the SOPHiA assay. The [REDACTED] addendum provided during the evaluation process stated that phase 1 of the validation was conducted using contrived control samples and mixed tumour type samples including high grade serous ovarian carcinoma, squamous cell carcinomas, endometrial carcinomas, prostate carcinomas, thyroid carcinomas all orthogonally tested with other HRR/HRD assays including Myriad myChoice CDx. PAOLA-1 (n=806) used Myriad myChoice HRD plus with a threshold of ≥ 42 to determine HRD positivity. Similarly, the FDA 2019 study investigated Myriad myChoice CDx for determining HRD status in patients with advanced ovarian cancer. Both studies compared to NGS testing. One additional study (the Myriad myChoice CDx PLUS Technical Specifications) identified during evaluation compared Myriad myChoice CDx with Myriad myChoice HRD plus. Hodson 2018 evaluated Myriad tumour <i>BRCA</i> assay for aiding in the determination of HRD status in patients with HGEOC and compared to the Foundation Medicine T5 panel.	k= ^a n=1,246 and SOPHiA validation: k=1 n=78 ^a	A QUADAS-2 assessment was provided in the submission. Risk of bias was likely to be high for all studies.
Prognostic evidence (longitudinal accuracy)	Longitudinal accuracy was assessed in the four trials (PAOLA-1, Coleman 2017, Coleman 2019, Gonzalez-Martin 2019) for the purpose of investigating clinical response to a PARP inhibitor (i.e. PFS, OS). Three studies used the Myriad myChoice® assay and one study used the Foundation Medicine assay to identify patients with HRD tumours.	k=4 ^b n=3,243	A risk of bias assessment tool for RCTs was provided in the submission. The risk of bias was assessed to be low by the submission, but the commentary assessed the risk of bias in HRD subgroups may be high in PAOLA-1 and Coleman 2017.

Assessment	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Change in patient management	Not explicitly assessed. The SOPHiA assay to be used at the [REDACTED] is being validated vs Myriad myChoice® using the GIS threshold in PAOLA-1 (42). Patients designated as HRD positive <i>BRCA</i> wt would be eligible for olaparib + bevacizumab treatment.	k=0 n=0	-
Predictive effect (treatment effect variation)	Based on PAOLA-1 using primary endpoint PFS (investigator assessed). Analysis of PAOLA-1 subgroups conducted (based on HRD and <i>BRCA</i> status, including HRD positive <i>BRCA</i> wt).	k=1 n=806	The submission considered the risk of bias to be low however, the commentary assessed the risk of bias as likely to be at least moderate given the retrospective determination of patient HRD status and the high proportion of patients with unknown HRD status (17.6% of the total PAOLA-1 population).

^a The [REDACTED] validation of the SOPHiA test used 32 samples for phase 1 and 46 samples for phase 2.

^b PAOLA-1 included for both accuracy and performance and for prognostic evidence

*BRCA*wt = breast cancer gene wild type; HGEOC = high grade epithelial ovarian cancer; HRD = homologous recombination deficiency; HRR = homologous recombination repair; k = number of studies; n = number of patients; NGS = next generation sequencing; PFS = progression-free survival; [REDACTED] = [REDACTED]; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2; RCT = randomised controlled trial
Source: Constructed during the evaluation

11. Comparative safety

Adverse events from testing

The submission reasonably stated that most patients with HGEOC undergo collection of a tumour sample for genetic testing as part of standard of care and it is therefore not expected that a new tumour sample would be required for the majority of patients, assuming that the first extraction was adequate. Failure in testing or inconclusive results from HRD tests occurred in around 17.6% of tests in PAOLA-1. The pre-ESC response considered the test failure rate in clinical practice would be approximately 10%. While the proposed HRD test uses less tissue than conducting *BRCA* and genomic instability testing one after the other, it is not clear if the proposed HRD test uses more tissue than the currently used *BRCA* test. The submission did not detail what would happen in clinical practice if the amount of tissue sample available proved to be inadequate for testing other than to state (p128) that in the instance a new tumour sample and subsequent biopsy is necessary, it was assumed that the risk/benefit profile of tumour extraction would be properly assessed and managed by radiologists, surgeons, oncologists and pathologists. No consideration for failed tests was included in the economic or financial estimates in the submission.

Adverse events from changes in management

The submission did not present any safety data specifically for patients whose HGEOC tumours were HRD positive *BRCA*wt. Only results for the PAOLA-1 safety analysis set (SAS) were available which allowed the comparison of olaparib plus bevacizumab versus bevacizumab monotherapy.

Overall, among patients in the safety population, there were generally more severe (Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3) AEs reported in the olaparib plus bevacizumab arm compared with the placebo plus bevacizumab arm, as shown in the table below.

Table 5 PAOLA-1 severe AEs of Grade ≥ 3 by system class, SAS (overall study duration)

AE by system organ class & preferred term, n (%)	Ola + beva N=535	Pbo + beva N=267	RR (95% CI)
Any AEs of CTCAE grade ≥ 3	311 (58.1)	137 (51.3)	1.13 (0.99, 1.31)
Blood and lymphatic system disorders	141 (26.4)	12 (4.5)	5.86 (3.36, 10.35)
Anaemia	94 (17.6)	1 (0.4)	46.9 (8.4, 267.3)
Lymphopenia	37 (6.9)	3 (1.1)	6.16 (2.05, 18.73)
Vascular disorders	108 (20.2)	82 (30.7)	0.66 (0.51, 0.84)
Hypertension	100 (18.7)	82 (30.7)	0.61 (0.47, 0.78)
General disorders and administration site conditions	34 (6.4)	8 (3.0)	2.12 (1.02, 4.46)
Fatigue	28 (5.2)	4 (1.5)	3.49 (1.30, 9.49)

AE = adverse event; Beva = bevacizumab; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; Ola = olaparib; Pbo = placebo; RR = relative risk; SAS = safety analysis set

Results in bold indicate statistically significant differences

Source: Table 24 p65-66 PAOLA-1 CSR DCO2 and, calculated during evaluation using StatsDirect v3

Due to patients requiring testing for both HRD and *BRCA* status in order to be eligible for olaparib plus bevacizumab, there may be false positive or false negative in either *BRCA* and/or HRD results which would lead to numerous different potential scenarios with implications for patients as shown in Table 6.

Table 6 Scenarios of treatment received for actual status by test result

Test result	Actual status			
	HRD- <i>BRCA</i> wt	HRD- <i>BRCA</i> m*	HRD+ <i>BRCA</i> wt	HRD+ <i>BRCA</i> m
False + HRD	4. Should receive beva mono. Receives ola + beva.	5. Should receive ola mono. If <i>BRCA</i> true + receives ola mono, if <i>BRCA</i> false – receives beva mono.	NA	NA
False - HRD	NA	NA	6. Should receive ola + beva. Receives beva mono.	5. Should receive ola mono. Receives beva mono.
False+ <i>BRCA</i>	2. Should receive beva mono. Receives ola mono.	NA	1. Should receive ola + beva. Receives ola mono.	NA
False - <i>BRCA</i>	NA	5. Should receive ola mono. Receives beva mono.	NA	3. Should receive ola mono. Receives ola + beva.

beva = bevacizumab; *BRCA* = breast cancer gene; HRD = homologous recombination deficiency; m = mutation; mono = monotherapy; ola = olaparib; wt = wild type

* The submission defined any patients who were *BRCA*m as automatically being HRD positive. However, Telli 2016 defined the GIS threshold of 42 so that 5% of these patients would be HRD negative.

Source: constructed during evaluation

The commentary highlighted that false positive or false negative *BRCA* and HRD results that occur in clinical practice will have the following consequences for patients:

1. HRD positive *BRCA*wt patients who incorrectly receive olaparib monotherapy instead of olaparib + bevacizumab do not receive the additive/synergistic benefits of bevacizumab, potentially leading to additional health benefits foregone. The efficacy of olaparib monotherapy in HRD positive *BRCA*wt has also not been established, potentially making them clinically worse off.
2. HRD negative *BRCA*wt patients who incorrectly receive olaparib monotherapy instead of bevacizumab monotherapy are unnecessarily exposed to olaparib, resulting in additional cost (due to the higher proposed cost of olaparib) and potentially leading to a higher rate of AEs. The efficacy of olaparib monotherapy in *BRCA*wt has not been established, potentially making them clinically worse off.

3. Patients who incorrectly receive olaparib + bevacizumab instead of olaparib monotherapy are unnecessarily exposed to bevacizumab, incurring the additional cost of bevacizumab and potentially resulting in additional AEs due to bevacizumab.
4. Patients who incorrectly receive olaparib + bevacizumab instead of bevacizumab are unnecessarily exposed to olaparib, resulting in additional cost of olaparib and likely leading to a higher rate of AEs.
5. Patients who incorrectly receive bevacizumab monotherapy instead of olaparib monotherapy would have the benefit of olaparib treatment foregone, while being exposed to bevacizumab unnecessarily. The ESCs considered that this may be of greater clinically consequence than other outcomes as patients may forego an effective treatment.
6. Patients who incorrectly receive bevacizumab monotherapy instead of olaparib + bevacizumab would have the benefit of olaparib foregone.

In the above matrix, patients who have been designated as receiving bevacizumab monotherapy could alternatively adopt a ‘watch and wait’ approach (as proposed by the submission would occur for 10% of patients). In which case, there could be additional benefits foregone with treatment. It was noted that ‘watch and wait’ was a nominated comparator in *BRC*Awt patients in the consideration of niraparib for HGEOC, and that up to 72.6% of all *BRC*Awt were assumed to be treated with ‘watch and wait’ in the financial estimates (Table 22, niraparib PBAC minutes March 2022). However, as patients who are unsuitable for bevacizumab maintenance therapy alone would likely also be unsuitable for olaparib plus bevacizumab maintenance therapy, it was unclear what proportion of patients who are able to use bevacizumab would choose to ‘watch and wait’ instead.

Additionally, it was unknown what treatment patients with failed, cancelled or inconclusive tests would receive in clinical practice and the implications of this treatment.

12. Comparative effectiveness

Effectiveness (based on linked evidence)

Table 7 below provides a summary of the data available to inform the comparisons of PARP inhibitor efficacy in biomarker positive and negative patients.

Table 7 Data availability to inform comparisons

Proposed test vs no test	Subgroup analysis of PAOLA-1.	
Proposed test vs alternative test	Preliminary results of the validation of the proposed HRD test carried out at the [redacted] based on the SOPHiA Genetics assay vs the Myriad myChoice® CDx assay.	
	No studies comparing the proposed HRD test (that also incorporates <i>BRCA</i> testing) vs the NGS <i>BRCA</i> test currently used in Australia are available.	
	Proposed medicine	Comparator medicine
Biomarker test positive	PAOLA-1	PAOLA-1
Biomarker test negative	PAOLA-1	PAOLA-1

BRCA = breast cancer gene; HRD = homologous recombination deficiency; NGS = next generation sequencing; [redacted] = [redacted]

Source: Constructed during evaluation

The NGS-based Myriad myChoice HRD plus assay was used to determine HRD status (including pathogenic *BRCA* variants) in patients enrolled in the PAOLA-1 study and is the clinical utility standard.

Tumours can be tested for HRD in several ways:

1. Tests which look for the cause of HRD

- *BRCA* tests use NGS to identify *BRCA1* and *BRCA2* likely pathogenic or pathogenic gene variants.
- Tests that assess specific homologous recombination repair (HRR) genes (HRRm) use multigene panels to identify likely pathogenic or pathogenic variants. *BRCA* is an HRR gene and HRR panels are routinely used in ovarian cancer. HRRm tests are not used in ovarian cancer but are more common in prostate cancer.

2. Tests which aim to find the effect of HRD

- GI tests look for genomic aberrations that are thought to be characteristic of HRR disruption. These tests are sometimes referred to as genomic scar or genomic instability tests.
- The genomic damage/scar can also be assessed by identifying biomarkers such as loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and/or large-scale state transitions (LST) (Pellegrino 2019).

The Myriad myChoice CDx and Myriad myChoice HRD plus assays use formalin-fixed paraffin embedded (FFPE) tumour tissue to quantitate the GIS of the tumour and, in parallel, detect and classify pathogenic variants in *BRCA1* and 2. The GIS is based on three biomarkers (LOH, TAI and LST) and is presented as a score between zero (low) and 100 (high). In PAOLA-1 HRD positivity was defined as the presence of a pathogenic *BRCAm* and/or a GIS ≥ 42 , with this threshold specific to the Myriad myChoice CDx and Myriad myChoice HRD plus assay. The GIS threshold was derived by analysing GIS scores in a training cohort of breast and ovarian chemotherapy-naive tumours with known *BRCA1/2* status and identifying a cut-off with 95% sensitivity to detect those tumours with *BRCA1/2* mutations or *BRCA1* promoter methylation (Telli 2016). The issues around the GIS threshold are discussed further below.

The proposed HRD test being validated by the [REDACTED] is an NGS-based in-vitro diagnostic test developed by SOPHiA Genetics. The submission (p27) reported that the SOPHiA assay relies on a Convolutional Neural Network, which is a deep learning algorithm that can take in an input image, assign importance (learnable weights and biases) to various aspects/objects in the image and be able to differentiate one from the other. The deep learning tool identifies mutational signatures and morphological patterns which indicate the presence of HRD. The output is a genomic instability result known as a Genomic Integrity Index (GII).

The genomic instability component of the SOPHiA assay could be considered a multifactorial algorithm. The MSAC Guidelines (p144-145) request a discussion of the biological plausibility of the algorithm, the process for developing the algorithm, and generalisability of the algorithm. This was not provided for the SOPHiA assay. The submission referred to a dataset used to train the deep learning algorithm (Nik-Zainal et al 2016), a study that assessed somatic variants in 560 breast cancers and non-neoplastic tissue from each individual using whole genome sequencing. The submission stated that the threshold for genomic instability was determined from a training set of approximately 150 samples with known Myriad myChoice status.

The SOPHiA assay reports the mutation status in 28 HRR-associated genes (as shown in the following table) including *BRCA1/2* and the GII as a quantitative measure of the amount of genomic instability and damage resulting from the inability of cells to perform HRR in a tumour. For this test anything above a threshold of “0” is considered GIS positive and anything below “0” is considered GIS negative. Validation of the SOPHiA assay with the Myriad myChoice CDx assay is ongoing at the [REDACTED] as discussed further below in cross-sectional accuracy.

Table 8 HRR genes analysed in SOPHiA HRD assay

<i>AKT1</i>	<i>CDK12</i>	<i>FGFR1</i>	<i>PPP2R2A</i>
<i>ATM</i>	<i>CHEK1</i>	<i>FGFR2</i>	<i>RAD51B</i>
<i>BARD1</i>	<i>CHEK2</i>	<i>FGFR3</i>	<i>RAD51C</i>
<i>BRCA1</i>	<i>ESR1</i>	<i>MRE11</i>	<i>RAD51D</i>
<i>BRCA2</i>	<i>FANCA</i>	<i>NBN</i>	<i>RAD54L</i>
<i>BRIP1</i>	<i>FANCD2</i>	<i>PALB2</i>	<i>TP53</i>
<i>CCNE1</i>	<i>FANCL</i>	<i>PIK3CA</i>	<i>PTEN</i>

Source: Table 1.3, p25 of the submission

Table 9 provides a summary of the reference standards for accuracy of biomarker detection and validity of the biomarkers.

