

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1658.1 – Testing of tumour tissue to determine a positive homologous recombination deficiency 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 Ltd

Date of MSAC consideration: 30-31 March 2023

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

1. Purpose of application

This was a resubmission by AstraZeneca Pty Ltd for the test component of the integrated codependent application considered at the July 2022 MSAC meeting that 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

MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item to test tumour tissue for genomic instability (GI) to determine homologous recombination deficiency (HRD) status (including *BRCA1/2* status) to define eligibility for treatment with a poly-ADP ribose polymerase (PARP) inhibitor for patients with advanced (FIGO stage III-IV), high grade serous or other non-mucinous high grade ovarian, fallopian tube or primary peritoneal carcinoma. MSAC considered that HRD and GI as biomarkers can predict benefit of treatment with PARP inhibitors, although some concerns (raised in Application 1658) remain. In particular there remains a need to standardise and harmonise test thresholds across different test methods. However, for this patient population with significant unmet need, MSAC considered the presence of GI, as defined in the key trial using the Myriad MyChoice® HRD assay with score of 42 or greater as the threshold for positivity, predicted a treatment benefit with olaparib in combination with bevacizumab. MSAC supported public funding for HRD tests that report an assessment of GI that has been validated against the Myriad MyChoice® HRD assay. MSAC advised that the threshold for GI positivity was defined as being at or above a threshold equivalent to 42 of the Myriad MyChoice® assay as used in the PAOLA trial. MSAC advised that treatment with olaparib in

combination with bevacizumab for eligible patients whose tumours are GI positive resulted in superior clinical effectiveness compared with the current standard of care. MSAC considered that generalising the MBS item for HRD testing to be for access to PBS-listed PARP inhibitors rather than olaparib alone was appropriate and would future-proof the listing. MSAC advised that review of the MBS item will be required once HRD testing is more widely available. MSAC considered that the testing was cost-effective, and that the financial cost to the MBS was modest and acceptable. MSAC noted that HRD test accreditation requirements must be met before the MBS item can be implemented.

Table 1 MSAC’s supported MBS item descriptor

Category 6 – Pathology Services Group P7 - Genetics
MBS item XXXXX
<p>A test of tumour tissue from a patient with advanced (FIGO III–IV), high-grade serous or other high-grade ovarian, fallopian tube or primary peritoneal carcinoma, requested by a specialist or consultant physician, to determine eligibility with respect to homologous recombination deficiency (HRD) status, including <i>BRCA1/2</i> status, for access to PARP inhibitor therapy under the Pharmaceutical Benefits Scheme (PBS).</p> <p>Evidence of homologous recombination deficiency (genomic instability) must be derived through a test that has been validated against the Myriad MyChoice® HRD assay.</p> <p>Applicable once per primary tumour diagnosis. Not applicable to a service to which 73295 or 73301 applies.</p> <p>Fee: \$3,000.00 Benefit: 75% = \$2,250.00 85% = \$2,906.80</p>
<p>Practice note: validation against the Myriad MyChoice® HRD assay should use a score of 42 or greater as the threshold for HRD (genomic instability) positivity.</p>

85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of \$93.20. All out-of-hospital Medicare services that have an MBS fee of \$621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Consumer summary

This was 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 ovarian, fallopian tube or primary peritoneal cancer. The test would determine whether the person was eligible for a medicine called olaparib in combination with another medicine called bevacizumab as maintenance therapy, funded on the Pharmaceutical Benefits Scheme (PBS). This was a codependent application with the Pharmaceutical Benefits Advisory Committee. This is the second time this application was considered by MSAC.

A genetic variant is a permanent difference in a gene's DNA sequence. A genetic variant can be inherited (called a germline variant) if it is present in a person's egg or sperm, and becomes incorporated into the DNA of cells throughout the body of their children, or it can 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 (if germline), or a variant of clinical significance (if somatic).

Mistakes in the DNA sequence are common when the genome is copied as part of normal cell division. Repair mechanisms fix these mistakes. Both somatic and germline variants can mean part or all of a person's body is unable to properly repair these mistakes in the DNA. One type of repair problem is called homologous recombination deficiency, or HRD. HRD is often caused by a variant in the genes *BRCA1* or *BRCA2*, but can also be caused by variants in other genes that make other proteins that normally work to repair certain types of error. 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. HRD tests look for variants in the genes involved in HRD, and also look at other parts of the genome for more errors than usual (called a genomic scar or genomic instability), which would suggest replication errors are not being repaired as well as usual.

HRD-positive cancers may be more easily killed by certain cancer drugs. For the cancer types proposed in this application, people with HRD-positive cancer are more likely to respond to treatment with olaparib than people who have HRD-negative cancer.

Olaparib comes from a family of medications called PARP inhibitors. Olaparib is already available on the PBS for people whose cancer has a variant in *BRCA1* or *BRCA2* (*BRCAm*). Another application also considered at this meeting proposed funding niraparib (another PARP inhibitor) for HRD-positive patients. MSAC supported HRD testing for both applications, and advised that the MBS item for HRD testing should be for access to PBS-listed PARP inhibitors in general (i.e., also including any future PARP inhibitors).

There are now at least two different HRD tests undergoing accreditation for use in Australia. MSAC noted that this process has not been completed and so a new MBS item will not be listed until at least one test is accredited for use.

MSAC noted that, when it previously considered HRD testing for olaparib in July 2022, there was no accepted definition of HRD, beyond having a cancer that is *BRCAm*. MSAC noted that broader understanding of HRD and HRD testing are still in development, and our understanding of HRD is likely to improve in future. Given some uncertainty around HRD testing remains, MSAC requested that this MBS item be reviewed in future.

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

MSAC supported funding of HRD testing to detect HRD status in patients for access to PARP inhibitors, including olaparib. MSAC considered that this group of patients has high clinical need for access to treatments. MSAC advised that although HRD is not fully understood, international guidelines suggest HRD testing is appropriate and there is clear benefit to patients from access to the treatment. MSAC considered that the test was safe, effective and cost-effective, and that testing would come at an acceptable financial cost to the MBS.

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

MSAC noted that this codependent application from Astra Zeneca was a resubmission for MBS listing for the detection of positive homologous recombination deficiency (HRD) status in tumour tissue testing in patients with newly diagnosed, advanced (FIGO Stage III–IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, for access to olaparib plus bevacizumab on the Pharmaceutical Benefits Scheme (PBS).

MSAC noted the similarity between this application and [Application 1726](#) (considered at this same meeting), which was for the detection of positive HRD status in tumour tissue testing in patients with newly diagnosed, advanced (FIGO Stage III–IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, for access to niraparib on the PBS. Olaparib and niraparib are both poly (ADP-ribose) polymerase inhibitors (PARPi).

MSAC noted that the 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 patients found to be positive for genomic instability (GI) without a pathogenic *BRCA1* or *BRCA2* variant (HRD-positive *BRCA* wild type [*BRCAwt*]).

MSAC recalled that it had not supported funding for Application 1658 in July 2022 due to the uncertainty around HRD testing. MSAC had 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.”*¹ MSAC requested the resubmission provide a:

- definition of HRD that can be applied confidently in clinical practice
- 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
- 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 GI positive)
- preferred method of reporting HRD results, and specify whether the results of underlying genetic variants (beyond *BRCA* status) will be included in reports and how interpretation will be considered in the light of discordance (e.g. *BRCAwt* but HRD positive)
- justification for the proposed fee, with separate justifications for the assay and algorithm components of the fee.