Table 9 Reference standards to determine the accuracy and prognostic validity of genetic testing

Type of test information	Reference standard
Accuracy of biomarker detection (cross-sectional accuracy)	<i>BRCA</i> testing using DNA from fresh tissue using NGS technology
Prognostic validity of biomarker (longitudinal accuracy)	Response to a PARP inhibitor in terms of PFS and OS in patients who are HRD positive <i>BRCA</i> wt compared with patients who are HRD negative. It was unclear if this was a valid comparison, or if any patient who is not HRD positive <i>BRCA</i> wt, i.e. <i>BRCA</i> m plus HRD negative <i>BRCA</i> wt, should be included as the complement subgroup for comparison.
Predictive validity of biomarker (longitudinal accuracy)	

BRCA = breast cancer gene; HRD = homologous recombination deficiency; m = mutation; NGS = next generation sequencing; OS = overall survival; PARP = poly adenosine diphosphate-ribose polymerase; PFS = progression-free survival; wt = wild type

Source: Constructed during evaluation

All commercial molecular pathology service providers for *BRCA*m testing in Australia currently conduct *BRCA* testing using DNA from fresh tissue using NGS technology. This was the reference standard for *BRCA* testing that was proposed in the submission. The submission (p83) noted that current literature and recommendations indicate that NGS platforms are widely accepted and utilised for detecting pathogenic *BRCA*m (Wu 2017) and is therefore considered the gold standard in this submission.

The submission defined the reference standard for the GIS component of HRD as how well it predicts response to treatment (i.e. longitudinal accuracy). Longitudinal accuracy is conducted for the purpose of determining a future health state, with the accuracy of this prediction measured against a “reference standard,” which is the health outcome of interest at a later time point (e.g., length of survival, response to treatment). In this case the clinical outcome of interest is the response to a PARP inhibitor in terms of PFS and OS in patients who are HRD positive *BRCA*wt compared with patients who are HRD negative. It was unclear if this was a valid comparison, or if any patient who is not HRD positive *BRCA*wt, i.e. *BRCA*m plus HRD negative *BRCA*wt, should be included as the complement subgroup for comparison.

As acknowledged by the submission, the literature review did not identify any head-to-head studies comparing the proposed test (SOPHiA assay and other NGS-based tests) or clinical utility standard (Myriad myChoice HRD plus assay) versus the reference standard (HRD testing using fresh tumour tissue) in detecting either the pathogenic *BRCA*m or GIS components of HRD in tumour tissue. FFPE archival samples rather than fresh tissue samples were used in all included studies. Therefore, the submission claimed that the diagnostic value of HRD testing was assessed using the following comparisons.

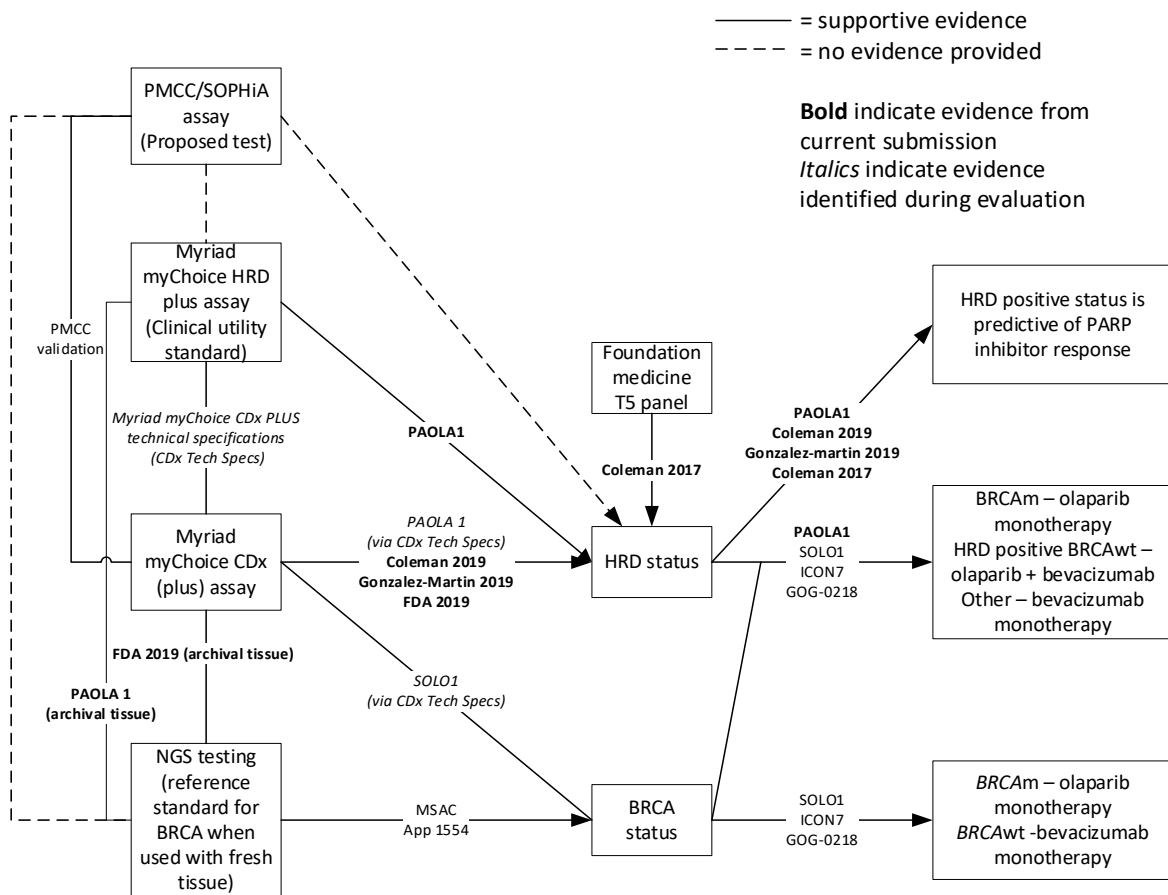
1. Cross-sectional accuracy of tumour HRD testing in detecting pathogenic *BRCA*m and GIS components using FFPE archival samples:
 - a. Comparison of the proposed test (including the SOPHiA assay and other NGS-based tests) vs the clinical utility standard to detect pathogenic *BRCA*m. This was

inaccurate, as no comparison of the proposed test with NGS tests for *BRCAM* was provided.

- b. Comparison of the proposed test (including the SOPHiA assay and other NGS-based tests) vs the Myriad myChoice CDx) to detect GIS component and overall HRD positivity. This was informed by the ongoing unpublished validation study.
2. Longitudinal accuracy of tumour HRD tests to predict treatment effect. Comparison of the clinical utility standard, and other tumour HRD tests to predict treatment effect response to a PARP inhibitor in terms of PFS and OS in patients who are HRD positive *BRCAt* compared with patients who are HRD negative or *BRCAM*. Given that the value of *BRCA1* and *BRCA2* testing in predicting treatment response to olaparib is already established, the submission focused on the longitudinal accuracy of the GIS component of HRD (i.e., HRD positive *BRCAt*). As there were no head-to-head studies of Myriad myChoice HRD plus or Myriad myChoice CDx and other tumour HRD tests to predict treatment response, the longitudinal accuracy of different tumour HRD tests were compared informally.

As no studies comparing the proposed SOPHiA assay with the NGS *BRCA* test currently used in Australia (using either FFPE or fresh tissue samples) and only limited evidence of concordance between the clinical utility standard of Myriad myChoice HRD plus and the Myriad myChoice CDx being compared to in the validation study were presented in the submission, the commentary considered that there were gaps in the available data for the linked evidence approach adopted by the submission. The evidence approach presented instead relied on a chain of assumed equivalence between the SOPHiA assay, the Myriad myChoice assays and NGS testing and application to PAOLA-1. A pictorial representation of the evidentiary chain presented by the submission is illustrated in Figure 2.

Figure 2 Illustration of the evidentiary chain of the current codependent submission



BRCA = breast cancer gene; BRCAm = BRCA mutation; BRCAwT = BRCA wild type; HRD = homologous repair deficiency; NGS = next generation sequencing; ■ Source: constructed during evaluation

Comparative accuracy/test performance

GIS threshold

The GIS threshold used in PAOLA-1 to define whether a tumour sample was HRD positive was specific to the Myriad myChoice HRD plus and Myriad myChoice CDx assays. The methods of determining this threshold were reported by Telli 2016. Both Telli 2016 and Takaya 2020 used the phrase “HRD score” to represent GIS.

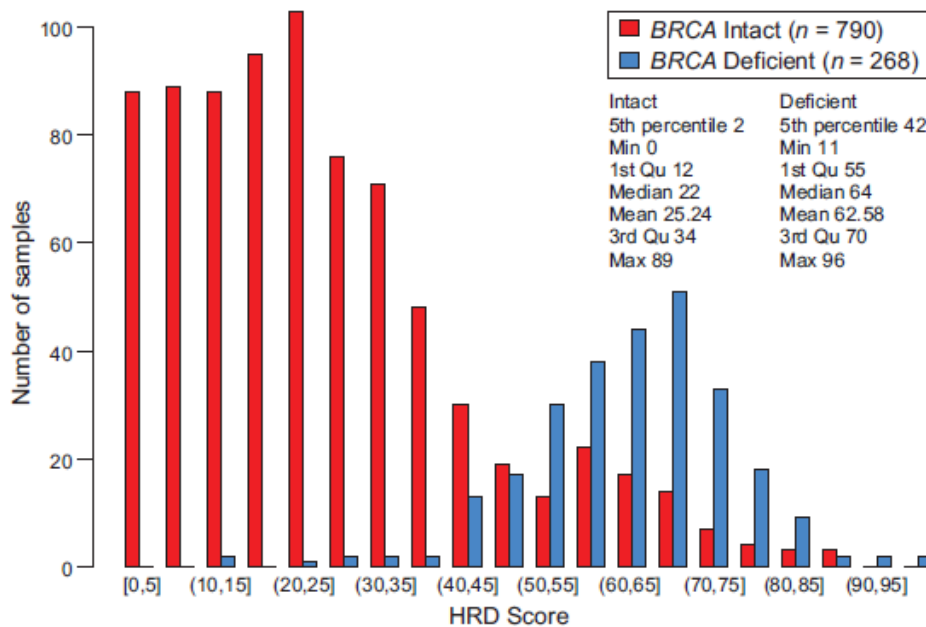
Telli 2016 reported a GIS threshold based on the unweighted average of three independent DNA-based measures of genomic instability (LOH, TAI and LST) that reflect underlying tumour homologous recombination DNA repair deficiency. Telli 2016 used a training set assembled from four publicly available or previously published cohorts (497 breast and 561 ovarian cases) that included 78 breast and 190 ovarian cancers lacking a functional copy of either *BRCA1* or *BRCA2* (i.e. *BRCA1/2* deficient, BRCAm).

The GIS threshold of 42 was selected to demonstrate a high sensitivity ($\geq 95\%$) for detecting *BRCA* positivity. To obtain a sensitivity of at least 95%, the threshold was set at the fifth percentile of the GIS in this training set of known *BRCA1/2*-deficient tumours. (The fifth percentile was 41.9 for *BRCA1/2*-deficient breast tumours and 42.9 for *BRCA1/2*-deficient

ovarian tumours). That is, 95% of patients with *BRCA*m had a GIS score of ≥ 42 in the sample tested in Telli 2016.

Figure 3 presents the GIS score distribution in the combined breast and ovarian training set from Telli 2016. While both the distribution for *BRCA*m and *BRCA*wt samples was presented, only the *BRCA*m sample distribution was used to determine the threshold of 42. As shown below the distribution for *BRCA* intact (*BRCA*wt) samples (shown in red) varied considerably to the distribution for *BRCA* deficient (*BRCA*m) samples (shown in blue). Patients who are *BRCA*wt ($n=790$) reported a 5th percentile score of 2 and a median score of 22. The commentary considered the GIS threshold of 42 does not appear to be particularly meaningful to patients with *BRCA*wt tumours, i.e. the requested patient population. It appears to represent around the 85th percentile for *BRCA*wt samples in Telli 2016. The submission (p85) stated that it was assumed that the loss of *BRCA* function results in HRD, and that the distribution of HRD scores in *BRCA*m samples would represent the distribution of scores in HRD samples due to any underlying pathogenic mechanism.

Figure 3 HRD score distribution in the combined breast and ovarian training set. *BRCA*-deficient tumours include those with a *BRCA1/2* mutation and/or *BRCA1* methylation



BRCA = breast cancer gene; HRD = homologous recombination deficiency
 Notes: *BRCA*-deficient tumours include those with a *BRCA1/2* mutation and/or *BRCA1* methylation
 Source: Figure 2.7, p85 of the submission

Consistent with the definition of the HRD score threshold defined by Telli 2016 and as is evident from the PAOLA-1 data shown in Table 10, most but not all patients with a *BRCA* pathogenic variant had an GIS of ≥ 42 . Similarly, not all patients with a *BRCA* pathogenic variant in the PAOLA-1 trial had a GIS of ≥ 42 .

Table 10 Number of patients who were HRD positive (score ≥ 42) compared with HRD negative (score < 42) with respect to *BRCA* pathogenic variant in the treatment arms of PAOLA-1

	Patient subgroup	Ola + Bev N (%)	Bev + Pbo N (%)
1	HRD positive including <i>BRCA</i> pathogenic variant	255 (47%)	132 (49%)
2	HRD positive, no <i>BRCA</i> pathogenic variant	97 (34%)	55 (39%)
3	<i>BRCA</i> pathogenic variant	161 (30%)	80 (30%)
4	HRD positive, no <i>BRCA</i> pathogenic variant (2) + <i>BRCA</i> pathogenic variant (3)	258 (48%)	135 (50%)
5	Patients who are HRD negative with a <i>BRCA</i> pathogenic variant (4) minus (1)	3 (1%)	3 (1%)
	Total randomised patients	537 (100%)	269 (100%)

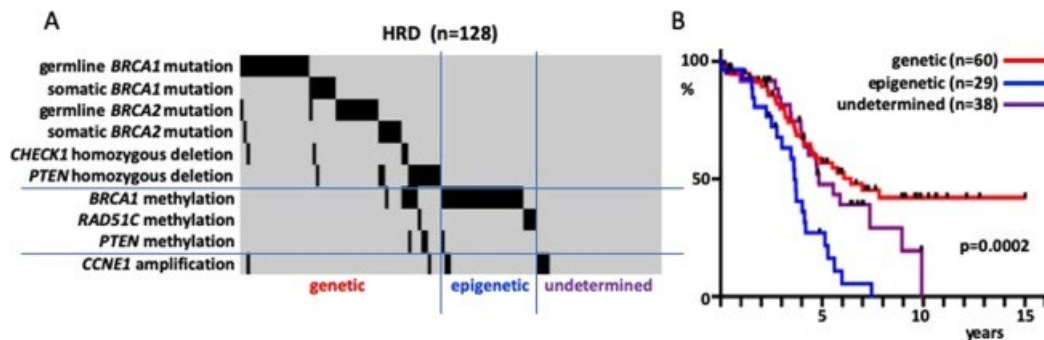
Bev = bevacizumab; *BRCA* = breast cancer gene; HRD = homologous recombination deficiency; N = number of patients; Ola = olaparib; Pbo = placebo

Source: PAOLA-1 [Ray-Coquard 2019 _supplementary appendix Table S2] #1 & #2 based on Myriad myChoice HRD plus; #3 based on tumour *BRCA* mutation test as per randomisation

In PAOLA-1, while 277 patients were reported as HRD (GIS) negative, it was unclear how many of these patients were *BRC*Awt or *BRC*Am. As such, a meaningful comparison between the proportion of GIS ≥ 42 and < 42 in the *BRC*Am and *BRC*Awt cohorts in PAOLA-1 with Telli 2016 was not possible during the evaluation. The applicant was requested to provide the proportion of patients with *BRC*Am and *BRC*Awt with GIS < 42 to allow comparison of distribution compared to Telli 2016. It should be expected that 95% of all *BRC*Am patients and around 15% of all *BRC*Awt patients in PAOLA-1 would have a GIS ≥ 42 based on distributions reported by Telli 2016.