MSAC noted that following Pharmaceutical Benefits Advisory Committee (PBAC) advice from its July 2022 meeting an early re-entry resubmission to list olaparib for use in combination with bevacizumab for maintenance therapy in patients with newly diagnosed HRD positive *BRCA* wild type advanced epithelial ovarian, fallopian tube or primary peritoneal cancer was considered by PBAC at its November 2022 meeting. MSAC noted that PBAC deferred its decision but was of a mind to recommend olaparib pending MSAC consideration of HRD testing.

¹ MSAC application 1658 PSD – available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1658-public>

MSAC noted that patients with high-grade serous/endometrioid/other non-mucinous ovarian, fallopian tube or primary peritoneal carcinoma usually presented with advanced disease and had poor outcomes (median 5-year survival rates of 15–55%). More specifically, high-grade ovarian carcinoma (especially serous) shows defects in homologous recombination repair (HRR) genes, which includes *BRCA1/2* variants or genomic instability (GI). Treatment with PARPi targets vulnerable tumour cells that are unable to repair double-stranded DNA breaks, leading to cancer cell death. MSAC noted that >80% of cases present as advanced disease, with a recurrence rate of 65% after initial cytoreductive platinum-based chemotherapy and surgical debulking.

MSAC noted that the Royal College of Pathologists of Australasia (RCPA) did not support the application. However, MSAC also noted the high levels of support from clinicians for access to HRD testing. MSAC advised that treatments for this group of patients comprised an area of unmet clinical need, as patients face poor outcomes and a lack of treatment options. MSAC noted that three HRD experts had provided their input on HRD and HRD testing.

MSAC noted that the *BRCA1/2* genes are large genes, and considered it appropriate that the fees associated with analysing larger genes would be higher than for smaller genes. MSAC noted another key issue for consumers was out-of-pocket costs and uncertainty related to test availability for MBS implementation. MSAC considered that HRD testing is a complex test. MSAC noted the proposed fee of \$2,500, and considered that a fee of less than \$2,500 was likely to lead to out-of-pocket costs. MSAC considered the Myriad MyChoice® Plus HRD overseas test cost of approximately AU\$REDACTED was likely overestimated. MSAC noted the pre-MSAC response stated that a fee of \$3,000 had minimal impact on the incremental cost-effectiveness ratios (ICERs) and presented an economic analysis showing an ICER of \$55,000 to < \$75,000 (for 95% sensitivity, 95% specificity, and 0% failed/inconclusive tests). MSAC requested further input from the RCPA on the appropriate fee. Following receipt of this input, MSAC considered (out-of-session) that a fee of \$3,000 would be appropriate given the cost to conduct HRD testing, and that testing would be acceptably cost-effective at a fee of \$3,000.

MSAC noted and agreed with the PICO and the clinical management algorithm presented in the submission. MSAC agreed with ESC that the proposed testing should be performed early in the clinical management algorithm, to better manage the patient and make best use of previous tumour tissue samples.

MSAC noted the proposed MBS item descriptor was specific to olaparib but that it also supported application 1726 at this meeting. MSAC considered that generalising the MBS item for HRD testing to be for access to PBS-listed PARP inhibitors rather than olaparib alone was appropriate and would future-proof the listing. This decision reflected the similar nature of Application 1726 for another PARPi, niraparib, for the same patient population. MSAC considered that “pathogenic or likely pathogenic” was terminology specific to germline genetic variants, and advised the wording should be altered to unambiguously also encompass somatic variants. MSAC also advised that the descriptor wording should be changed from “cancer” to “carcinoma” as this is the correct terminology.

MSAC noted ESC had proposed this test be restricted from co-claiming with existing MBS items 73295 and 73301. MSAC considered this was reasonable, as those items provide testing of *BRCA1/2*, which is a component of HRD testing. MSAC advised the co-claiming restriction should be added to the item descriptor, and also that the item descriptor should indicate that *BRCA1/2* status is part of HRD status.

MSAC noted that, in this resubmission, the comparator was not defined but assumed to be the same as in the original submission (*BRCA1/2* testing alone [MBS item 73301]), which MSAC considered to be appropriate.

MSAC noted that, currently, there is no uniformly accepted “gold standard” HRD test or threshold to determine HRD, or threshold to determine which patients would benefit from PARPi. MSAC noted the HRD assays considered across the 1658.1 and 1726 applications were the Myriad MyChoice® CDx, Illumina TSO 500 HRD and SOPHiA DDM™ HRD Solution. MSAC noted that the Myriad MyChoice® assay was unlikely to become available in Australia. MSAC considered that the different brands of test have different scoring systems and thresholds for defining HRD positivity, and advised that the definition of “positive” should be the validated cut-off for that specific test (e.g. threshold of ≥ 42 for the Myriad MyChoice HRD CDx assay as used in the PAOLA-1 trial). MSAC noted that the Illumina assay requires a minimum 2 mm³ tissue from a biopsy or FFPE sample, but considered fresh tissue is not routinely collected and sample requirements may vary between brands of HRD assay so the appropriate sample type was an appropriately fixed specimen with sufficient tumour material. MSAC considered that while not current practice, it is likely that there will be a move to collection of fresh tissue at diagnosis. MSAC noted that the REDACTED was in the process of validating the SOPHiA assay, a next-generation sequencing (NGS) based low-pass whole genome sequencing assay, on tumour samples to generate a Genomic Integrity Index, that examines variants in genes encoding components of the HRR pathway (including *BRCA1/2*) and genomic scarring (rather than on the combination of LOH, telomeric allelic imbalance and large-scale state transitions as per the Myriad test). The National Association of Testing Authorities (NATA) and the Therapeutic Goods Administration (TGA) had initiated the assessment of the SOPHiA assay, and the REDACTED was awaiting next steps regarding validation as an in-house in vitro diagnostic (IVD) assay. MSAC considered that there was therefore no assay with direct trial evidence (clinical utility standard), such as Myriad’s MyChoice® CDx, available in Australia to test HRD status.

MSAC noted that NATA accreditation of HRD testing was underway but not yet completed. In this case, as Class 3 in-house *in vitro* diagnostic devices the laboratory is required to be accredited by NATA for this individual test followed by notification to the Therapeutic Goods Administration (TGA) through its in-house notification process. MSAC noted NATA’s role is to accredit laboratories based on compliance with specific International Organization for Standardization (ISO) standards and ensure that they meet the validation requirements specified in the National Pathology Accreditation Advisory Council’s standard for in-house IVDs.

MSAC queried whether it could support public funding of an assay that has not yet met regulatory requirements in Australia. MSAC noted that tests that laboratories have not received test-specific NATA accreditation for are ineligible for MBS reimbursement. MSAC noted that one of the aims of the PBAC-MSAC codependent pathway is to enable coordinated MBS and PBS listings. MSAC noted Departmental advice that MSAC can support public funding for HRD testing, however the Department will not implement the MBS item for HRD testing until a NATA-accredited laboratory test is available. MSAC recalled it had previously supported public funding before accreditation was in place for extended *RAS* testing in colorectal carcinoma (MSAC application 1363²), and in this situation the laboratory includes a disclaimer on the test results that the test is not NATA-accredited so is ineligible for Medicare funding. MSAC considered that many laboratories will have a scope of practice that includes similar complex genomic testing.

MSAC noted that the work of the Friends of Cancer Research Harmonization Project was aiming to harmonise HRD testing and definitions. Although this was not a clinical trial, MSAC agreed that it would provide valuable advice regarding HRD testing in the future. MSAC noted that the project had faced delays, and that interim findings had been published as a poster³. MSAC considered it was not necessary to wait until publication of the final findings, as there were people who could

² MSAC application 1363 PSD available at - <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1363-public>

³ Stires et al., 2022. Available at: <https://friendsofcancerresearch.org/wp-content/uploads/AMP-Poster-FINAL.pdf>

benefit from accessing treatment now in terms of delaying recurrence and prolonging survival. MSAC agreed with ESC that the Harmonization Project's findings could be used to eventually evaluate the different HRD assays that become available.

MSAC noted that the resubmission did not present any updated safety data. MSAC considered that the implications of false positive and false negative test results were important, as there were implications for treatment eligibility and a risk of adverse events from medicines with uncertain treatment benefits. However, MSAC considered the assay itself had no safety issues. MSAC assumed that the risk-benefit profile of tumour extraction would be properly assessed and managed by radiologists, surgeons, oncologists and pathologists.

Regarding clinical effectiveness, MSAC noted updated data from PAOLA-1 (data cut-off 3 [DCO3] data, sourced from slides of a presentation to the European Society of Medical Oncology in 2022) showed a statistically significant benefit in overall survival (OS) in the intention-to-treat population in the presence of substantial crossover. MSAC noted that the updated DCO3 data from the PAOLA-1 clinical trial supported previous findings – that trends in treatment effect for the *BRCAm* and HRD subgroup are generally consistent between the PFS results (previously considered by the Pharmaceutical Benefits Advisory Committee [PBAC] and MSAC) and the updated OS results. MSAC noted that, for HRD-positive patients and patients who harbour a homologous recombination repair mutation (HRRm) in a non-*BRCA* gene from the Pujade-Lauraine (2021) study:

- non-*BRCA* HRRm, in contrast to HRD (GI), was not predictive of PFS benefit regardless of the HRR gene panel used in the PAOLA-1 study
- non-*BRCA* HRR gene panels captured a small proportion of patients with newly diagnosed high-grade ovarian cancer (3.7–9.8%) compared with GI excluding *BRCAm* (19%).

MSAC also noted the applicant's definition of HRD-positive status – either tumour *BRCAm* or a GIS greater than a predefined threshold (≥ 42 for the Myriad MyChoice® HRD plus and Myriad MyChoice® CDx). This definition was consistent with the definitions used to define subgroups in PAOLA-1, which was the primary evidence base for the application. However, MSAC also noted that:

- thresholds to define GI may vary for different brands of HRD tests, but MSAC considered that the thresholds may be valid if validated against the GIS cut off of 42 or greater as in the Myriad MyChoice® test for defining HRD positivity.
- concordance for Myriad and SOPHiA for HRR + genomic instability score (GIS) was 91%, but also that pre-analytical and analytical variables might explain some of the non-concordance of different test methods as accurate testing relied on high tumour purity and DNA quality
- the usefulness of the assay relied on sequencing depth and the genomic analysis pipeline.

MSAC considered that, beyond *BRCAm*, non-*BRCA* HRRm and HRD (GI) are not interchangeable and should not be considered as substitutes for each other in clinical practice for determining eligibility for first-line maintenance in ovarian cancer. MSAC advised the PBAC that eligibility for olaparib should be for patients whose tumours are HRD (genomic instability) positive, defined by a test with a threshold that has been validated against the Myriad MyChoice® HRD assay and the associated GI score of 42 or greater to define HRD (GI) positivity.

MSAC noted that the economic evaluation and financial impact did not change from the original submission. MSAC agreed with ESC that the test's placement in the clinical management algorithm affected the MBS costs, but already considered that it was more practical to perform

the HRD testing first, as the quality and age of the tissue deteriorates with time. MSAC also considered the population to be relatively small (1,131 per year).

MSAC recalled that the ICERs were sensitive to the prevalence of HRD-positive results, but this also varied depending on the assay and GIS thresholds used. MSAC noted the pre-ESC response that provided new agreement data on the GIS of the SOPHiA HRD test versus the MyChoice® test, showing that there would be a negligible change to the ICER (increasing to between \$55,000 to < \$75,000) when the positive percent agreement and negative percent agreement are based on the updated meta-analysis of 5 cohorts. MSAC also noted that the costs of failed tests (about 13% of all tests), the consequences for patients and any possible follow-up costs were not considered in the economic evaluation or financial impact, but considered that these uncertainties would not have a large impact on either cost-effectiveness or the budget. MSAC noted that while HRD testing might be more reliable on fresh tissue this is generally unavailable and almost all testing will therefore usually be performed on archival FFPE tissue. MSAC noted that the ADAR considered sample age is a contributing factor in failed tests.

MSAC noted that the financial impact to the MBS ranged from \$1.5 million in year 1 to \$1.6 million in year 6. MSAC noted that, although this impact was not significant, the overall costs to the health budget were substantial (about \$10 million to < \$20 million to \$20 million to < \$30 million) due to the cost of the drugs. MSAC agreed with ESC that a renegotiated drug price could positively affect the economic evaluation and overall budget impact, and that there is also a potential cost relating to reporting HRD genes in cascade testing (additional germline test of \$400) that would result in an additional budget impact of \$30,000 per year.

MSAC considered that HRD and *BRCA1/2* testing do not normally need hospital treatment or accommodation.

MSAC noted the advice from the HRD experts, and considered that there is not yet consensus around HRD as a biomarker. Overall, MSAC supported the application, but acknowledged that HRD testing is in its early stages of development. However, MSAC considered that the tests were demonstrating clinical validity in an area of unmet clinical need, and noted that there were international guidelines and efforts to harmonise HRD testing. MSAC also considered the financial cost of testing to be relatively low.

MSAC advised that genetic counselling would only be necessary if testing identified a germline *BRCA1/2* variant, following subsequent testing using MBS item 73295. People found to carry tumour tissue *BRCAm* would likely require counselling, after which further testing would be appropriate to determine if the variant is germline. For identified germline *BRCAm*, cascade testing would be recommended, and MSAC considered that there would be value in knowing of *BRCA* status for relatives. However, MSAC noted that not all patients with tumour tissue *BRCAm* would carry germline *BRCAm*, as it is common for the variant to be somatic.

MSAC recommended that the listing be reviewed after 3 years to examine aspects including utilisation, outcomes from the Friends of Cancer Harmonization Project, test availability (e.g. SOPHiA, Illumina TruSight, REDACTED), out-of-pocket payments, and the latest data cuts of relevant clinical trials.

4. Background

This is the first resubmission for the codependent application for HRD testing which was not supported by MSAC in July 2022 (MSAC 1658). 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.

The PBAC considered olaparib for use in combination with bevacizumab for maintenance therapy in patients with newly diagnosed HRD positive *BRCAwt* advanced epithelial ovarian, fallopian tube or primary peritoneal cancer; it was not recommended by the PBAC in July 2022 (Olaparib PSD, July 2022). The PBAC considered an early re-entry resubmission for olaparib at its November 2022 meeting. The PBAC deferred its decision on whether to recommend olaparib. The PBAC was of a mind to recommend olaparib pending MSAC consideration of HRD testing (paragraph 5.1, PBAC minutes).

The resubmission presented information and responses to address six key matters (Table 1) as outlined in the July 2022 Ratified Minutes and Public Summary Document (PSD) for Application 1658 (p7).

In addition, the Department undertook targeted consultation, to which three experts responded (referred to as ‘Expert 1’, ‘Expert 2’ and ‘Expert 3’ herein).

Table 2 presents the six key matters identified by MSAC at its July 2022 meeting, as well as how the resubmission sought to address these matters.