By requesting that genomic instability be assessed at a fixed threshold irrespective of *BRCA* status, the submission is suggesting that HRD, being a measure of genomic instability and effectively a level of DNA damage, was agnostic to *BRCA* status. That is, while *BRC*Am patients were likely to have a higher GIS (and more DNA damage) than *BRC*Awt patients, patients with the same GIS will have the same level of damage irrespective of the genomic cause of damage, and that *BRC*Awt patients with a GIS of ≥ 42 would have (at least) the same level of DNA damage as 95% of *BRC*Am patients, which would be predictive of the same prognosis/level of response to olaparib plus bevacizumab treatment irrespective of the underlying cause of the DNA damage. However, Takaya 2020 reported that HRD cases caused by genetic alterations (genetic HRD including germline and somatic *BRCA1/2* mutations) had better prognosis than those caused by epigenetic changes and those caused by undetermined reasons ($p = 0.0002$) (see Figure 4), suggesting that the cause of HRD appears to have an impact on patient outcomes and possibly treatment response. This may suggest that despite the same GIS supposedly suggesting the same level of DNA damage, the cause of HRD plays a role in the determination of prognosis and possibly treatment response, and that the prognosis and outcome for a *BRC*Am patient with a GIS of 63 would differ to that of a *BRC*Awt patient with a GIS of 63 and that using the same threshold irrespective of *BRCA* status may not be appropriate (Takaya 2020 did not present results at the threshold of 42).

Figure 4 Relationship between the molecular mechanism of HRD and prognosis



A) Classification of HRD cases. (B) Survival rate of HRD cases.

Source: Figure 4A, Takaya 2019

The commentary considered that while PAOLA-1 used the Myriad myChoice HRD plus assay and a threshold score of ≥ 42 to define HRD positivity in patients who were *BRCA*wt, this threshold may not have been appropriate for the *BRCA*wt population as:

- The GIS threshold of 42 reported by Telli 2016 and used in PAOLA-1 was selected to obtain a sensitivity of at least 95% at detecting *BRC*Am, with the threshold set at the fifth percentile of the HRD scores in the training set of known *BRCA1/2*-deficient breast or ovarian tumours. However, the significance of the threshold in the *BRCA*wt ovarian cancer patients (which was the requested PBS population) was unclear, and the submission has not explained why a threshold of 42 should be used in the *BRCA*wt ovarian cancer population nor was it is apparent what threshold should be used;
- Results from Takaya 2020 and Marquard 2015 suggest that HRD scores in ovarian cancer tumours were higher than in breast cancer tumours, and as such using the threshold from a mixed sample as in Telli 2016 may not be appropriate; and
- Takaya 2020 also reported that HRD cases caused by genetic HRD such as germline and somatic *BRCA1/2* mutations had better prognosis than those caused by epigenetic changes and those caused by undetermined reasons ($p=0.0002$), suggesting that the cause of HRD has a significant impact on prognosis and possibly treatment response, and that the prognosis and outcome for a *BRC*Am patient with a HRD score of 42 would differ to that of a *BRCA*wt patient with a HRD score of 42 and that using the same threshold irrespective of *BRCA* status may not be appropriate.

Cross-sectional accuracy

Four cross-sectional accuracy studies of ovarian cancer samples were identified in the submission. Of these, one study (PAOLA-1) evaluated the Myriad myChoice HRD plus assay with other NGS-based assays in determining pathogenic *BRC*Am, one study evaluated the Myriad myChoice CDx assay with other NGS-based assays in determining pathogenic *BRC*Am (FDA 2019) and one compared the Myriad myChoice assay (not commercially available) and an assay from Foundation Medicine to detect pathogenic *BRC*Am in patients with HGEOC (Hodgson 2018). Additionally one ongoing validation study from the ■ compared the proposed SOPHiA Genetics test with the Myriad myChoice CDx assay was provided. One additional study was identified during the evaluation. The Myriad myChoice CDx PLUS technical specification document reported some concordance outcomes between the Myriad myChoice HRD plus assay and the Myriad myChoice CDx assay as well as some comparative information of the Myriad myChoice CDx with NGS in determining *BRC*Am status.

Table 11 provides an overview of these studies.

Table 11 Summary of cross-sectional accuracy studies for HRD test to identify *BRCA*, GIS and overall HRD status

Study	N	Level of evidence ^a	Risk of bias	Sensitivity ^b	Specificity ^b	Area under the ROC curve (%)	PPV	NPV
<i>BRCA</i> status								
■ validation (submission, mixed)	46	Level III-2	High	100%	97%	Not reported	92%	89%
■ validation (pre-ESC, ovarian) ^c	60	Level III-2	High	100%	100%	Not reported	100%	NR
PAOLA-1	728	Level II	Low	91.3%	98.6%	Not reported	96.8%	96.1%
FDA 2019	200	Level III-2	Moderate	100%	100%	Not reported	100%	100%
Hodgson 2018	193	Level III-2	Moderate	100%	96.6%	Not reported	97.3%	100%
myChoice CDx tech spec ^d	292	Unknown	High	97.3%	NR	Not reported	NR	NR
GIS								
■ validation (submission, mixed)	31	Level III-2	High	86%	94%	Not reported	92%	89%
■ validation (pre-ESC, ovarian) ^e	51	Level III-2	High	83%	91%	Not reported	92%	NR
FDA 2019	200	Level III-2	Moderate	98.5%	97.4%	Not reported	98.5%	97.4%
myChoice CDx tech spec ^d	755	Unknown	High	98.6%	96.6%	Not reported	NR	NR
HRD status								
FDA 2019	200	Level III-2	Moderate	98.5%	98.6%	Not reported	99.3%	97.2%

BRCA = breast cancer gene; GIS = Genomic Instability Score; HRD = homologous recombination deficiency; NPV = negative predictive value; NR = not reported; PPV = positive predictive value

^a Level II = a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation; Level III-1 = a study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation; Level III-2 = a comparison with reference standard that does not meet the criteria for level II and III-1 evidence; Level III-3 = diagnostic case-control study; Level IV = study of diagnostic yield (no reference standard).

^b FDA 2019 report sensitivity and specificity as positive percent agreement and negative percent agreement

^c Ovarian 'Myriad' data set *BRCAm* Accuracy (Table 12, pre-ESC response)

^d Only information reported was that Myriad myChoice correctly classified 284 as *BRCAm* out of 292 patients classified as *BRCAm* using NGS in SOLO1

^e Ovarian 'Myriad' data set GIS Accuracy (Table 14, pre-ESC response)

^f The Myriad myChoice CDx technical specifications reported overall percentage agreement, positive percentage agreement and negative percentage agreement for the Myriad myChoice CDx assay against the clinical utility standard of Myriad myChoice HRD plus

Despite the submission claiming there were only 728 samples available for the concordance study in PAOLA-1, the CSR indicated that 755 patients were given a *BRCA* classification using the Myriad myChoice HRD plus assay, and Ray-Coquard 2019 reported a *BRCA* status using NGS for all 806 patients enrolled in PAOLA-1. It was unclear what happened to the result from the 27 patients who were given a *BRCA* classification but not included as part of the concordance evidence.

While the cross-sectional accuracy studies generally reported a high level of concordance between the Myriad myChoice assays and the NGS or Foundation Medicine assay, false positive or false negative *BRCA* and HRD results will have implications for patients. There were also potential issues with the claimed number of samples available for the concordance study in PAOLA-1. The submission assumed perfect concordance (100% sensitivity and specificity) in detection of *BRCA* in the economic evaluation, which was not supported by the evidence provided.

Validation of proposed test vs Myriad MyChoice HRD tests

The [REDACTED] laboratory is undertaking the local analytic validation and concordance of the SOPHiA Genetics HRD solution versus the Myriad myChoice CDx assay. The two-phase validation process includes an early access program that was conducted to assess the SOPHiA Genetics assay for initial test performance and laboratory workflow assessment, and a second phase that is aiming to demonstrate concordance of the SOPHiA Genetics HRD solution vs the Myriad MyChoice CDx assay. The pre-MSAC response provided the full validation data.

This process is summarised in Table 12.

Table 12 Summary of validation process

Phase of testing	1: Early Access Program	2: Bridging phase
Number of samples	32	Total of approximately 122 samples, with initial run of 48 samples reported in preliminary report (46/48 included in the <i>BRCA</i> analysis and 31/48 included in the GIS analysis)
Origin of sample	Mixed tumour type samples including high grade serous ovarian carcinoma, squamous cell carcinomas, endometrial carcinomas, prostate carcinomas, thyroid carcinomas provided by SOPHiA Genetics.	High grade serous ovarian carcinoma tumours provided by Avaden BioScience on behalf of AstraZeneca AND a local Australian Clinic.
Previous testing conducted	Myriad pre-tested	Samples pre-tested with Myriad myChoice® CDx PLUS.
Issues impacting samples		Of the first 48 samples, 2 did not meet variant calling criteria and excluded from <i>BRCA</i> analysis and 15 failed QC due to wet lab issues and were excluded from the GIS analysis. The 15 samples which failed QC will be re-analysed.
Results	The assay showed promising performance and lab workflow and analysis fit for purpose. Results will not be included in NATA accreditation.	The analysis showed a 90% agreement (PPA 86%, NPA 94%) for the GIS analysis based on 31 samples showed and a 98% agreement (PPA 100%, NPA 97%) for the <i>BRCA</i> analysis based on 46 samples. Results to be submitted for NATA accreditation.
Timing	The EAP was completed in December 2021.	Phase 2 was scheduled for completion in May/June 2022.

BRCA = breast cancer gene; GIS = Genomic Instability Score; NATA = National Association of Testing Authorities; [REDACTED]

Source: Table 1 of additional correspondence provided by sponsor during evaluation (ADDENDUM response to DoH questions re HRD test validation [REDACTED]_AZ_220310)

The complete validation study results were provided with the pre-MSAC response. It reported the results for genomic instability for the following subgroups: i) all samples (n=115), ii) samples with a Myriad myChoice result (n=81), and iii) ovarian samples with a Myriad myChoice result (n=76). Of 76 ovarian samples with a Myriad myChoice result, 4 samples (5%) were rejected due to low quality assurance status, and a further 10 samples (13%) resulted in an inconclusive SOPHiA genomic instability result. The results of validation study are presented in the figures below. The validation reported stated that the SOPHiA HRD assay failed to achieve the target accuracy of 95% compared with the Myriad myChoice CDx assay.

Figure 5 Error matrix for genomic instability (mixed tumour cohort)

		SOPHIA HRD		
		Positive	Negative	
MyChoice HRD	Positive	TP 28	FN 6	34
	Negative	FP 3	TN 30	33
		31	36	67
PPA=82% (Sensitivity)				
NPA=91% (Specificity)				
PPV=90%				
OPA=87%				

		SOPHIA HRD		
		Positive	Negative	
MyChoice HRD	Positive	TP 34	FN 4	38
	Negative	FP 3	TN 30	33
		37	34	71
PPA=89% (Sensitivity)				
NPA=91% (Specificity)				
PPV=92%				
OPA=90%				

BRCA = breast cancer gene; FN = false negative; FP = false positive; GHRD = homologous recombination deficiency; GIS = Genomic Instability Score; HRR = homologous recombination repair; NPA = negative percent agreement; OPA = overall percentage agreement; PPA = positive percent agreement; TP = true positive; TN = true negative
 Source: Validation Report, p11 (provided with the pre-MSAC response)

a) Confusion Matrix for genomic instability alone, b) Confusion Matrix for GISs combined with HRR mutation status, whereby biallelic loss of function in a canonical HRR gene (*BRCA1* or *BRCA2*) overrides a negative or inconclusive GIS

Figure 6 Validation phase 2 - Error matrix for *BRCA1/2* variant detection (ovarian samples)

		SOPHIA		
		Positive	Negative	
Reference Method	Positive	TP 29	FN 0	29
	Negative	FP 0	TN 60	60
		29	60	89
PPA=100% (Sensitivity)				
NPA=100% (Specificity)				
PPV=100%				
OPA=100%				

BRCA = breast cancer gene; FN = false negative; FP = false positive; NPA = negative percent agreement; OPA = overall percentage agreement; PPA = positive percent agreement; TP = true positive; TN = true negative
 Source: Figure 1, p8 of the Validation Report (provided with the pre-MSAC response). The validation report reported results for ovarian samples with a valid *BRCA1/2* results

Figure 7 Updated validation data for the ovarian samples

		SOPHIA HRD		
		Positive	Negative	
MyChoice HRD	Positive	TP 26	FN 6	32
	Negative	FP 2	TN 28	30
		28	34	62
PPA=81% (Sensitivity)				
NPA=93% (Specificity)				
PPV=93%				
OPA=87%				

		SOPHIA HRD		
		Positive	Negative	
MyChoice HRD	Positive	TP 32	FN 4	36
	Negative	FP 2	TN 28	30
		34	32	66
PPA=89% (Sensitivity)				
NPA=93% (Specificity)				
PPV=94%				
OPA=91%				

BRCA = breast cancer gene; FN = false negative; FP = false positive; GIS = Genomic Instability Score; HRD = homologous recombination deficiency; HRR = homologous recombination repair; NPA = negative percent agreement; OPA = overall percentage agreement; PPA = positive percent agreement; TP = true positive; TN = true negative

Source: Validation Report, p12 (provided with the pre-MSAC response)

a) Confusion Matrix for genomic instability alone, b) Confusion Matrix for GISs combined with HRR mutation status, whereby biallelic loss of function in a canonical HRR gene (*BRCA1* or *BRCA2*) overrides a negative or inconclusive GIS

Additional information provided during the evaluation period reported that the 15 samples being analysed for genomic instability failed QC because of a wet lab issue and there was insufficient coverage of the genome to allow HRD GIS or mutation status assessment. The [REDACTED] advised that a wet lab issue was caused by evaporation from the tube specified in the SOPHiA Standard Operating Procedure which was corrected on the second run by switching to a standard [REDACTED] workflow tube. This issue was considered to be resolved and the 15 samples which failed QC were to be re-analysed as part of the full validation dataset. The [REDACTED] advised that it is not uncommon for such issues to arise during the early phase of assay validation and confirmed that no further changes to the workflow methodology are required.

The ESCs noted the pre-ESC response that the [REDACTED] validation is being repeated using 100 ng input DNA due to the high number of inconclusive results when using 50 ng input DNA (as per manufacturer recommendation). The ESCs noted the pre-ESC response reported the proportion of samples with a $\geq 30\%$ tumour purity as a quality metric for the SOPHiA HRD assay. The ESCs queried whether this meant that some samples will not be suitable for testing or if microdissection is needed to enable testing. The final validation report stated that samples with insufficient tumour cells result in an inconclusive genomic instability call but can also manifest in false negative (FN) calls.

The pre-MSAC response considered the major determinant of the inconclusive result is sample age (particularly samples older than 2 years) and is not necessarily a true indicator of a negative result. The final validation report considered the rate of inconclusive test results observed the validation study (13%, 15/115) not reflective of real-world testing outcomes. The final validation report estimated reported a non-diagnostic rate of about 6% (personal communication with an experienced clinician).