Table 2 Summary of key matters of concern

Component	Matter of concern	How the current assessment report purports to address it
Intervention	Provide a justification for the proposed fee, with separate justifications for the assay component of the fee and the algorithm component of the fee.	The resubmission presented a list of workflow processes entailed in the fee. The commentary noted that the resubmission did not provide the fees, nor justifications for the assay component of the fee and the algorithm component of the fee.
Population	Provide a definition of HRD which can be applied confidently in clinical practice	The commentary considered that the resubmission presented a definition for HRD as per updated clinical guidelines and academic publications. The commentary noted that the experts responding to targeted consultation undertaken by the Department agreed that HRD can be defined as a phenotype that is characterised by the inability of a cell to effectively repair DNA double-strand breaks using the HRR pathway.

Component	Matter of concern	How the current assessment report purports to address it
	<p>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</p>	<p>The resubmission considered that harmonisation of test thresholds and future proofing an MBS listing was beyond the scope of submission. The resubmission also included correspondence from Dr Michael Friedlander, Medical Oncologist, that the goal of harmonisation should not be a barrier to women accessing olaparib treatment. Similarly, the experts responding to the Department's targeted consultation considered:</p> <ul style="list-style-type: none"> • There is currently no uniformly accepted standard HRD test or test threshold; • HRD thresholds do not specifically rely on the presence or absence of <i>BRCA</i>m and should reflect whether genomic scarring is evident; • A confounding issue with the implementation of a numerical HRD threshold score is determining a robust cut-off between HR-deficient and HR-proficient, as the measures tend to be continuous in patient cohorts; and • Cutoffs tested in the clinical trials or validation studies should be used to at least approve access for women who are most likely to benefit, while acknowledging there are some patients who may miss out. <p>One of the experts also discussed the Friends' HRD Harmonization project, suggesting that once the project reports its findings in ~2023 Q2, accreditation of HRD tests in Australia could be reduced to those best performing tests.</p>
	<p>Provide the preferred method of reporting HRD results and specify whether the results of underlying genetic mutations (beyond <i>BRCA</i> status) will be included in reports and how interpretation will be considered in the light of discordance (e.g., <i>BRCA</i>wt but HRD positive).</p>	<p>The resubmission stated that <i>BRCA</i> 1/2 pathogenic variant and HRD status would be reported, and the status of pathogenic variants in HRR genes, other than <i>BRCA</i>, will not be reported in the HRD reports. The commentary considered that the exclusion of other pathogenic variants in HRR genes may be justified by the results of Pujade-Lauraine (2021). However, the experts responding to targeted consultation preferred reporting of pathogenic variants in non-<i>BRCA</i> HRR genes. One expert stated that the HRR gene that carries a mutation (with the type of mutation and a clear definition of its effect) must accompany the HRD score. Additionally, the experts considered that the variant status of the main HRD genes would be useful to report. While acknowledging that the majority of other HRD genes are not necessarily useful now, as data accumulates they may become so. They also expressed that in the event no pathogenic mutation has been revealed this must be reported as well such that there is accumulating knowledge pointing towards more cryptic events that may be associated with HRD.</p>

Component	Matter of concern	How the current assessment report purports to address it
Clinical effectiveness	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 <i>BRCAwt</i> ovarian cancer	The resubmission presented the REDACTED concordance study, comparing Myriad MyChoice® with SOPHiA. The experts responding to the targeted consultation indicated that two test options are becoming available in Australia, SOPHiA, and Illumina TSO-500 assay (TruSight Oncology 500 HRD), the latter essentially being a version of Myriad MyChoice®. The resubmission did not provide any updated analyses of the REDACTED validation study that had been presented in the pre-MSAC response prior to the July 2022 meeting. Among 66 ovarian cancer samples tested by Myriad and SOPHiA for HRR + GIS, positive, negative and overall per cent agreement were 89%, 93% and 91%, respectively. A further poster presented by Buisson et al at ESGO 2022 was provided by the applicant during the evaluation. The study reported an overall agreement of 93.03% (95% CI: 89.48, 95.44%) between SOPHiA DDM Dx HRD and Myriad MyChoice® CDx from 318 samples (195 were from patients in PAOLA-1). The poster also reported progression free survival among the 195 patients enrolled in PAOLA-1 who tested HRD positive and negative according to the respective tests. The authors concluded that “PFS validation metric was non-inferior with the SOPHiA DDM™ Dx HRD Solution compared to Myriad MyChoice® CDx on the subset of 195 PAOLA-1 samples with clinical response data”. While further details of the methods and results of the study(ies) are necessary, the concordance results described are consistent with MSAC’s consideration that the tests are not fully concordant. As such, the commentary considered that a clearer description of consequences of discordant results (with regard to patient management, treatment effect, and costs) is necessary and has not been provided in the resubmission.
	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) <i>BRCAm</i> or (b) <i>BRCAwt</i> and HRD positive (e.g., algorithm-based genomic instability positive)	The resubmission presented updated DCO3 data from the PAOLA-1 clinical trial. Regarding the variation in treatment effect by subgroup, the commentary noted that the trends in treatment effect by <i>BRCA</i> and HRD subgroup were generally consistent between the PFS results previously considered by the PBAC and MSAC and the updated OS results. The commentary considered the difference in treatment effect among HRD positive and HRRm positive patients from Pujade-Lauraine (2021) was also of interest, where use of HRR gene panels indicated: <ul style="list-style-type: none"> • non-<i>BRCA</i> HRRm, in contrast to HRD (genomic instability), was not predictive of PFS benefit with olaparib + bevacizumab vs placebo + bevacizumab as first line maintenance regardless of HRR gene panel used in the PAOLA-1 study; • non-<i>BRCA</i> HRR gene panels captured a small proportion of patients with newly diagnosed HGOC (3.7-9.8%) compared with genomic instability excluding <i>BRCAm</i> (19%); and • beyond <i>BRCAm</i>, non <i>BRCA</i> HRRm and HRD (genomic instability) are not interchangeable and should not be considered as substitutes for each other in clinical practice for first line maintenance in ovarian cancer.

Source: adapted from Table 1, pp5-6 of the resubmission

BRCA = *Breast Cancer* gene; *BRCAm* = *Breast Cancer* gene mutation; *BRCAwt* = *Breast Cancer* gene wild type; DCO3 = data cut-off 3; HRD = homologous recombination deficiency HRR = homologous recombination repair; HRRm = homologous recombination repair mutation (pathogenic variants in specific genes involved in homologous recombination repair); MSAC = Medical Services Advisory Committee; PARP = poly(adenosine diphosphate [ADP]-ribose) polymerase; REDACTED; PSD = Public Summary Document.

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 2022).

HRD positive status was defined as having either tumour *BRCA* mutation (*BRCAm*) or a genomic instability score (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 (the primary evidence base for the application). Given this relationship, GIS positivity implies HRD positivity, and they are therefore used interchangeably at times. The term ‘HRD positive’ has been used 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 here rather than ‘HRD threshold’ when describing specific threshold criteria to reflect more accurately what was being tested.

5. Prerequisites to implementation of any funding advice

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

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.

At the time of this ADAR resubmission lodgement, the SOPHiA HRD assay had not completed NATA accreditation. The ADAR stated that a NATA accreditation was expected in Q4, 2022. The commentary considered that the applicant should provide an update in its pre-ESC response.

6. Proposal for public funding

Although not presented by the resubmission, the commentary assumed the proposed item descriptor and fee remained unchanged (see Table 3):

Table 3 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 2, p8 of the MSAC 1658 PSD

Justification for the proposed fee

MSAC previously advised that a resubmission would need to provide “a justification for the proposed fee, with separate justifications for the assay component of the fee and the algorithm component of the fee”. The commentary noted that the applicant did not provide the fees, nor justifications for the assay component of the fee and the algorithm component of the fee.

The resubmission presented the following breakdown of workflow associated with performing the SOPHiA test at the REDACTED, as well as some associated costs.