The additional information provided by the sponsor during the evaluation period also stated that although nine *BRCA1* or *BRCA2* variants were detected by the Myriad MyChoice CDx assay in this sample set, the SOPHiA HRD assay detected an additional case because it was in *BRIP1*, an HRR gene that is not present in the Myriad assay. However according to the Myriad myChoice CDx technical specifications, mutations in *BRIP1* should be detectable with the Myriad myChoice CDx assay. The sponsor claimed that, although scored as a false positive, this is not technically true since it was a mutation that was not possible to detect by the Myriad MyChoice CDx assay. As noted above, HRD tests, using different algorithms, will detect different types of genomic

instability including LOH, TAI, and/or LST as well as different *BRCA* gene mutations. As such, it is possible (as demonstrated in this ‘false positive’ case in the validation) that the tests will identify different patients as genomic instability positive depending on the causes of genomic instability and type of *BRCA* mutation.

The submission provided an additional analysis comparing genomic instability of the SOPHiA Genetics assay versus the Myriad myChoice CDx assay for three cohorts (n=225 samples). It was claimed that an analysis that combined the results of these cohorts plus the addition of 31 samples from the validation data resulted in the calculation of a sensitivity of 95% and specificity of 95%. The submission stated that data was provided by SOPHiA Genetics and is confidential. Consequently, this data could not be independently verified (such as via a peer-reviewed publication). The 95% sensitivity and specificity (for HRD only) were used in the base case of the economic evaluation. However, different values were estimated during the evaluation (see Table 13).

Table 13 Error matrix for genomic instability between SOPHiA Genetics HRD assay and Myriad (based on 4 cohorts, including validation)

		myChoice® CDx		
		Detected	Not detected	Total
SOPHiA Genetics	Detected	109	6	115
	Not detected	7	121	128
	Total	116	127	243
Agreement	PPA	93.97% (95%CI 87.96, 97.54)		
	NPA	95.28% (95% CI 90.00, 98.25)		

NPA = negative percent agreement; PPA = positive percent agreement
Source: Table 2.36, p96 of the submission.

Longitudinal accuracy

Four studies were identified by the submission that considered the longitudinal accuracy of the HRD test to predict a response to PARP inhibitor treatment in ovarian cancer. Three studies used Myriad myChoice assays to determine HRD status in patients with newly diagnosed HGEOC or HGSOC status (PAOLA-1, González-Martín 2019, Coleman 2019) and one study used the Foundation One assay to determine HRD status in patients with recurrent HGEOC (Coleman 2017). A summary of the studies is provided in Table 14.

Table 14 Summary of study characteristics of included longitudinal accuracy studies

Study ID	N	Study design	Patient source	Treatment	Line of therapy	Disease severity	Primary outcome
PAOLA-1	806	Randomised, double-blind, placebo-controlled, international phase 3 trial	11 countries	Ola + beva vs pbo + beva	First	Newly diagnosed, high-grade serous or endometrioid ovarian cancer, FIGO stage III or IV	Investigator-assessed disease progression or death
Coleman 2017	564	Randomised, double-blind, placebo-controlled phase 3 trial	87 hospitals and cancer centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, UK, US	Rucaparib vs placebo	Second	Platinum-sensitive, high-grade serous or endometrioid ovarian cancer	Investigator-assessed PFS
Coleman 2019	1140	Randomised, double-blind, placebo-controlled phase 3 trial	202 sites in 10 countries	Veliparib vs placebo	First	Newly diagnosed, high-grade serous or endometrioid ovarian cancer, FIGO stage III or IV	Investigator-assessed PFS in the intervention throughout group compared to control group
González-Martín 2019	733	Randomised, double-blind, placebo-controlled phase 3 trial	20 countries at 181 clinical sites in the US, Canada, Spain, Belgium, Italy, France, Denmark, Germany, UK, Israel, Finland, Switzerland, Ireland, Sweden, Norway, Russia, Ukraine, Czechia, Poland, Hungary	Niraparib vs placebo	First	Newly diagnosed, high-grade serous or endometrioid ovarian cancer, FIGO stage III or IV	PFS in patients with HRD tumours and in the overall population

Abbreviations: Beva = bevacizumab; FIGO = International Federation of Gynaecology and Obstetrics; HRD = homologous recombination deficiency; Ola = olaparib; Pbo = placebo; PFS = progression-free survival; UK = United Kingdom; US = United States

Source: Table 2.48, p114 of the submission

The test and definitions used to determine whether patients were HRD positive varied between the longitudinal accuracy studies, as presented in Table 15.

Table 15 GIS thresholds used in longitudinal accuracy studies

Study ID	HRD test	HRD positive threshold	Rationale
PAOLA-1	Myriad myChoice HRD Plus / myChoice CDx	≥42 and ≥33	Based on Myriad recommended threshold
Coleman 2017	Foundation Medicine T5 NGS assay	≥16%	Based on retrospective analysis of data from ARIEL2 Part 1, which applied a cut-off value of 14% (Coleman 2016)
Coleman 2019	“Myriad myChoice HRD CDx”	≥33	Applying a lower threshold increases the sensitivity of detecting a response to PARP inhibitor
González-Martín 2019	“Myriad myChoice, HRD test”	≥42	Based on Myriad recommended threshold

HRD = homologous recombination deficiency; PARP = poly (ADP-ribose) polymerase
 Source: Table 2.52, p119 of the submission

As a GIS threshold of 42 from Myriad myChoice HRD plus was used in PAOLA-1 in the results relied upon by the submission, it is uncertain whether the results of Coleman 2017, Coleman 2019 or Gonzalez-Martin 2019 would be comparable as they use different HRD positive definitions and/or different HRD tests, though it was noted that PAOLA-1 results using a GIS threshold of 33 (with the Myriad myChoice HRD plus assay) and results for HRD positive and HRD negative subgroups using the Myriad myChoice CDx were also reported. The validation study conducted by ■ did not include any longitudinal results.

Table 16 provides a summary of the longitudinal accuracy studies.

Table 16 Summary of longitudinal accuracy studies ^a

Study ID	HRD+ <i>BRCAM</i>			HRD+ <i>BRCAwT</i>			HRD-		
	PFS, months (95% CI)	HR (95% CI)	p-value	PFS, months (95% CI)	HR (95% CI)	p-value	PFS, months (95% CI)	HR (95% CI)	p-value
Myriad myChoice HRD plus assay									
PAOLA-1 (GIS ≥42) ^b	Intervention	37.2	0.33	28.1	0.43	Not reported	16.6	1.00	Not reported
	Control	17.7	(0.25, 0.45)	16.6	(0.28, 0.66)	reported	16.2	(0.75, 1.35)	reported
PAOLA-1 (GIS ≥33) ^b	Intervention	36.0	0.37	23.2	0.47	Not reported	16.4	1.16	Not reported
	Control	17.0	(0.28, 0.48)	16.5	(0.33, 0.68)	reported	16.5	(0.85, 1.61)	reported
Myriad myChoice CDx assay									
Gonzalez-Martin 2019	Intervention	22.1 (19.3, NE)	0.40	19.6 (13.6, NE)	0.50	0.006	8.1 (5.7, 9.4)	0.68	0.020
	Control	10.9 (8.0, 19.4)	(0.27, 0.62)	8.2 (6.7, 16.8)	(0.31, 0.83)		5.4 (4.0, 7.3)	(0.40, 0.94)	
Foundation Medicine assay									
Coleman 2017 ^c	Intervention ^d	<i>13.6 months</i>	0.32	<i>NR</i>	0.44	<0.0001	<i>NR</i>	0.58	0.0049
	Control	<i>5.4 months</i>	(0.24, 0.42)	<i>NR</i>	(0.29, 0.66)		<i>NR</i>	(0.40, 0.85)	

BRCAM = breast cancer gene mutation; *BRCAwT* = breast cancer gene wild type; HR = hazard ratio; HRD = homologous recombination deficiency; NE = not estimable; NR = not reported; PFS = progression-free survival

^a Details for Coleman 2019 and PAOLA-1 using Myriad myChoice CDx were not presented in the table as results for the HRD+*BRCAwT* and HRD+*BRCAM* subpopulations were not reported.

^b HRD+ *BRCAM* results reflect all HRD positive including *BRCAM* but does not explicitly exclude HRD positive *BRCAwT*.

^c HRD positive status determined by high-LOH above 16%

^d Intervention group received PARP inhibitor throughout (defined as chemotherapy plus PARP inhibitor followed by PARP inhibitor maintenance)

Results in italics indicate values extracted during evaluation as incorrect text was provided in the submission.

Source: Table 2.53, p121 of the submission.

Results for Coleman 2019 and PAOLA-1 using Myriad myChoice CDx were not presented in the table as results for the HRD positive *BRCA*wt and HRD positive *BRCA*m subpopulations were not reported. Instead:

- In Coleman 2019, results comparing treatment with veliparib versus the placebo arm for the HRD positive (PFS HR = 0.58, 95% CI 0.44, 0.76), the HRD negative (PFS HR = 0.81, 95% CI 0.60, 1.09) and the nonmutated *BRCA* (PFS HR = 0.80, 95% CI 0.64, 1.00) subpopulations were provided.; and
- When using Myriad myChoice CDx and a GIS threshold of 42 to define HRD positivity for HRD in PAOLA-1 (as reported in the Myriad myChoice CDx technical document), the PFS HR in HRD positive tumours was 0.35 (95% CI 0.26, 0.48) and in HRD negative tumours it was 1.00 (0.75, 1.34).

PAOLA-1 (using Myriad myChoice HRD plus) reported that patients with HRD positive *BRCA*wt and HRD positive *BRCA*m tumours had improved median PFS with olaparib plus bevacizumab compared to patients receiving placebo plus bevacizumab whereas in patients with HRD negative tumours PFS similar between the treatment arms, indicating that HRD positivity appears to be predictive of a response to olaparib. However, HRD subgroups in PAOLA-1 were considered exploratory and were not included in the statistical analysis plan therefore results should be interpreted with caution.

Results from the other studies however did not necessarily support the conclusion of PAOLA-1. For example, Gonzalez-Martin 2019 (which used a threshold of 42) reported that niraparib was effective in both HRD positive (PFS HR = 0.50, 95% CI 0.31, 0.83) and negative patients (PFS HR = 0.68, 95% CI 0.40, 0.94) though it was marginally more effective in the HRD positive population. Coleman 2017 (HRD positive status determined by high-LOH above 16%, second line study) reported that patients with HRD positive *BRCA*wt tumours (PFS HR = 0.44, 95% CI 0.29, 0.66), HRD positive *BRCA*m tumours (PFS HR = 0.32, 95% CI 0.24, 0.42) and HRD negative tumours (PFS HR = 0.58, 95% CI 0.40, 0.85) were all benefited by rucaparib treatment versus placebo.

Overall, the commentary considered that not all studies supported the claim that HRD positivity was correlated with improved PFS with treatment with PARP inhibitors, with PAOLA-1 (using Myriad myChoice HRD plus classification) reporting the largest difference between HRD positive *BRCA*wt (PFS HR = 0.43) and HRD negative patients (PFS HR = 1.00). Additionally, no evidence on the longitudinal accuracy using OS, which was likely more clinically relevant, was provided. It is noted that OS results were not statistically significantly different between patients treated with olaparib plus bevacizumab compared to bevacizumab monotherapy in PAOLA-1 (OS HR = 0.84, 95% CI 0.46, 1.52) though it is acknowledged that the data is immature.

Prognostic evidence

The submission identified seven ovarian cancer studies that investigated the prognostic impact of HRD, including five RCTs (PAOLA-1, Coleman 2017, Gonzalez-Martin 2019, Mirza 2016, VELIA) and two population-based cohort studies (Hjortkjaer 2019, Lecuelle 2021). Hjortkjaer 2019 and Lecuelle 2021 reported overall survival results by HRR mutation, *BRCA*ness phenotypes and germline *BRCA* status, and the relevance of these subgroups to the requested population (HRD positive *BRCA*wt) was unclear, therefore these results have not been presented here but can be found in Table 2A.6 and 2A.7 of the commentary. The VELIA study appears to be the same as Coleman 2019 reported for the longitudinal study. Table 17 reports the median PFS from five out of the seven prognostic studies.

Table 17 Summary of PFS according to tumour mutation in prognostic studies in patients receiving standard of care

Study ID	Setting	<i>BRCAm</i>	<i>BRCAwt</i>	HRD positive	HRD positive <i>BRCAm</i>	HRD positive <i>BRCAwt</i>	HRD negative
PAOLA-1	First-line	21.7 months/ 18.8 months ^a	16.4 months ^a	17.7 months	Not reported	16.6 months	16.2 months
Coleman 2017	PSR	5.4 months	NR	Not reported	Not reported	5.4 months	5.4 months
González-Martín 2019	First-line	Not reported	NR	Not reported	10.9 months	8.2 months	5.4 months
Mirza 2016	PSR	5.5 months	3.9 months	Not reported	11 months	3.7 months	3.8 months
VELIA	First-line	22.0 months	15.1 months	20.5 months ^b	Not reported	19.8 months	11.5 months

^a Differs depending on whether NGS classification or Myriad myChoice HRD plus assay was used. For *BRCAm*, the Clinical Study Report reported a median PFS of 18.8 months (n=77) and Ray-Coquard 2019 reported a median of 21.7 months (n=80).

^b HRD cohort consisted of all patients in the *BRCAm* cohort plus all patients with HRD tumours

BRCAm = breast cancer gene mutation; *BRCAwt* = breast cancer gene wild type; HRD = homologous recombination deficiency; NGS = next generation sequencing; PFS = progression-free survival; PSR = platinum-sensitive recurrent

Source: Table 2.29, p80 of the submission

The median PFS in *BRCAwt* and *BRCAm* patients differed in PAOLA-1 in the CSR, which reported *BRCA* status using the Myriad myChoice HRD plus assay, with the publication Ray-Coquard 2019, which used one of two NGS testing methods. The commentary considered differences could represent a testing accuracy issue with regards to accuracy for *BRCA* testing and in determining whether or not a patient should be treated with olaparib monotherapy or bevacizumab monotherapy (if they were HRD negative). As the composite HRD/*BRCA* status was only determined by the Myriad myChoice HRD plus assay, the commentary considered that this also did not affect the interpretation of the differences in PFS in the HRD subgroups.

The magnitude of PFS results across studies varied widely. HRD positive *BRCAwt* patients had PFS durations of 3.8 months (Mirza 2016) to 19.8 months (VELIA study), and the studies were also inconsistent in suggesting whether there was a difference in PFS between HRD positive *BRCAwt* and HRD negative patients, with PAOLA-1, Coleman 2017 and Mirza 2016 suggesting no difference but Gonzalez-Martín 2019 and the VELIA study suggesting longer median PFS in HRD positive *BRCAwt* patients compared to HRD negative patients. Ideally, investigation of prognostic validity of the requested biomarker would require demonstration of the prognostic validity of tumours being HRD positive *BRCAwt* vs its complement (HRD positive *BRCAm* plus HRD negative). While no evidence was available specifically for the complement population, the commentary considered that there was evidence to support the prognostic effect of patients with HGEOC having HRD positive *BRCAwt* tumours vs a HRD negative population based on PFS results as demonstrated by González-Martín 2019.

Predictive evidence

The PAOLA-1 trial provides the pivotal clinical data used to support the use of olaparib plus bevacizumab versus placebo plus bevacizumab for the treatment of patients with HGEOC, with PBS listing requested specifically in the subpopulation of patients whose tumours are HRD positive *BRCAwt*. The clinical utility standard for determining HRD and *BRCA* status as per the MSAC Guidelines is the Myriad myChoice HRD plus assay, as was used in PAOLA-1 with a threshold of ≥ 42 determining HRD positivity.

Table 18 PAOLA-1 PFS results for FAS and by retrospectively determined HRD status (DCO1 and DCO2)

	Ola + beva N=537	Pbo + beva N=269	HR for disease progression or death (95% CI)
Data cut-off 1			
FAS			
Median PFS	22.1 months	16.6 months	0.59 (0.49, 0.72)
Events, n/N (%)	280/537 (52.1)	194/269 (72.1)	
HRD positive <i>BRC</i>Awt (subgroup of interest)			
Median PFS	28.1 months	16.6 months	0.43 (0.28, 0.66)
Events, n/N (%)	43/97 (44.3)	40/55 (72.7)	
HRD positive tumours ^a			
Median PFS	37.2 months	17.7 months	0.33 (0.25, 0.45)
Events, n/N (%)	87/255 (34.1)	92/132 (69.7)	
HRD negative tumours			
Median PFS	16.6 months	16.2 months	1.00 (0.75, 1.35)
Events, n/N (%)	145/192 (75.5)	66/85 (77.6)	
Tumour <i>BRC</i>Am			
Median PFS	37.2 months	18.8 months	0.28 (0.19, 0.42)
Events, n/N (%)	44/158 (27.8)	52/77 (67.5)	
Tumour <i>BRC</i>Awt			
Median PFS	18.2 months	16.4 months	0.77 (0.62, 0.96)
Events, n/N (%)	223/346 (64.5)	130/174 (74.7)	
HRD unknown			
Median PFS	NR	NR	0.71 (0.46, 1.10)
Events, n/N (%)	NR/90	NR/52	
Data cut-off 2^b			
All HRD tested population ^c			
Median PFS (95% CI)	23.1 months (22.0, 27.4)	16.7 months (15.8, 18.8)	0.62 (0.51, 0.75)
Events, n/N (%)	276/447 (61.7)	172/217 (79.3)	
HRD positive <i>BRC</i>Awt (subgroup of interest)			
Median PFS	30.0 months	16.6 months	0.44 (0.29, 0.66)
Events, n/N (%)	51/97 (52.6)	45/55 (81.8)	
HRD positive			
Median PFS	42.6 months	17.6 months	0.38 (0.29, 0.50)
Events, n/N (%)	115/255 (45.1)	100/132 (75.8)	

Beva = bevacizumab; *BRC*Am = breast cancer gene mutation; *BRC*Awt = breast cancer gene wild type; FAS = full analysis set; HR = hazard ratio; HRD = homologous recombination deficiency; Ola = olaparib; Pbo = placebo

^a Includes patients with tumour *BRC*Am.

^b Table 2.84, p183 of the submission referred to the source "PAOLA-1 CSR Addendum 1" for DCO2 data. *This reference was incomplete. The PFS DCO2 efficacy results could not be located in the CSR and could not be verified.*

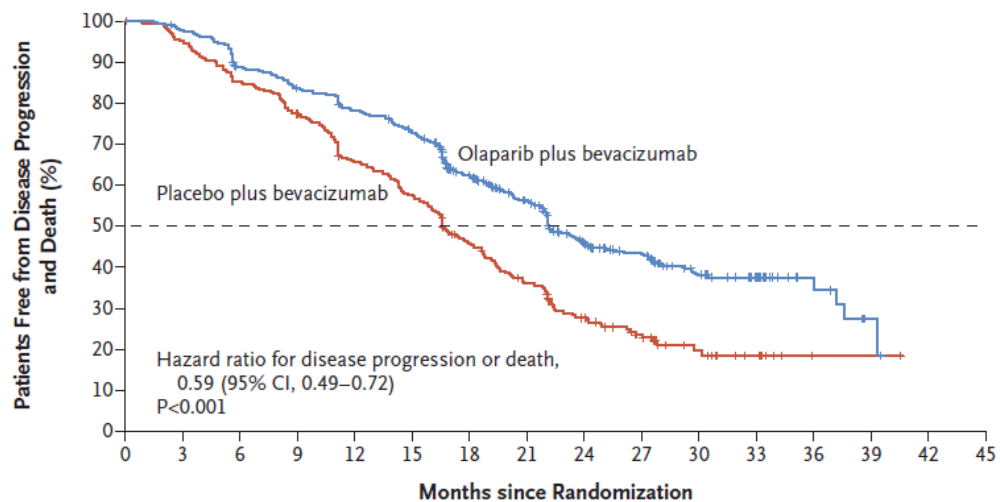
^c All HRD tested patients constituted 82% of the overall PAOLA-1 population.

Text in italics indicate values extracted during evaluation.

Bold text indicates statistically significant differences between treatment groups.

Source: Tables 2.70, 2.83 and 2.84, p162 and 164 of the submission, Table 38, p142 of the CSR, Table 2, p12 1658 ratified PICO.

Figure 8 Kaplan-Meier plots of investigator assessed PFS, FAS (DCO1)



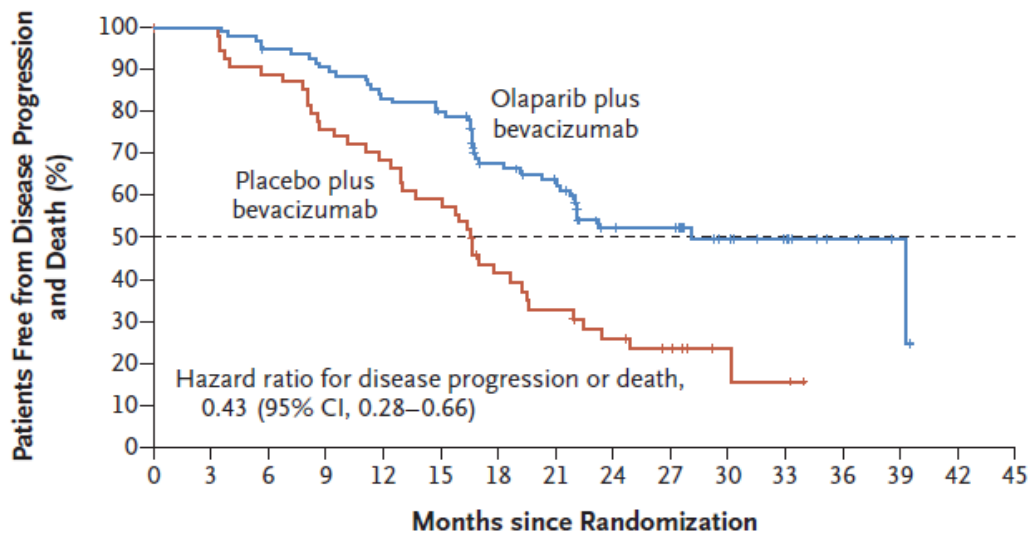
No. at Risk

Olaparib plus bevacizumab	537	513	461	433	403	374	279	240	141	112	55	37	12	3	0
Placebo plus bevacizumab	269	252	226	205	172	151	109	83	50	35	15	9	1	1	0

DCO1 = data cut-off 1; FAS = full analysis set; PFS = progression-free survival

Source: Figure 2.13, p163 of the submission

Figure 9 Kaplan-Meier plots of PFS among patients with HRD positive *BRCAwt* tumours (DCO1)



No. at Risk

Olaparib plus bevacizumab	97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
Placebo plus bevacizumab	55	54	48	41	37	32	19	15	11	8	3	2	0		

BRCAwt = breast cancer gene wild type; DCO1 = data cut-off 1; HRD = homologous recombination deficiency; PFS = progression-free survival

Source: Figure 2.20, p184 of the submission

The commentary noted that differences in the PFS results for the *BRCAwt* and *BRCAm* subgroups were observed when comparing the clinical study report (CSR) (with these results also presented in the submission), which were classified using the Myriad myChoice HRD plus assay, with the Ray-Coquard 2019 publication, which was classified using NGS) (see table below). The commentary requested the sponsor to explain this discrepancy.

Table 19 PFS by BRCA status in PAOLA-1 CSR and Ray-Coquard 2019

Source	Olaparib + bevacizumab		Placebo + bevacizumab		HR for disease progression or death (95% CI)	Total patients classified
	Median PFS	n/N (%)	Median PFS	n/N (%)		
PAOLA-1 CSR (BRCA status by Myriad myChoice)						
BRCAm	37.2 months	44/158 (27.8)	18.8 months	52/77 (67.5)	0.28 (0.19,0.42)	235
BRCAwT	18.2 months	223/346 (64.5)	16.4 months	130/174 (74.7)	0.77 (0.62, 0.96)	520
Ray-Coquard 2019 (BRCA status by NGS)						
BRCAm	37.2 months	41/157 (26)	21.7 months	49/80 (61)	0.31 (0.20, 0.47)	237
BRCAwT	18.9 months	239/380 (63)	16.0 months	145/189 (77)	0.71 (0.58, 0.88)	569

BRCA = breast cancer gene; CI = confidence interval; HR = hazard ratio; NGS = next generation sequencing; PFS = progression-free survival

Source: Table 38, p142 of the CSR, Ray-Coquard 2019

The commentary noted that there were differences in the PFS results by BRCA status depending on whether the Myriad myChoice HRD plus classification was used (as presented in the submission) or if NGS classification was used, as reported by Ray-Coquard 2019. In Ray-Coquard 2019, the PFS HR for BRCAm was 0.31 (95%CI 0.20, 0.47) and for BRCAwT was 0.71 (95%CI 0.58, 0.88). However, the commentary considered that it was unclear whether the difference was clinically significant.

The OS results available for PAOLA-1 were not yet considered mature (37.6% maturity). A summary is shown in the table below along with the OS Kaplan-Meier plots for the FAS and for the HRD positive BRCAwT subgroup, which showed a wide confidence interval with no true separation between the two treatment arms.

Table 20 PAOLA-1 OS according to tumour variant (DCO2) ^a

	Ola + beva	Pbo + beva ^b	HR ^c (95% CI)
FAS			
Median OS	NR	45.8 (43.2, NR)	0.93 (0.74,1.18)
Events, n/N (%)	195/537 (36.3)	108/269 (40.1)	p=0.5631
ITT HRD tested population			
Median OS	NR	45.8 (43.2, NR)	0.91 (0.70,1.19)
Events, n/N (%)	156/447 (34.9)	86/217 (39.6)	p=0.4833
HRD positive BRCAwT			
Median OS	NR	45.8	0.84 (0.46,1.52)
Events, n/N (%)	30/97 (30.9)	19/55 (34.5)	
HRD positive			
Median OS	NR	NR	0.70 (0.47,1.04)
Events, n/N (%)	61/255 (23.9)	42/132 (31.8)	

Beva = bevacizumab; BRCAwT = breast cancer gene wild type; FAS = full analysis set; HR = hazard ratio; HRD = homologous recombination deficiency; NR = not reached; Ola = olaparib; Pbo = placebo

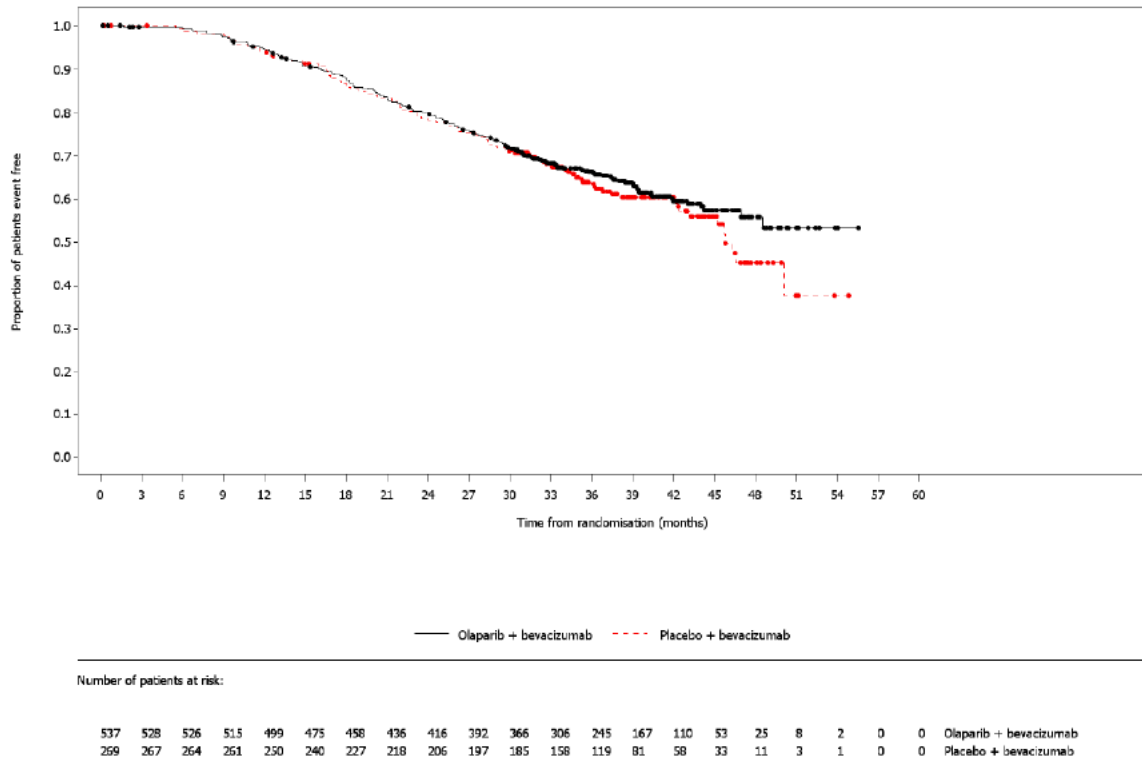
^a Table 2.90, p191 of the submission referred to the source "PAOLA-1 CSR Addendum 1". This reference was incomplete. The subgroup results for OS provided in the submission could not be located in the Clinical Study Report and could not be verified for the commentary.

^b It was unclear how median OS could have been reached in the bevacizumab plus placebo arm already given that fewer than 50% of patients have died, and the reported median OS in the bevacizumab plus placebo arm was likely unreliable.