- Pathology review with identification of tumour, cellularity and tumour area.
- Slide microdissection and DNA extraction.
- Reagent cost with access to pipeline listed at \$1878.33 per sample at current exchange rates (linked to USD exchange rate).
- Sequencing of target sequence x1000 and low coverage of whole genome sequencing (WGS; single or low sample throughput increases this cost substantially through loss of economies of scale).
- Analysis and reporting.
- Other costs including training/competencies, quality assurance program, preventative maintenance/machine upkeep, labour for pathologist, scientist and analyst.

The resubmission noted that the SOPHiA Data Driven Medicine (DDM) User guide details all componentry and consumables required to perform test.

The commentary highlighted that consideration of whether the proposed fee had been adequately justified was required. The commentary noted that MSAC-supported fees associated with whole exome or genome sequencing and analysis of germline variants known to cause monogenic disorders (items 73358 and 73359) and germline gene variants in one or more of the genes implicated in heritable cystic kidney disease (items 73401 and 73402) range from \$2,100 to \$2,900.

The resubmission also stated that the Myriad MyChoice® Plus HRD cost is currently priced at \$REDACTED

7. Population

The proposed MBS item descriptor was intended to allow testing of tumour tissue from patients with HGEOC and would provide HRD status (both *BRCA* and genomic instability result in parallel). 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 *BRCA*wt (referred to as HRD positive *BRCA*wt herein) under the proposed PBS listing.

7.1 Definition of HRD

A key current challenge to measuring HRD is that there is no standardised method to define, measure, and report HR status using diagnostics in the clinical setting⁴.

MSAC considered that that a resubmission would need to provide “a definition of HRD which can be applied confidently in clinical practice”.

⁴ Stewart MD 2022 Homologous Recombination Deficiency: Concepts, Definitions, and Assays. *Oncologist*. 2022 Mar 11;27(3):167-174.

The resubmission claimed to have addressed this by:

- 1) Demonstrating that acceptable definitions for HRD are available as per updated clinical guidelines and academic publications.
- 2) Providing primary evidence that HRD is predictive of clinical response and outlining updated DC03 data from the PAOLA-1 clinical trial.
- 3) Outlining the clinical need for HRD testing.

The resubmission presented a biological or molecular definition of HRR and HRD from the updated European Society for Medical Oncology. The resubmission considered this was the accepted definition of both HRR and HRD which was used to inform the development of guidelines to define best practice for HRD testing in high-grade serous or epithelial ovarian, primary peritoneal or fallopian tube cancer, and that this was the internationally accepted definition of HRD:

Homologous recombination repair (HRR) is a mechanism often used by cells to repair DNA double stranded breaks. During HRR, parts of DNA sequences around the double stranded breaks are removed (resection), revealing regions of single stranded DNA (ssDNA). The DNA recombinase *RAD51* binds the ssDNA and invades the DNA sequence on a homologous sister chromatid, using this as a template for the synthesis of new DNA at the DSB site. Crucial proteins involved in mediating HRR include those encoded by *BRCA1*, *RAD51*, *RAD51C*, *RAD51D*, and *PALB2*.

The corollary to HRR is homologous recombination deficiency (HRD). HRD is a defect in DNA repair by hampered HRR. In cancers, HRR will often be the result of loss of function mutations in the aforementioned crucial proteins which mediate HRR. Loss of function mutations in *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* or *PALB2*, hypermethylation of the *BRCA1* gene promoter (leading to reduced expression of *BRCA1*) or a series of yet to be defined causes.

The commentary considered that the resubmission's definition was a molecular description based on ESMO's 2020 guidelines, which had already been available at the time of the previous MSAC consideration. Two of the experts (Experts 1 and 3) responding to the targeted consultation defined HRD similarly. Expert 2 stated that HRD can be inferred from the 'causes', such as deleterious alterations in *BRCA1* or *BRCA2*; the 'consequences', such as genomic instability and structural chromosomal aberrations; or measured directly by 'functional' assays (e.g. *RAD51* focus formation). Expert 2 further stated that HRD in high-grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma can be inferred from:

- Deleterious germline or somatic mutations in *BRCA1* or *BRCA2*, or in related genes, that are known to cause homologous recombination DNA repair deficiency.
- Measures of genomic instability, chromosomal aberrations, and other characteristic genomic features that reflect homologous recombination DNA repair deficiency with high specificity.

The commentary noted that 'Expert 2' stated that "restoration of HR DNA repair, through mechanisms including *BRCA* reversion mutations, may contribute to discordance between HRD scores and clinical treatment response".

The commentary also noted that MSAC requested a definition '*that could be confidently applied in clinical practice*' (1658 Final PSD, July 2022; p7). Related to this point was MSAC's consideration 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' (1658 Final PSD, July 2022; p1).

The commentary considered that the definition provided may not address MSAC's concern. Further discussion of clinically applicable definitions as they relate to test thresholds is below.

The extent to which the DC03 data demonstrate HRD is predictive of clinical response is discussed in the 'PAOLA-1 update' sub section in 'Comparative effectiveness' below.

7.2 Basis to define and ideally harmonise test thresholds of HRD positivity

MSAC advised that a resubmission would need to 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”. The resubmission sought to address this as follows:

- 1) Outlining the specific characteristics of the SOPHiA and Myriad tests. The commentary noted that this information had already been reviewed by MSAC.
- 2) Demonstrating cross-sectional concordance between the SOPHiA and Myriad tests. This is discussed in the 'Concordance' sub-section in 'Comparative effectiveness' below.
- 3) Demonstrating the longitudinal concordance between SOPHiA and Myriad tests. This is discussed in the 'Concordance' sub-section in 'Comparative effectiveness' below.
- 4) Providing the basis for concordance between existing and potential tests. The commentary considered that the resubmission did not actually provide any discussion of this and instead commented that it was beyond the scope of the application to “provide solutions for the broader global protocols for HRD testing or accreditation”.

The commentary considered that overall the resubmission did not explicitly provide any new or actionable information or arguments regarding the harmonisation of tests.

'Expert 1' asserted that "test thresholds that harmonise the results between different assays designed to measure HRD have not been established" and "the most appropriate approach will be for any assay to clearly define the criteria for an absence of HRR thereby defining HRD". Until now there is no consistency in defining HRD that makes it challenging to decide when to use a particular PARPi. They also stated that "any assay that is developed should clearly state the cut-offs for either outcome with the recognition that sometimes the results may be equivocal and a call on the presence or absence of HRR is unable to be made".

'Expert 2' stated that although the utility of different HRD and genomic instability scores to support PARPi treatment in patients with ovarian cancer was examined in several studies, until now there is no accepted test thresholds of HRD positivity for different proprietary tests. The commentary noted that the experts further provided points that should be considered for harmonising thresholds of HRD tests:

1. A high, pre-specified proportion of cases with known deleterious *BRCA1/2* mutations that have a HRD score above the set test threshold (e.g. >95% of *BRCA1/2* mutation-positive cases with a score above the threshold).
2. A high proportion of cases that lack known HR-related alterations having scores that fall below the set test threshold, i.e. a threshold that ensures high specificity.
3. A test threshold that shows consistency with tests used in PARPi clinical trials and has been shown to differentiate between patients that benefitted from PARPi treatment and those that did not.
4. Reproducibility of assignment of samples above and below the test threshold, e.g., reproducibility of results in the same sample within and between laboratories; reproducibility of results in different samples from the same patient.

5. Reproducibility of test results in DNA from a cell line panel, or similar ‘control’ DNA, for lab-to-lab calibration and reliability for assigning scores above and below the threshold (internal and external QA).

However, ‘Expert 2’ also indicated that there were issues related to results close to the threshold of HRD positivity. They noted that “In most reports there are cases with intermediate GIS scores close to the threshold, including cases with known *BRCA1/2* alterations under the threshold, in an intermediate zone. The approach used by Myriad has been to combine deleterious *BRCA1/2* mutations, and a high GIS score, to report an overall HRD status. FoundationFocus™ CDxBRCA LOH cites as a limitation that the performance of the assay has not been established for cases with LOH scores near the cut-off of 16. A basis to define and harmonise test thresholds would need to consider the limitation of correctly assigning cases that may fall in an ‘equivocal’ zone, close to the set test threshold.”

Expert 3 was of the opinion that the cut-off defined for the various HRD tests used in clinical trials had identified a group of patients who sustain meaningful impact from PARPi, if they are determined to be HRD positive. The expert further stated that “[t]here are now four trials which report a *BRCA* WT HRD positive group of women, using three different PARPi and three different HRD tests and for all trials, a clinically-meaningful difference in PFS or OS (if sufficiently mature data) with PARPi is observed, despite a high cross-over rate. This means that, although the specifics of each HRD test may not yet be known to us, nor which cases close to the cut-off should truly receive PARPi, these data demonstrate with certainty that using the tested cut-offs, a very appreciable group of women, who have a lethal, aggressive cancer, stand to benefit, including with prolongation of survival.”

In terms of harmonisation, Expert 3 referred to the Friends’ HRD Harmonization Project⁵. A poster⁶ authored by Stires et al. (2022) was presented on the website and detailed a project assessing 20 HRD assays. Among the 20 HRD assays, all test for *BRCA1/2* pathogenic variant status, while none of the assays reported testing of methylation in HRR pathway genes. Of the 20 assays, 75% assess LOH, 45% include TAI, 45% assess LST and 55% test for non-*BRCA* HRR gene pathogenic variants. An *in silico* analysis of 348 The Cancer Genome Atlas (TCGA) ovarian samples was conducted by 11 HRD assay developers; the developers measured and reported HR status calls and the contributing factor(s) for each sample. The authors reported there was variability in the HR status calls across assays and samples, with samples with *BRCA 1/2* pathogenic variants being more uniformly identified as HRD. Positive/negative agreement across the 11 assays varied from 9% to 67%, with a median of 49% HRD positive. There was also more variability in approaches for measuring consequences (genomic instability) versus causes (e.g. inactivation of genes in the HR pathway) across the 11 assays and concordance for causes (0.87) was greater than concordance for consequences (0.68). The authors concluded that inter-assay agreement on HR status calls was variable but did not appear to be strongly driven by which factors were included in the HRD scores, emphasising the importance of developing best practices. Stires et al. (2022) states that an analysis of freshly extracted formalin-fixed paraffin-embedded human archival ovarian tumour samples is planned for early 2023, which will provide additional context for interpreting the findings from the *in silico* dataset.

The resubmission stated that while AstraZeneca understands the importance of future proofing the process for assessing analytical validity of follow on HRD tests, it is beyond the scope of this application to provide solutions for the broader global protocols for HRD testing or accreditation.

⁵ <https://friendsofcancerresearch.org/hrd/>

⁶ <https://friendsofcancerresearch.org/wp-content/uploads/AMP-Poster-FINAL.pdf>

The resubmission also included correspondence from Dr Michael Friedlander, Medical Oncologist, who made the following arguments the commentary considered relevant:

- “The accepted definitions of HRD should be used in clinical decision making as they formed the basis for all the clinical trials that have investigated PARP inhibitors. The ESMO guidelines [Colombo & Ledermann 2021] recommended that all women with ovarian cancer have *BRCA* testing and HRD testing at diagnosis to inform treatment decisions and specifically stated that women with HRD+/*BRCA*wt should be offered either olaparib and bevacizumab or niraparib as first-line maintenance therapy”.
- “More recently, a European consensus statement on HRD and HRD testing was published in March 2022 ⁷and based on the recommendations of a panel of experts from across Europe. There was general agreement that biomarkers of HRD using the accepted definitions were effective at predicting sensitivity to PARP inhibitors as maintenance therapy after first-line chemotherapy and that testing should be carried out at the time of initial diagnosis”.
- “[The consensus statements] did not recommend or suggest modifying the thresholds for what constitutes HRD, in contradistinction to the MSAC view. Neither did they recommend harmonising all propriety tests as suggested by MSAC”.
- “[T]here are some promising tests in the pipeline which should be more cost effective, but we will need additional trials to determine if they are better at identifying women most likely to benefit. This is a work in progress and women with HRD+/*BRCA*wt advanced ovarian cancer shouldn’t have to wait until we have a better test before they can access a PARP inhibitor”.
- “[A Canadian consensus statement considered that] ‘standardization and optimization of HRD tests, a better understanding of mechanisms of resistance to PARP inhibitor therapy, and improved therapies for patients with HRP will increase the utility of HRD testing for guiding treatment decisions’. However, the need for these improvements did not result in them depriving women with an HRD+/*BRCA*wt test result from benefiting from therapy based on available evidence”.
- “There is general agreement that HRD assays are not ideal, and I share this view, but they are the best we have. They will likely improve over time, but the overwhelming consensus nationally and internationally, as described above, demonstrated by the USA, UK and Canada, is that they have clinical utility and are valid tests and should be used to inform practice.”

The resubmission also included correspondence from REDACTED, on behalf of the Australia New Zealand Gynaecological Oncology Group (ANZGOG) who also included arguments the commentary considered relevant, including:

- Access to a funded HRD test would significantly benefit women with HRD+/*BRCA*wt ovarian cancer, enabling them to make treatment decisions with their cancer specialists for PARP inhibitor therapy that cannot be prescribed without this information.
- The fact that HRD tests are not yet perfect does not prevent them providing significant advantage to women who would find themselves to be in this HRD+/*BRCA*wt group, in terms of delaying recurrence and prolonging survival.

The commentary considered that it may be reasonable to interpret this correspondence to suggest that issues with the test should not be a reason to deny access to olaparib, and that delaying funding to the test, when the benefit of PARPi treatment has been demonstrated, is detrimental to patients. In light of this, the commentary considered that MSAC may wish to

⁷ Vergote I, 2022 European experts’ consensus group. European experts consensus: *BRCA*/homologous recombination deficiency testing in first-line ovarian cancer. *Ann Oncol*. 2022 Mar;33(3):276-28.

consider whether the lack of clear resolution for several of the issues it raised regarding test efficacy need to be evaluated on the basis of unmet need and equity.

Published guidelines:

Table 4 presents recommendations for HRD testing in relevant guidelines and consensus statements.

Table 4 Guidelines that support HRD testing in high-grade serous or epithelial ovarian, primary peritoneal or fallopian tube cancer

Organisation	Guideline/recommendation
European society for medical oncology (ESMO)	Testing for genomic instability (HRD) is recommended. It identifies a subgroup of women who are <i>BRCA</i> wild type but derive greater benefit from a PARP inhibitor. Patients with a positive HRD test and a partial or complete response to front-line platinum-based chemotherapy (ChT), with or without bevacizumab, should receive maintenance treatment with a PARP inhibitor, either olaparib-bevacizumab (if started with ChT) or niraparib monotherapy [I, A; ESMO-MCBS v1.1 score: 3]
European experts' consensus: <i>BRCA</i> /homologous recombination deficiency testing in first-line ovarian cancer	Biomarkers of HRD are effective at predicting sensitivity to PARP inhibitors as maintenance therapy after first-line chemotherapy for ovarian cancer (level of contributor agreement: 88%)
	HRD tumour testing should be carried out at primary diagnosis (level of contributor agreement: 92%)
A Pan-Canadian Consensus Statement on First-Line PARP Inhibitor Maintenance for Advanced, High-Grade Serous and Endometrioid Tubal, Ovarian, and Primary Peritoneal Cancers	Tumour HRD status is a predictive biomarker of treatment benefit from PARP inhibitors, and testing should be publicly funded.
	There is evidence to support the combination of olaparib with bevacizumab as a maintenance regimen in patients with advanced, high-grade, HRD-positive EOC who respond to first-line treatment with platinum chemotherapy and bevacizumab

Source: Table 4, p11 of the resubmission.