^c estimated from a stratified Cox Proportional Hazards model stratified by first-line treatment outcome and tumour BRCA status

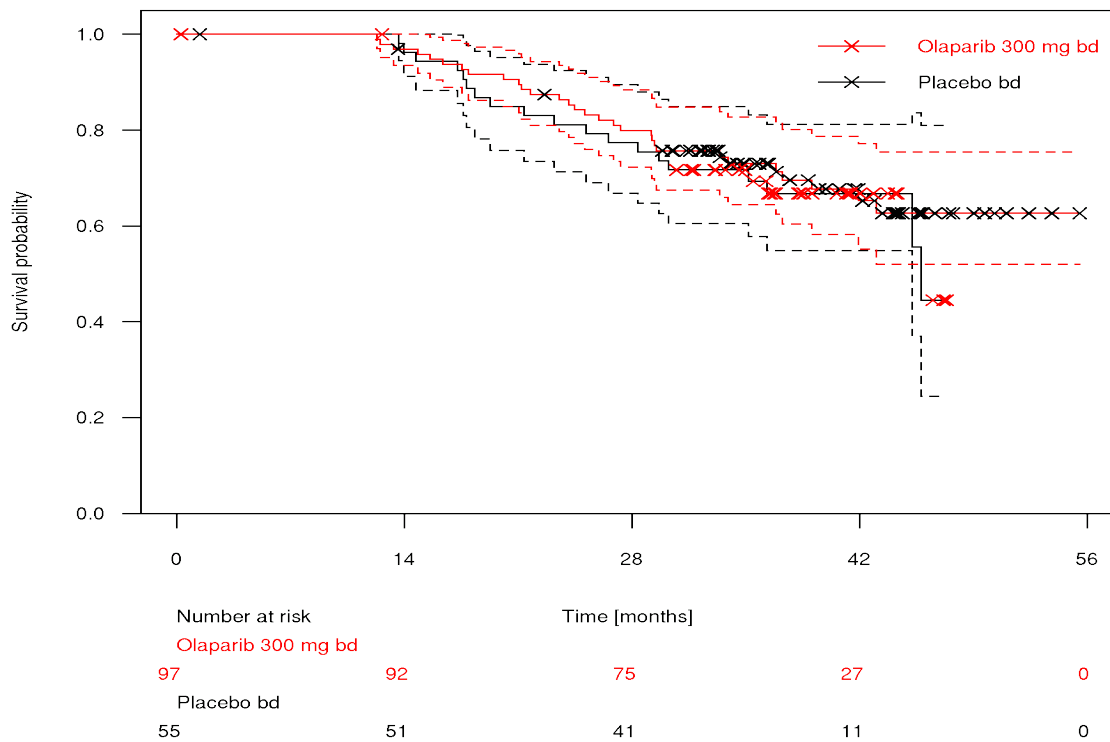
Source: Tables 2.73 and 2.90, p167 and 191 of the submission

Figure 10 PAOLA-1 overall survival Kaplan-Meier plots, FAS (DCO2)



DCO2 = data cut-off 2; FAS = full analysis set
 Source: Figure 2.16, p167 of the submission

Figure 11 PAOLA-1 overall survival Kaplan-Meier plots for patients with HRD positive BRCAwt tumours with confidence intervals



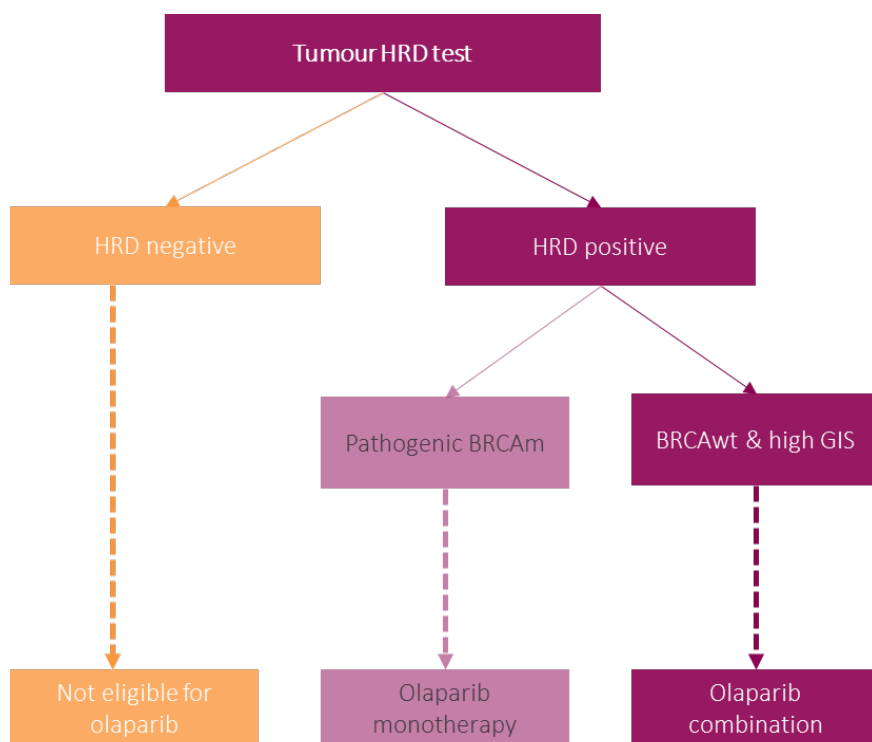
Source: Attachment_Section 3.2, OS_HRD+BRCAwt_parametric report_DCO2, Section 2.1.1

Change in management in practice

The submission requested that at diagnosis, patients with HGEOC receive a HRD tumour test to determine HRD status based on pathogenic breast cancer gene mutation (*BRCAM*) (i.e. germline or somatic class IV or V) and/or GI. As shown in the figure below, their subsequent treatment depends on the outcome of this test:

- HRD positive based on positive GIS or GII and the absence of pathogenic *BRCAM* (i.e., *BRCAwT*): patient is eligible for maintenance olaparib in combination with bevacizumab following response to first-line platinum-based chemotherapy;
- HRD positive according to a pathogenic *BRCAM* only: patient is eligible for maintenance olaparib monotherapy following response to first-line platinum-based chemotherapy; or
- HRD negative: patient is not eligible for olaparib, however, may receive maintenance bevacizumab as per current standard of care.

Figure 12 Tumour HRD testing to determine patient eligibility for olaparib combination therapy



BRCAM = breast cancer gene mutation; *BRCAwT* = breast cancer gene wild type; GIS = Genomic Instability Score; HRD = homologous recombination deficiency

Note: GIS is a measure of genomic instability

Figure 2.1, p16 of the submission

The submission claimed that the cross-sectional studies show that all components of HRD testing (including *BRCAM* status and GIS) are highly concordant compared to other NGS-based assays thereby demonstrating that HRD testing will continue to identify pathogenic *BRCAM* status at the same rate as other NGS-based assays in addition to identifying HRD positive *BRCAwT* patients who would also benefit from a PARP inhibitor.

While the cross-sectional accuracy studies generally reported a high level of concordance between the Myriad myChoice assays and the NGS or Foundation Medicine assay, it was not perfect and false positive or false negative *BRCA* and HRD results will have implications for patients. In some circumstances this would lead to patients receiving incorrect treatment

resulting in additional cost and a higher rate of AEs or receiving a treatment for which the efficacy was unknown, or patients receiving incorrect treatment resulting in a treatment benefit foregone.

Claim of codependence

The commentary noted that while the codependency between HRD status and PARP inhibitors has not previously been accepted by MSAC and PBAC, they have both accepted that variation in the size of the treatment effect of more than one PARP inhibitor is predicted by *BRCA1/2* status as one HRD biomarker. This application raises a related codependency issue for MSAC and PBAC consideration: whether variation in the size of the treatment effect of the combination of olaparib and bevacizumab is predicted by the proposed combination of *BRCA1/2* status and genomic instability and, if so, whether this is sufficiently differentiated from the predictive value of *BRCA1/2* status alone or by the predictive value of genomic instability alone.

While the submission did not explicitly state that there is a biological plausibility for the use of PARP inhibitors for the treatment of HRD positive tumours the submission appears to make the underlying claim that, when using the combined HRD test, genomic instability positive status has greater predictive value than *BRCA* status, because olaparib plus bevacizumab therapy has effectiveness in patients with genomic instability positive *BRCAwt* tumours that is similar to effectiveness in *BRCAm* patients. However, based on the results of Gonzalez-Martin 2019 (niraparib) and Coleman 2017 (rucaparib), a class effect in ovarian cancer is not strongly supported. However, results for the HRD positive *BRCAm*, HRD positive *BRCAwt* and HRD negative subpopulations all indicate that PARP inhibitor use resulted in improved PFS, although the magnitude of benefit varied. The ESCs noted it is unclear to what extent the variation in pivotal trial results for PARP inhibitors (olaparib, niraparib and rucaparib) may be explained by differences in patient populations (due to different HRD testing protocols or thresholds), as compared with pharmacologic differences between the individual PARP inhibitors.

13. Economic evaluation

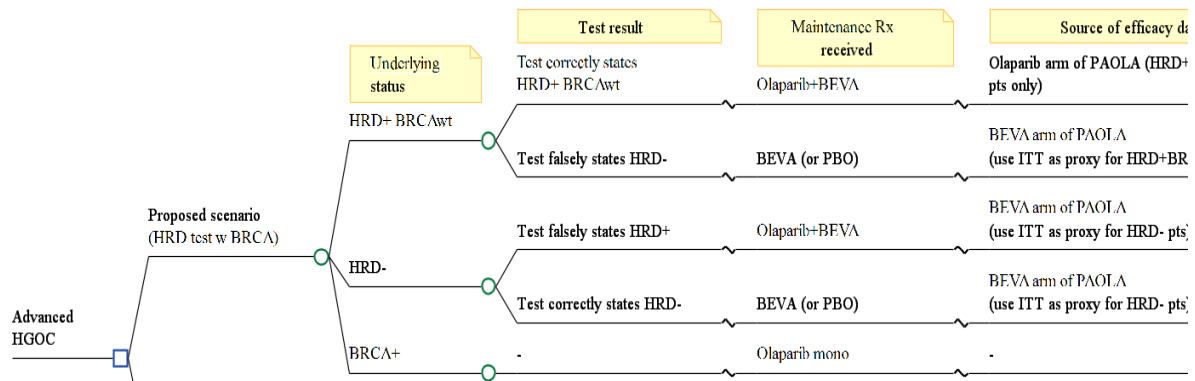
The submission presented a modelled economic evaluation, based on subgroup results from PAOLA-1, a direct randomised trial comparing olaparib plus bevacizumab versus bevacizumab monotherapy in the first-line maintenance treatment of patients with platinum-sensitive high grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

The basis of the economic evaluation was a cost effectiveness analysis (CEA). The economic model compared the proposed scenario where all patients undergo HRD testing versus the comparator/current scenario where patients receive *BRCA* testing only.

The model used a partitioned survival analysis with a base case time horizon of 20 years. Parametric mixture cure models were fitted directly to PFS data from PAOLA-1 to estimate the cure fraction and to model PFS for uncured patients (the complement to the cure fraction). Cured patients were assumed to have the same life expectancy as the general Australian population with mortality based on Australia life tables while OS data from PAOLA-1 was used to inform mortality in uncured patients. Observed OS Kaplan-Meier data was used up to the follow-up duration (up to 38 months) after which a parametric extrapolation of PAOLA-1 data was used.

The model structure presented in the submission was comprised of a testing phase, relating to the determination of patient tumour HRD and *BRCA* status, and a maintenance treatment phase, as shown below. A total of seven patient groups depending on HRD and *BRCA* status as well as treatments received were considered.

Figure 13 Structure of testing component of the model



Note: HRD unknown are assumed to be combined with HRD negative.
 Source: Figure 3.1, p217 of the submission

The submission (p221) reported that advice from the MSAC/PASC meeting requested that additional HRD/BRCA testing populations be considered, as shown in the table below.

Table 21 Patient populations requested by PASC

Population	Population details
PASC population 1	HRD testing (<i>BRCA</i> and genomic instability in parallel) occurs upfront at diagnosis of advanced HGEOC.
PASC population 2	Tumour <i>BRCA</i> testing occurs upfront at diagnosis of advanced HGEOC. Patients returning a negative <i>BRCA</i> result will then be tested for genomic instability status.
PASC population 3	It is assumed that only patients receiving bevacizumab treatment with first-line platinum-based chemotherapy are eligible for HRD testing. These patients are tested to identify genomic instability status. Patients who have not been determined to receive bevacizumab as part of initial first-line platinum-based chemotherapy will be tested for tumour <i>BRCA</i> . (Referred to as PASC population 3a in the submission).

Population 1 was the base case presented by the submission. The submission presented scenarios for the populations requested by PASC and for one additional population (labelled “Population 3b”) that investigated the scenario in which all patients undergo *BRCA* testing at diagnosis. Immediate subsequent HRD testing is restricted to *BRCA*wt patients who received bevacizumab with their platinum-based chemotherapy.

Sensitivity and specificity in the economic model were assumed to be 100% for the *BRCA* test and 95% for the HRD test. The commentary considered that this may not be reasonable. No diagnostic accuracy studies comparing the proposed HRD test (the SOPHiA assay) with NGS for *BRCA* testing were presented.

The base case ICERs for the trial-based analysis and the modelled analysis are presented below.

Table 22 Results of the economic evaluation

Component	Olaparib + bevacizumab (proposed scenario)	Bevacizumab (current scenario)	Increment
Trial-based ICER (38 months)			
Discounted cost		\$17,271	
Progression-free years gained	2.29	1.64	0.65
Incremental cost per progression-free year gained			
Modelled cost per QALY versus bevacizumab (20 years)			
Discounted costs	\$55,216	\$32,046	\$23,170
Discounted LYG	4.10	3.59	0.52
Discounted QALYs	2.80	2.34	0.46
Incremental cost per LY gained			\$ ¹
Incremental cost per QALY gained			\$¹

ICER = incremental cost-effectiveness ratio; LY = life year, QALY = quality-adjusted life year

^a based on PFS results from HRD positive *BRC*Awt in PAOLA-1

^b based on PFS results from ITT population in PAOLA-1

^c The submission did not include any medicine or management costs or outcomes for patients who were *BRC*Am and treated with olaparib monotherapy. As such, the absolute costs, LYG and QALY in each scenario were not reflective of the entire cohort. However the incremental results and resultant ICER is accurate.

Source: Tables 3.33, 3.34 and 3.35, p273-274 of the submission

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

The submission stated that as per the MSAC Guidelines, the codependent technology (test treatment) model should consider the costs/outcomes for all subgroups of patients, however this was not the case for the P5 and C1 subgroups (scenarios where patients have *BRC*Am) in which no false results were considered.

Moreover, the submission claimed that as *BRC*Am patients in both scenarios will have the same treatment cost and outcome, they were not modelled and the only cost considered was the incremental cost of testing. While it was accurate that the P5 and C1 branches will effectively cancel each other out in the model (as stated by the submission) when incremental differences are calculated, the omission of all other costs and efficacy in the *BRC*Am subgroup led to incorrect reporting of aggregate results for each scenario and therefore this approach may be inappropriate. Instead, a comparison of subgroups P1 (patients who are HRD positive *BRC*Awt, correctly identified) and C2 (comparator scenario, *BRC*Awt) may be considered relevant as these would be patients who would benefit from the proposed listing. This is presented in the table below.

Table 23 Results of the economic evaluation when comparing sub-populations P1 and C2

Component	Olaparib+bevacizumab	Bevacizumab	Increment
Modelled cost per QALY versus bevacizumab (20 years)			
Discounted costs	\$ ¹	\$42,391	\$ ¹
Undiscounted LYG	9.675	5.935	3.74
Discounted LYG	7.00	4.80	2.19
Discounted QALYs	5.10	3.13	1.96
Incremental cost per LY gained			\$ ¹
Incremental cost per QALY gained			\$¹

LY = life year, QALY = quality-adjusted life year

Source: Constructed during evaluation

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

Results of the key univariate sensitivity analyses are summarised in the table below.

Table 24 Results of key sensitivity analyses versus bevacizumab (PASC population 1, P1)

Variable or assumption	Incremental costs	Incremental effectiveness (QALYs)	ICER versus bevacizumab	% change from base case
Base case	\$23,170	0.4616	\$¹	NA
<i>Prevalence of HRD+ (base case = 50%)</i>				
<i>40%, 25.3% BRCAm</i>	\$	0.2747	\$ ²	+12.55%
<i>60%, 25.3% BRCAm</i>	\$	0.6485	\$ ¹	-5.23%
<i>Sensitivity and specificity (base case 95% sensitivity and 95% specificity)</i>				
<i>Lowest estimate of diagnostic accuracy (86% for sensitivity and 94% for specificity)</i>	\$	0.4191	\$ ¹	+2.91%
<i>Highest estimate of diagnostic accuracy (98.5% for sensitivity and 97.4% for specificity)</i>	\$	0.4781	\$ ¹	-3.96%
<i>BRCA test cost \$1,000 (base case = \$1,200)</i>	\$	0.4616	\$ ¹	+1.08%
<i>BRCA and HRD test costs = 0 (base case: BRCA = \$1,200; HRD = \$2,500)</i>	\$	0.4616	\$ ¹	-7.01%
<i>ESCs re-specified base case: Assume Weibull extrapolation for bevacizumab monotherapy PFS, time horizon 15 years and using progressed disease utility from PAOLA-1 (0.720) and BRCA testing \$1,000</i>	\$	0.2434	\$ ³	+93.91%
<i>ESCs SA 1: Assume Weibull extrapolation for bevacizumab monotherapy PFS, time horizon 15 years and using progressed disease utility from PAOLA-1 (0.720) and BRCA testing \$1,000, and test being uninformative (sensitivity for GI component = 100%, specificity = 0%)</i>	\$	0.2556	\$ ⁴	+355.39%
<i>ESCs SA 2: Assume Weibull extrapolation for bevacizumab monotherapy PFS, time horizon 15 years and using progressed disease utility from PAOLA-1 (0.720) and BRCA testing \$1,000, and test not used (sensitivity for GI component = 100%, specificity = 0% and remove HRD testing cost)</i>	\$	0.2556	\$ ⁴	+331.04%
<i>ESCs SA 3: Assume Weibull extrapolation for bevacizumab monotherapy PFS, time horizon 15 years and using progressed disease utility from PAOLA-1 (0.720) and BRCA testing \$1,000, test not used (sensitivity for GI component = 100%, specificity = 0% and remove HRD testing cost) and 25.45% cure fraction for olaparib plus bevacizumab</i>	\$	0.1483	\$	+649.8%

BRCA = breast cancer gene; HRD = homologous recombination deficiency; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

Text in italics indicates information determined during evaluation using Economic Evaluation.xls.