BRCA = Breast Cancer Gene; EOC = epithelial ovarian cancer; ESMO = European Society of Medical Oncologists; HRD = homologous recombination deficiency HRR = homologous recombination repair; MCBS = Magnitude of Clinical Benefit Scale; MSAC = Medical Services Advisory Committee; PSD = Public Summary Document.

Overall, the commentary considered that the resubmission did not address MSAC's concerns. However, the included correspondence from local experts provided arguments for why harmonisation was (i) not practicable, (ii) inconsistent with international guidelines, and (iii) is delaying access to treatment.

7.3 Preferred method of reporting HRD results

MSAC considered that a resubmission would need to 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).”* Expert 3 did not consider *BRCAwt* but HRD positive to be discordant, however, they did suggest that it could be described as *“[a] BRCAwt HRD positive result identifies a subgroup of women who do not have a BRCA1/2 mutation in their OC [ovarian cancer] but have a BRCA-like OC and are likely to derive benefit from a PARP inhibitor.”*

The resubmission outlined the preferred reporting method and included the report form provided by the REDACTED to clinicians. The resubmission stated the report will provide clinicians with the genomic integrity status and *BRCA* status of their patient (positive or negative). Results are then stratified into genomic integrity status and *BRCA* status. Results for genomic instability status will report proposed HRD status (positive or negative) a GI score (a score of greater than 0 corresponds to a positive HRD status) and a quality assurance score of low, medium or high, which describes the risk of GI status misclassification. All experts responding to the targeted consultation agreed that the GI score should be reported, with Expert 3 adding the range and cut-off should also be stated. Expert 3 further stated that the GI score should be combined for the

three components (LOH [loss of heterozygosity], TAI [telomeric allelic imbalance], LST [large-scale state transitions]) for the Myriad test or a stand-alone score for SOPHiA. Expert 3 also stated that they would like to see a breakdown of LOH, TAI and LST. The resubmission stated that the reporting of *BRCA* status will be consistent with the current practice, where only *BRCA1* or *BRCA2* mutation status will be reported.

The resubmission further discussed the precision of the SOPHiA genomic instability index (GII), where in instances where the GII is in the range of -1.3 to +1.3, in the absence of corroborating *BRCA* positive status; an additional cautionary comment will be included in the clinician report: “This result is within the range of uncertainty for GI status measured by this method. Please consider all other pathological, radiological and clinical information when considering PARPi eligibility.”

The resubmission stated that patients who harbour a homologous recombination repair mutation (HRRm) in a non-*BRCA* gene will not automatically be considered HRD positive. For example, a patient with a *BRCAm* will be classified as HRD positive, however a patient with a non-*BRCAm* HRRm biomarker gene mutation would not be considered HRD positive on this basis alone, and HRD status would be considered on the basis of the GII score. The resubmission stated the form will not report on the presence of additional HRRm.

The commentary considered that the rationale for not reporting additional HRRm was not provided in the resubmission, although it may be justified on the basis of the results presented in Pujade-Lauraine (2021)⁸, see below.

The commentary considered that while it was clear that the resubmission stated the report would not report on non-*BRCA* HRR gene pathogenic variants, the experts responding to the targeted consultation all agreed that the report should consider HRR gene pathogenic variants:

- ‘Expert 1’ considered that “[t]he HRR gene that carries a mutation (with the type of mutation and a clear definition of its effect) must accompany the HRD score”. In addition to that, the report must include whether the mutation is an inherited or a somatic pathogenic variant. Expert 1 further stated “In the event no pathogenic mutation has been revealed this must be reported as well such that there is accumulating knowledge pointing towards more cryptic events that may be associated with HRD. The presence of HRR and the identification of a mutation in an HRR gene predicting HRD must also be reported.”
- ‘Expert 2’ stated that “consideration would need to be given to the interpretation of mutations in non-*BRCA1/2* HRR genes in cases with a HRD score below the test threshold. Non-*BRCA1/2* HRR-related gene variants are not equivalent in association with GIS and response to PARPi. Damaging mutations in genes including *RAD51C* and *RAD51D* are associated with a high GIS, whereas other HRR genes that are commonly on mutation panels including *CDK12* and *ATM* have been reported to be associated with a low GIS”.
- Expert 3 would like the tumour status for the main HRD genes (mutation or deletion in *BRCA1/2*, *RAD51C/D*, *PALB2*, *BRIP1*) to be reported. They also stated that additional genes could be added, such as *CHEK2*. The expert further noted that the majority of other HRD genes are not necessarily useful now, although as data accumulate they may become so.

⁸ Pujade-Lauraine, Eric, et al. 2021 "Homologous recombination repair mutation gene panels (excluding *BRCA*) are not predictive of maintenance olaparib plus bevacizumab efficacy in the first-line PAOLA-1/ENGOT-ov25 trial." *Gynecologic Oncology* 162 (2021): S26-S27.

8. Comparator

Although not presented by the resubmission, the commentary assumed the proposed comparator remained unchanged.

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) was 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. The commentary noted that MSAC had previously 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).

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, the commentary 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 or the resubmission.

9. Summary of public consultation input

A summary of consultation feedback received for MSAC Application 1658 is available in the Public Summary Document:

<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1658-public>

In its consideration of MSAC Application 1658, MSAC had requested the Department seek targeted consultation from Australian and overseas experts on HRD. Responses were received from three Australian experts.

Consultation feedback further to this resubmission was received from four organisations, two of which were medical and two other were consumer organisations:

- The Royal College of Pathologists of Australasia (RCPA)
- Australian Genomics
- Pink Hope
- Ovarian Cancer Australia

The consumer organisations were in favour of public funding for the service. Input received from the RCPA indicated support for MSAC's original decision to not support application 1658.

Advantages of the proposed testing were:

- The National Action Plan for Ovarian Cancer includes a focus on molecular profiling for therapeutic targets.

- This testing will identify patients who are most likely to benefit, and consequently avoid the prescribing and self-funding of treatments for those who are unlikely to have improved outcomes.
- The patient community sees firsthand the benefits that come from information related to cancer risk and increasing treatment options available to patients, especially non-*BRCA* women who currently have limited treatment options.
- Subsidising HRD testing under the MBS will make access to testing available to those who cannot self-fund it, which will result in better equity of access.
- HRD testing is already being used internationally.

Disadvantages of the proposed testing were:

- The proposed fee is insufficient given the technology and cost required to perform the test. Nonetheless, the fee for the test in general is too high. In addition, not all labs may be able to afford the technology required to perform and validate the test.
- Other assays that address a range of factors may be better utilised to determine HRD status of patients to determine eligibility for PARP inhibitors rather than referring explicitly to the proposed technology in this application.
- There was a risk of incidental findings and misinterpretation of clinical significance of variants using large panels. It may be safer to perform focussed gene panels.
- There is not enough information available about the methodology or utility of HRD testing. It is hard to find more information about HRD testing.
- Studies show concordance of around 90% between different brands of HRD test, which does not seem to support a high degree of accuracy.