Source: Table 3.39, p280 of the submission

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$95,000 to < \$115,000

⁴ \$155,000 to < \$255,000

Based on the sensitivity analyses conducted by the submission and during the evaluation, the model was most sensitive to changes in the cure fraction (both for olaparib plus bevacizumab and bevacizumab monotherapy as well as the incremental difference), extrapolation function (which directly affects the cure fraction), utility values for the progressed disease health state, proportion of patients who were HRD positive *BRC*Awt and time horizon.

The following issues relating to modelling the olaparib effectiveness may have resulted in the ICER being underestimated:

- The assumptions behind the extrapolations (i.e. that the same function must be applied to both treatments, ignoring statistical fit) and the cure fractions estimated in the base case for olaparib plus bevacizumab and bevacizumab monotherapy) may not be justified and strongly favoured olaparib plus bevacizumab.
- The utility for the progressed disease health state calculated by the submission (0.544) which was based on an average of several publications was likely inappropriate. The utility value based on post-progression patients in PAOLA-1 (0.720) was likely a more appropriate source to inform the utility of the progressed disease health state in the model.
- A time horizon of 20 years was nominated although the PBAC has previously noted that 20 years may be too long for the non-*BRC*Am population in the consideration of niraparib for the maintenance treatment of patients with FIGO Stage III-IV high grade epithelial ovarian cancer who are in response to platinum-based chemotherapy (paragraph 7.15, p43, niraparib PSD, July 2021 PBAC Meeting).
- Despite PAOLA-1 not reporting any OS difference in the subgroup of HRD positive *BRC*Awt patients (OS HR = 0.84, 0.46, 1.52), the economic model assumed an OS difference between patients treated with olaparib plus bevacizumab and patients treated with bevacizumab monotherapy, with an absolute increase of 3.74 years.
- The inclusion of an adjustment factor of 0.96 for branches P3, P4 and C2 may not be justified,
- The omission of any consideration for the cost and consequences of failed or inconclusive tests (e.g. cost of retesting, re-sampling, and/or risk of using suboptimal treatment) was not considered in the economic evaluation, which likely favoured olaparib.

Using more conservative and likely more reasonable inputs (15-year time horizon, assume Weibull extrapolation for bevacizumab monotherapy PFS extrapolation, using post-progression utility from PAOLA-1, and changing *BRCA* testing cost to \$1,000 to reflect proposed MSAC change) increased the ICER by 94%, from a base case of \$45,000 to < \$55,000/QALY to \$95,000 to < \$115,000/QALY. The ESCs agreed this ICER could be a revised base case. The ESCs agreed with the commentary that this ICER could be considered optimistic, as the cure fraction for olaparib plus bevacizumab was still assumed to be 38%, around one and a half times that of the assumed cure fraction for olaparib monotherapy in *BRC*Am patients in July 2020.

As the submission stated that placebo (watch and wait) might be the comparator in around 10% of patients, the results from a supplementary analysis (using PFS and OS hazard ratios from the GOG-218 and ICON7 trials that compared bevacizumab versus placebo), were also provided by applying a reverse hazard ratio to the bevacizumab arm in the model to estimate efficacy in placebo. The ICER assuming a comparator of 90% bevacizumab and 10% placebo was \$50,758.

The ICERs for alternative *BRCA* and HRD testing populations proposed by PASC (see Table 21), assuming a *BRCA* testing fee of \$1,000 (see table below) resulted in small changes to the base case (i.e. population 1) ICER (+0.4% to +1.9%). The (additional) HRD testing cost per additional patient treated was also estimated and presented in the table below.

Table 25 Sensitivity analyses for each population requested by PASC (assume \$1,000 per BRCA test)

	PASC population 1 (base case)	PASC population 2	PASC population 3a	PASC population 3b
Incremental QALYs	0.4616	0.4616	0.4154	0.4154
Incremental costs	\$	\$	\$	\$
ICER	\$ ¹	\$ ¹	\$ ¹	\$ ¹
% change from base case	NA	+2.0%	-0.4%	+1.6%
Average HRD testing cost per patient responding to platinum chemotherapy ± beva ^a	\$3,125	\$3,834	\$2,886	\$3,524
Proportion of patients treated with ola + beva	26.0%	26.0%	23.4%	23.4%
Proportion of true positive patients treated	23.5%	23.5%	21.1%	21.1%
HRD testing cost per patient treated	\$12,035	\$14,767	\$12,350	\$15,082
HRD testing cost per true positive patient treated	\$13,318	\$16,341	\$13,666	\$16,689
Additional testing cost per patient ^a	\$1,875	\$2,584	\$1,636	\$2,274
Additional testing cost per patient treated	\$7,221	\$9,953	\$7,001	\$9,733
Additional testing cost per true positive patient treated	\$7,991	\$11,014	\$7,747	\$10,770

Beva = bevacizumab; HRD = homologous recombination deficiency; ICER = incremental cost-effectiveness ratio; NA = not applicable; ola = olaparib; QALY = quality-adjusted life year

^a Cost per patient for both HRD and BRCA test estimated as test fee multiplied by 1.25 to account for only 80% of patients respond to first line platinum chemotherapy with or without bevacizumab.

Source: Table 3.38, p279 of the submission (Economic Evaluation.xls, [ICER Results tab] and [Testing costs tab])

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

The submission did not propose the PBS listing of olaparib in all patients with HGEOC (i.e. both HRD positive and negative), which would have allowed the elimination of HRD testing. The commentary noted that reason for this was not explicitly stated in the submission, and advised that it was not possible to conduct a sensitivity analysis investigating this scenario without extensively changing the model, as it would require the use of Kaplan-Meier data for the ITT population whereas the model only investigated the subpopulation of interest.

14. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the number of patients who would be eligible for the proposed HRD test, likely uptake of the test and the estimated number of patients with HRD positive BRCAwt tumours. Patients then need to be treated with and have a response to first-line platinum-based chemotherapy to be eligible for olaparib plus bevacizumab maintenance treatment.

The submission (p306) stated that the cost of relevant MBS items was used as in the MBS schedule and included the cost of BRCA testing of \$1,200. As the MSAC have previously stated that the cost of BRCA testing should be reduced to \$1,000, financial estimates assuming an MBS fee of \$1,000 for BRCA testing was included during the evaluation. The commentary noted that both the proposed HRD test (MBS fee \$2,500) and BRCA test (MBS fee \$1,200/\$1,000) exceed the threshold for the greatest permissible gap (GPG) as of 1 November 2021, meaning that the fee rebated will be MBS item fee minus \$87.90. The financial estimates have been updated to reflect the GPG rebate.

Table 26 Estimated number of patients accessing HRD testing and with HRD positive *BRCA*w status over six years (using mean number of doses in PAOLA-1)

	2023	2024	2025	2026	2027	2028
Incidence ovarian cancer	1,733	1,765	1,798	1,831	1,865	1,900
Proportion tested positive for <i>BRC</i> Am ^a	283	288	293	299	304	310
Proportion tested positive for HRD+ <i>BRCA</i> w	283	288	293	299	304	310
Total patients treated with olaparib + bevacizumab	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of HRD and <i>BRCA</i> tests to the MBS						
Total test numbers	1,131	1,152	1,174	1,195	1,218	1,240
Cost of testing HRD test to MBS	\$2,728,664	\$2,779,281	\$2,830,836	\$2,883,348	\$2,936,835	\$2,991,313
Net cost of testing <i>BRCA</i> test to MBS	-\$1,258,052	-\$1,281,389	-\$1,305,159	-\$1,329,369	-\$1,354,029	-\$1,379,146
Net cost of tests to MBS	\$1,470,612	\$1,497,892	\$1,525,678	\$1,553,979	\$1,582,805	\$1,612,166
Net bevacizumab administration cost	\$14,035	\$44,305	\$45,127	\$45,964	\$46,817	\$47,686
Cost of replacing <i>BRCA</i> test in <i>BRC</i> Am patients ^b	\$424,125	\$432,000	\$440,250	\$448,125	\$456,750	\$465,000
Net financial implications						
Net cost to PBS	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost to MBS	\$1,484,647	\$1,542,197	\$1,570,805	\$1,599,944	\$1,629,623	\$1,659,852
Total net MBS costs (\$1,000 <i>BRCA</i> test)	\$1,710,895	\$1,772,642	\$1,805,525	\$1,839,017	\$1,873,131	\$1,907,878
Net cost health budget	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost health budget (\$1,000 <i>BRCA</i> test)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²

^a Based on submission's assumption of 50% HRD positive and 25% HRD positive *BRCA* wild type

^b Assumed 25% of all patients tested would be *BRC*Am, and multiplied by incremental cost of \$1,500 per test

Source: Table 4.4 and 4.6, p292, 295 of the submission, Olaparib (PAOLA1) UCM_final.xlsx

The redacted values correspond to the following ranges:

¹ < 500

² \$10 million to < \$20 million

³ \$20 million to < \$30 million

Between March 2021 to February 2022, there were 788 services for *BRCA* testing to determine eligibility for olaparib monotherapy (MBS item 73301) and 2,815 services for germline *BRCA* testing (MBS item 73296). It is possible that patients with ovarian cancer who would have been billed under the MBS Item 73296 may switch to the proposed HRD testing.

Further, there were several issues with the MBS usage estimated in the submission:

- The submission's estimates for MBS usage were inconsistent with the estimates for PBS usage. For the estimation of MBS item numbers, the submission inappropriately assumed only 14.3 and 13.1 bevacizumab injections per patient when used with olaparib and as monotherapy, respectively, whereas the PBS estimates assumed 15.93 and 15.35 doses, respectively. Similarly, for grandfathered patients, 7.97 doses were assumed in the PBS estimates but 7.15 was assumed for the MBS usage. For consistency, all the MBS usage per patient have been updated to reflect the PBS usage.

- There was a further error in the estimation of MBS usage, as the number of grandfathered patients was doubled that of PBS usage.
- The submission’s MBS financial estimates workbook continued to assume only ‘continuing’ rather than ‘incident’ patients were treated with bevacizumab when used with olaparib, and changing the toggle to ‘incident’ in sheet 3a did not resolve the issue with the MBS sheet.
- The submission’s assumed uptake rate of olaparib plus bevacizumab (65%) in year one was lower than the proportion who were assumed to stop using bevacizumab monotherapy (80%) which was implausible and led to fewer bevacizumab infusions in year one resulting in greater cost offsets.
- It was assumed that there will be 15.35 fewer bevacizumab administrations for each grandfathered patient, when grandfathered patients receive only 7.97 bevacizumab administrations during year 1.

As such, several changes were made to the financial spreadsheet and the financial estimates presented in Table 26 differed to the submission’s estimates.

During the evaluation, sensitivity analyses around the financial estimates using the different testing scenarios proposed by PASC were conducted. The results are summarised below:

Table 27 Sensitivity analyses around financial impact assuming different testing scenarios assuming \$1,000 BRCA test fee

	2023	2024	2025	2026	2027	2028
Base case (no BRCA test, all patient use HRD test)						
Net cost to MBS	\$1,710,895	\$1,772,642	\$1,805,525	\$1,839,017	\$1,873,131	\$1,907,878
Net cost to PBS/RPBS	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Net cost health budget	\$█ ¹	\$█ ¹	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Scenario 2 (All BRCA test, BRCAwt tested for HRD)^a						
Net cost to MBS	\$2,060,533	\$2,128,766	\$2,168,255	\$2,208,476	\$2,249,443	\$2,291,170
Net cost to PBS/RPBS	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Net cost health budget	\$█ ¹	\$█ ¹	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Scenario 3a (only pt using beva with chemo [90%] test for HRD, others BRCA test)^b						
Net cost to MBS	\$1,548,300	\$1,607,366	\$1,637,182	\$1,667,552	\$1,698,485	\$1,729,992
Net cost to PBS/RPBS	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Net cost health budget	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Scenario 3b (All pt tested with BRCA, only BRCAwt pt using beva with chemo [90%] test for HRD)^b						
Net cost to MBS	\$1,862,974	\$1,927,877	\$1,963,639	\$2,000,065	\$2,037,166	\$2,074,955
Net cost to PBS/RPBS	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹
Net cost health budget	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹

^a Results in same number of treated patients as in base case. Incremental BRCA admin cost is same as base case, no offset from BRCA testing.

^b Results in 10% fewer patients than in base case, therefore incremental BRCA admin cost is lower, and PBS cost lower

The redacted values correspond to the following ranges:

¹ \$10 million to < \$20 million

² \$20 million to < \$30 million

Overall, Scenario 3a had the lowest MBS costs (around 9.0% lower than base case) and the lowest overall costs due to having 10% fewer patients treated compared to the base case. Scenario 2 represented the highest MBS costs (around 20% higher than base case).

15. Other relevant information

The ESCs considered that there were substantial implementation issues to ensure that only clinically validated HRD tests are used and reimbursed to determine eligibility for olaparib and bevacizumab therapy.

The Greatest Permissible Gap is currently set at \$87.90, which means that *BRCA* testing (and HRD testing if implemented) will attract a benefit that is greater than 85% of the MBS fee so that patients do not incur a gap fee greater than \$87.90. As the cost of *BRCA* testing has decreased such that 85% of the MBS fee may be sufficient to cover the test with no out of pocket payments (e.g. private laboratories are listing a fee of \$400 for non-Medicare rebated *BRCA* tests)⁷. Therefore patients may incur out-of-pocket costs for HRD testing that they would not incur for *BRCA* testing alone. Patients may incur further out-of-pocket costs for HRD testing if pathology providers charge a fee higher than the proposed fee of \$2,500 as this would not be covered by the Greatest Permissible Gap.

The potentially high out of pocket costs could also lead to potential equity issues.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The available study results showed that proposed test's assessment of genomic instability (SOPHiA HRD test, genomic instability index) was not fully concordant with the clinical utility standard (Myriad MyChoice Genomic Instability Score [GIS]). The available results suggest the SOPHiA HRD test would identify a slightly different patient cohort as having genomic instability. MSAC may wish to consider the implications of the discordant results. The interpretation of the results is affected by a high risk of bias, incomplete results, limited reporting of study methods, sample sources and patient characteristics, use of HRD tests other than the clinical utility standard, and high rates of inconclusive test results.
- HRD is a broad concept that includes testing for pathogenic genetic variants (such as *BRCA* and others), assessment of genomic signatures and instability, and functional assessment. The submission focussed on genomic instability. There are different scoring methods and algorithms for assessing genomic instability that identify different but potentially overlapping populations.
- The ESCs considered parallel testing of *BRCA* status and genomic instability as preferable as this is simpler, uses less tissue, produces faster test results, and avoids testing at multiple sites. However, there is a potential for lower testing costs where the addition of genomic instability testing to *BRCA* testing is limited to those patients treated with bevacizumab and chemotherapy before starting maintenance therapy with olaparib.
- The SOPHiA HRD test also tests for other genes involved in the HRD pathway. Clinical guidelines recommend germline testing for some genes. MBS items for germline and cascade testing involving these additional genes may be required but have not been considered in the submission.

⁷ <https://www.sonicgenetics.com.au/our-tests/all-tests/breast-and-ovarian-cancer-germline/> Accessed 17 April 2022

Economic issues:

- The economic evaluation did not consider the impact of test failures and is also affected by uncertainty in the comparative analytical performance of the SOPHiA HRD test against the clinical utility standard test.
- Uncertainty in the treatment phase of the economic model has greater implications than the testing phase of the model. The respecified base case that changed parameters in the treatment phase substantially increased the ICER.

Other relevant information:

- It is important that only validated HRD tests with sufficient level of concordance with the clinical utility standard are funded on the MBS for the intended codependent purpose. Further advice with stakeholders may be needed to achieve this.

ESCs discussion

The ESCs noted that the integrated codependent submission sought Medicare Benefits Schedule (MBS) listing of homologous recombination deficiency (HRD) testing of tumour tissue to establish genomic instability (GI) and breast cancer gene (*BRCA*) status to determine eligibility for olaparib in combination with bevacizumab on the Pharmaceutical Benefits Scheme (PBS) for the treatment of newly diagnosed advanced high grade epithelial ovarian cancer (HGEOC).

HRD occurs where cells cannot effectively repair double-strand breaks in DNA using the homologous recombination repair (HRR) pathway. The ESCs noted that this could occur due to pathogenic genetic alterations (germline or somatic) or epigenetic alterations of genes involved in the HRR pathway. HRD can be assessed by different methods. This includes testing for pathogenic genetic variants that result in a loss of function of the HRR pathway (such as *BRCA1/2* and other genes), functional assessment, or by assessing genomic signatures such as chromosomal instability and other genomic instability. The focus of the submission was HRD status as defined by genomic instability. The ESCs noted that unlike detection of gene variants, there are different scoring methods and algorithms for assessing genomic instability. The ESCs considered that these different tests identify different but potentially overlapping populations. The ESCs noted the biological rationale that impairment of the HRR pathway can sensitise tumours to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors such as olaparib and platinum-based chemotherapy.

The ESCs noted that the proposed test, the SOPHiA HRD assay, is a next generation sequencing (NGS) based test. The ESCs noted that this appeared to be different test to that considered by PASC at its April 2021 and August 2021 considerations of the application. The SOPHiA HRD assay assesses tumour samples for *BRCA1/2* variants and pathogenic variants in several other HRR genes, while also estimating genomic instability via a Genomic Integrity Index (GII). The ESCs noted that low-pass whole genome sequencing (lpWGS) data is processed by a deep-learning analytical algorithm capable of quantifying genomic integrity to produce the GII. The proposed GII threshold for HRD-positivity in Australia is a score greater than zero. The codependent submission sought to demonstrate that the SOPHiA HRD assay's GII (using a threshold of >0) identified the same group of patients for as the clinical utility standard – the Myriad myChoice HRD Plus test's Genomic Instability Score (GIS, using a threshold of ≥ 42). The submission claimed that treatment with olaparib and bevacizumab as maintenance therapy following a response to platinum-based chemotherapy and bevacizumab is superior to standard of care (represented by maintenance therapy with placebo + bevacizumab) in terms of efficacy and non-inferior in terms of safety with manageable adverse events for the treatment of HGEOC patients who test HRD positive *BRCA* wild type (wt).

The ESCs noted that the GII component of the test is a 'black box' and there is limited information about the genomic signature being assessed. The Myriad myChoice HRD tests assess GIS based on loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST). The ESCs noted that the Myriad GIS threshold of 42 was developed to have 95% sensitivity for *BRCA* pathogenic variants. However, the PAOLA-1 trial suggests that this test threshold may also identify a larger group of *BRCA* ovarian tumours as having genomic instability.

The ESCs noted the submission sought to amend MBS item 73301 for *BRCA* testing of ovarian tumour tissue to add genomic instability testing in parallel with *BRCA* testing. The ESCs noted that parallel testing requires less tumour tissue and would have a faster turnaround time than sequential testing.

The ESCs considered that a single test that uses less tumour tissue would be beneficial for consumers. The ESCs considered that consumers should be informed of the 'black box' nature of the test. The ESCs considered this lack of transparency could be problematic for consumers. The ESCs considered that consumers should be informed that the proposed test does not necessarily produce the same result as the clinical utility standard. The ESCs considered that it was important that consumers were informed that some patients would be incorrectly classified and the implications of this as a part of the informed consent process. The ESCs noted that some patients who have non-*BRCA* somatic HRR gene variants would not be eligible for treatment. The ESCs considered that consumers should receive genetic counselling.

The ESCs noted that clinical guidelines recommend germline testing for some non-*BRCA* HRR genes identified in tumour tissue which are not covered by MBS item 73296: *BRIP1*, *RAD51C*, and *RAD51D*. The ESCs noted that guidance for germline testing of other pathogenic variants are dependent on other factors such as the specific variant detected, the age of the patient at cancer diagnosis and their family history. The ESCs therefore queried whether specific HRD-relevant genes should be identified in the proposed item descriptor and whether germline and cascade testing items would need to be created if pathogenic variants were detected and reported for these genes in tumour tissue.

The ESCs noted the MBS fee of \$2,500 included in the submission for the proposed test. The ESCs considered the fee was not fully justified. The ESCs considered that it was difficult to benchmark the test cost with that of similar tests as the SOPHiA HRD test includes lpWGS. The ESCs noted the fee is lower than MBS fees for whole exome/genome sequencing (\$2,100 to \$2,900) and substantially lower than the Myriad MyChoice (US\$4,040). The ESCs considered a breakdown of the costs of the proposed test (such as sequencing, quality control, bioinformatics, consumables) may be informative. The ESCs considered the fee might be reasonable due to the complexity of the test, including reviewing samples for purity, tumour area, and bioinformatics. The ESCs considered that patients could incur out-of-pocket costs if pathology providers charge fees higher than the MBS rebate.

The ESCs also supported modifying item 73301 to determine eligibility for PARP inhibitors rather than olaparib alone, consistent with the April 2022 advice of the MSAC Executive to accommodate PBAC's recommendation for the PBS listing of niraparib with reference to *BRCA* status. The ESCs considered that a technology agnostic item descriptor would be appropriate. The ESCs queried whether the other HRR genes tested should be included in the item descriptor.

The ESCs suggested the amended MBS item descriptor could refer to a 'clinically validated' test, but considered that there are several, complex implementation issues for testing genomic instability as part of HRD testing. The ESCs considered that it was important that genomic instability tests are clinically validated as HRD tests identify different (potentially overlapping) populations and so the MBS should only fund HRD tests with sufficient level of concordance with the clinical utility standard for the intended codependent purpose. The ESCs noted that other

pathology providers were also developing HRD tests. The ESCs noted advice from National Pathology Accreditation Advisory Council (NPAAC) that validation of clinical utility is a major issue. NPAAC advised that the concordance of HRD assays is unclear and there is no external quality assurance program which is a prerequisite to MBS listing. NPAAC advised that a sample exchange program would need to be developed for the purpose of external quality assurance. To increase confidence that such clinical validation would ensure that any other test option would identify similar patients as the clinical utility standard, the ESCs recommended that the PBS restriction include a criterion that ensures that such test options have been validated against the clinical utility standard including its GIS threshold of ≥ 42 .

The ESCs supported the Department's advice that the criteria for HRD/genomic instability positivity should be stated in the PBS restriction (rather than the MBS item descriptor) as the threshold for positivity is a criterion for the eligibility for the medicine and not an eligibility criterion for the test. The ESCs considered the threshold for test positivity should be clear for the validation of any HRD test used to perform the proposed 73301 MBS service. The ESCs noted that the policy and implementation issues for HRD testing may apply to other types of cancer as the predictive evidence for HRD positivity may emerge for other cancer types.

The ESCs noted that the majority of consultation feedback was received during the PASC considerations and responses were not specific to the SOPHiA HRD test which was not included in the original application form. The ESCs noted feedback from the Royal College of Pathologists of Australasia (RCPA) that an MBS item should not be funded for a test that is not clearly defined and is not currently widely available in Australia. The ESCs considered it may be beneficial to seek further advice from RCPA and NPAAC on how to ensure that only clinically validated tests are used and reimbursed on the MBS.

The ESCs noted that the SOPHiA HRD assay was currently being validated by the [REDACTED] ([REDACTED]). The pre-ESC response advised that accreditation by the National Association of Testing Authorities (NATA) and subsequent Therapeutic Goods Administration (TGA) notification is expected to occur by September (Q3) 2022. The ESCs agreed with the pre-ESC response that the [REDACTED] may be able to meet national demand for HRD testing as it already performs over [REDACTED] % of tumour *BRCA1/2* testing in Australia. However, the ESCs considered that if HRD testing was performed by a single pathology provider, this would not facilitate a competitive environment that was beneficial for consumers by reducing the risks of being charged out-of-pocket payments.

The ESCs noted that the [REDACTED] validation study was the key evidence to support the submission's claim that genomic instability as assessed by the SOPHiA HRD assay's GII (using a threshold of >0) identified the same group of patients for as the clinical utility standard using a GIS threshold of ≥ 42 . The ESCs noted that the full results of the [REDACTED] validation study were delayed and were expected by the applicant to be included in the pre-MSAC response.

The ESCs noted that the pre-ESC response stated that high quality tissue is needed. The ESCs noted that PAOLA-1 study had a test failure rate of 17.6%. The rates of test failure were higher in the [REDACTED] validation study. The ESCs considered that this could be due to use in the research setting where testing is performed using leftover samples. The pre-ESC response considered that 10% of patients will, in clinical practice, require subsequent testing due to an inconclusive HRD result. The ESCs noted the pre-ESC response that the [REDACTED] validation is being repeated using 100 ng input DNA due to the high number of inconclusive results when using 50 ng input DNA (as per manufacturer recommendation). The ESCs noted the pre-ESC response reported the proportion of samples with a $\geq 30\%$ tumour purity as a quality metric for the SOPHiA HRD assay. The ESCs queried whether this meant that some samples would not be suitable for testing or if microdissection would be needed to enable testing.

The [REDACTED] validation study assessed the comparative analytical performance of the SOPHiA HRD test and the Myriad MyChoice CDx test. The ESCs noted that there were multiple Myriad MyChoice HRD tests that the submission referred to as the clinical utility standard. The ESCs noted that the various exploratory subgroup analyses from the PAOLA-1 trial using the Myriad MyChoice CDx test compared with the Myriad MyChoice HRD Plus test presented in the commentary showed only small differences in progression-free survival (PFS) outcomes as the basis for supporting that the Myriad MyChoice CDx test also had predictive value. The ESCs therefore accepted the applicant's arguments that it is reasonable to consider either the Myriad MyChoice HRD test and the Myriad MyChoice CDx test as the clinical utility standard.

The ESCs noted that the available results from the [REDACTED] validation study showed that the SOPHiA HRD test GII was not fully concordant with the Myriad MyChoice GIS score and would identify a somewhat different patient cohort as having genomic instability. The ESCs considered that MSAC would need to consider the implications of this discordance. The ESCs considered the false negative results may have greater clinical consequence as patients may forego an effective treatment.

The ESCs considered the risk of bias in the [REDACTED] validation study to be high as there was likely selection bias in the source of samples and prior HRD testing. The ESCs considered that there was limited information about the source of the samples in the study or the characteristics of patients who provided the samples. The ESCs considered that it was unclear how many of the 92 unique samples contributed to the 'Myriad tested' samples (n=72) and the 'HRD tested' samples (n=88). The ESCs noted the updated results reported 86% agreement (PPA 83%, NPA 91%) for genomic instability based on 51 samples. The ESCs noted that some of the updated analyses included comparisons that had undergone 'proxy' assessments of HRD positivity (rather than the Myriad MyChoice CDx test). These included:

- Whole genome sequencing with algorithmic measurement by HRDETECT2 and CHORD3 (\pm assessment of carboplatin sensitivity)
- Comprehensive genomic profiling for mutational evidence for (or against) HRR. This was defined as canonical activating *RAS/RAF* variants or high tumour mutation burden and non-ovarian/breast/prostate/sarcoma histology considered strong evidence against HRR. For ovarian samples, canonical activating *RAS* variants with low grade histology was considered strong evidence against HRR.

The ESCs considered that there was no information provided on the validity of the proxy but noted that the pre-ESC response considered this study to reflect strong evidence.

The ESCs noted that the [REDACTED] evidence comparing the analytical performance of *BRCA* testing in the Sophia HRD test was limited to a comparison with *BRCA* testing by the Myriad MyChoice CDx test rather than also [REDACTED]'s NGS-based *BRCA* testing.

The ESCs considered that PAOLA-1 trial supported that genomic instability using the Myriad MyChoice GIS threshold of ≥ 42 was predictive of variation in response (progression-free survival) to olaparib with bevacizumab. The ESCs considered that the predictive value appeared to be smaller for patients with *BRC*Awt HRD-positive tumours (based on genomic instability) than patients with *BRC*Am tumours. The ESCs considered that the studies presented in the submission consistently showed a numerical interaction between response to PARP inhibitors and HRD-positivity. The ESCs noted that some other studies of PARP inhibitors showed evidence of treatment benefit for HRD-negative patients which appears to be smaller than for patients with HRD-positive tumours. However, the ESCs noted that in many of the trials, including PAOLA-1, the analysis of outcomes by HRD status based on genomic instability status other than *BRCA* status was not prespecified. The ESCs also noted that updated overall survival results from PAOLA-1 are

expected but considered that the trial may be underpowered to detect differences in overall survival.

The ESCs noted the economic model presented a cost-utility analysis where patients undergo testing and treatment phases. The ESCs considered a key limitation of the economic model in the testing phase for MSAC consideration was the uncertainty in the comparative analytical performance between the SOPHiA HRD assay and clinical utility standard. The economic model assessed three testing populations requested by PASC. The ESCs noted that some of the sequential testing scenarios had higher testing costs than parallel testing. The ESCs considered that this, in combination with other benefits (less tumour tissue, faster result) supported parallel testing. The ESCs noted the economic model had not considered test failure. The ESCs considered the full data should also present clinical and economic analysis, with inconclusive results and negative results classified together. The ESCs considered the scenario analysis where testing was uninformative (all *BRCA*wt patients receive olaparib + bevacizumab) and test costs were removed provided support for the codependency from an economic perspective if MSAC and PBAC accept that the codependency has been sufficiently demonstrated. The ESCs considered the treatment phase of the economic model had several limitations. The ESCs considered a respecified base-case with a 15-year time horizon, Weibull extrapolation for bevacizumab monotherapy PFS, post-progression utility values from PAOLA-1, and revised *BRCA* testing costs resulted in an incremental cost-effectiveness ratio of \$95,000 to < \$115,000. The ESCs considered that the ICER could still be underestimated due to the inability to respecify further to account for the high cure fraction, test failures and the uncertain comparative analytical performance of the SOPHiA HRD assay against the clinical utility standard test.

The ESCs noted that the financial estimates also modelled the different testing scenarios with the base case (parallel testing) being less costly than two of the three sequential testing scenarios. The ESCs noted that the testing costs accounted for a larger proportion of net costs than is typical for most codependent submissions due to the relatively high cost of genetic testing.

17. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)