10. Characteristics of the evidence base

The resubmission provided results from the REDACTED validation study that were presented in the pre-ESC response to the previous ADAR. The concordance study included 66 ovarian cancer samples that were assessed for GIS + HRR by MyChoice[®] and SOPHiA.

The resubmission provided updated (data cut-off 3; DCO3) data from the PAOLA trial. PAOLA-1 enrolled 806 patients with HGEOC who were randomised to olaparib plus bevacizumab (n=537) or bevacizumab alone (n=269).

11. Comparative safety

The commentary noted that the resubmission did not present any updated safety results. The commentary presented a summary of the safety results based on the 1658 submission.

Adverse events from testing

The commentary highlighted that as noted in the MSAC 1658 PSD, 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 for 1658 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 1658 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.

Adverse events from changes in management

The commentary highlighted that as noted in the MSAC 1658 PSD, 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.

The commentary also noted that as in the MSAC 1658 PSD, 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:

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 clinical 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.

Additionally, the commentary considered 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

12.1 Sufficient concordance

MSAC previously considered that a resubmission would need to 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*” (1658 Final PSD July 2022; p7).

Specifically, MSAC considered that, “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” (1658 Final PSD July 2022; p4).

‘Expert 2’ presented two studies that described the inadequacy of prediction of HRD LOH with a cut-off of 16%. For example, Marchetti et al (2022)⁹ observed no difference in the magnitude of benefit between patients with *BRCA*wt/LOH-high and *BRCA*wt/LOH-low and suggested that the HRD assessment by LOH was inaccurate in around 80% of the entire population. They concluded that further work was required to establish HRD tests that are predictive of PARPi effectiveness in clinical practice. In addition, Mills et al (2020)¹⁰ noticed that LOH with a cut-off of 16% identified a much smaller percentage of tumours with a *BRCA* mutation, only 53.45% compared to 92% identified by MyChoice® HRD score ≥ 42 . The authors concluded that despite the concordance of the genomic instability scores, these two tests are not equivalent and should not be considered interchangeable in predicting response to PARP inhibitors in clinical practice.

MSAC concluded that “these different methods may not consistently provide concordant results nor identify similar populations as having genomic instability” (1658 Final PSD July 2022; p4)

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” (1658 Final PSD July 2022; p7).

In considering the concordance data from the REDACTED validation study, MSAC noted that (1658 Final PSD July 2022; p5):

- The study was not performed prospectively, rather the validation study sourced archival samples that had previously been tested using the Myriad MyChoice® CDx assay.
- 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).

The resubmission claimed to have addressed this in the following ways:

- 1) Outline published guidelines for demonstrating harmonisation for HRD tests and outlines and discuss why these guidelines are not practicable for the validation between the proposed test (SOPHiA) and the clinical utility standard (Myriad MyChoice®) in the Australian setting. The commentary noted that this appeared consistent with the resubmission table (Table 10, p37 of the resubmission) describing how the SOPHiA algorithm was consistent with the Stewart harmonisation guidelines. Overall, the commentary considered that this did not address the issue of whether there was sufficient concordance.
- 2) Discuss data from the PAOLA-1 study providing evidence that the Myriad MyChoice® assay confidently distinguishes clinically meaningful variation in the treatment effect of PARP inhibitors in ovarian cancer. This is discussed below.

⁹ Marchetti, C et al 2023. Rucaparib maintenance in upfront ovarian cancer: The long-lasting challenge of predicting response to poly (ADP-ribose) polymerase inhibitors. *J Clin Oncol*, 41(4), 935-936.

¹⁰ Mills GB et al 2020. Comparison of genomic instability (GI) scores for predicting PARP activity in ovarian cancer. *Gynecologic Oncology* 159, 139-40

- 3) Recommend that the methodology applied in validation analysis by REDACTED provides appropriate certainty that the SOPHiA assay is concordant to the Myriad MyChoice® assay. As noted above by the commentary, MSAC previously expressed substantial concerns with the REDACTED analysis that have not been addressed in the resubmission.
- 4) Note that SOPHiA Genetics is scheduled to present additional data and information at the European Society of Gynaecological (ESGO) conference this month (October 2022) to support the clinical utility of the SOPHiA assay to confidently distinguish clinically meaningful variation in treatment effect of PARP inhibitors in ovarian cancer. The commentary noted that during the evaluation, a conference abstract from ESGO was identified; in addition to the applicant providing a poster presented at ESGO; suggesting a level of concordance that was consistent with previous MSAC considerations. This is discussed below.

Basis for concordance:

The resubmission explained that, considering that Myriad MyChoice® CDx was the reference standard, REDACTED explored licensing Myriad MyChoice® CDx in Australia. For commercial reasons, Myriad did not support a local implementation of their assay. Further complicating implementation, only the GIS component of the MyChoice® assay would have been supported due to perceived commercial sensitivity surrounding Myriad Genetic's proprietary *BRCA1/2* database. The resubmission considered that for these reasons, 'a hybrid bioinformatic solution necessitating substantial local development but with attendant clinical risks would be required.'

The resubmission also noted that a version of the Myriad MyChoice® assay will eventually be available outside of the US with the release of an HRD-capable version of Illumina's comprehensive genomic profiling RUO assay, TruSight Oncology 500. The resubmission stated that the cost of this product is currently not known but considered it is likely to significantly exceed rebates currently under discussion for HRD testing in Australia, therefore necessitating a significant out-of-pocket contribution from patients.

According to 'Expert 1' and 'Expert 3', two test options are becoming available in Australia, SOPHiA, and Illumina TSO-500 assay (TruSight Oncology 500 HRD). Expert 1 stated both tests are very similar and represent similar sensitivities and specificities to the Myriad My Choice assay. Even though the Myriad My Choice assay is considered as a leading assay for HRD assessment, this is not based on any rigorous assessment. Similarly, 'Expert 3' pointed out that Myriad was the reference, not gold, standard and there is a possibility that any discordant results between SOPHiA and Myriad may result from improved and correct classification by SOPHiA. 'Expert 1' also stated that "the test options should also include what components of the HRD test are being focussed on as this is likely to result in different outcomes with respect to the level of HRD. Both the NCCN and ASCO still suggest a level of uncertainty and inconsistency in how to best use assays that measure HRD for clinical purposes and that uniform reporting requirements should be established to minimise error. A minimum set of requirements are needed to provide consistency". 'Expert 3' suggested that once the Friends' HRD Harmonization project reports its findings in ~2023 Q2, accreditation of HRD tests in Australia could be reduced to those best performing tests.

According to 'Expert 2', test options that might become available in Australia could potentially be validated by the following approaches:

- Demonstrating concordance with the MyChoice® HRD assay that has been used in clinical trials such as PAOLA1.
- Testing samples from PARP inhibitor clinical trials to directly assess association with response to treatment, in particular in *BRCAwt* cases. For example, EMBRACE (ACTRN12617000855325) a phase II clinical trial of the PARP inhibitor, olaparib, in HR-

deficient metastatic breast and relapsed ovarian cancer in patients without germline mutations in *BRCA1* and *BRCA2*). Although, there may be significant barriers to the secondary use of clinical trials samples.

- Determining the ability of the test to predict platinum-sensitivity (as a surrogate; highly associated with response to PARP inhibitors).

REDACTED validation study

The resubmission did not provide any updated analyses of the REDACTED validation study that had been presented in the pre-MSAC response prior to the July 2022 meeting. Among 66 ovarian cancer samples tested by Myriad and SOPHiA for HRR + GIS, positive, negative and overall per cent agreement were 89%, 93% and 91%, respectively. Rather, the resubmission stated that the applicant 'recommends' that the methodology applied in validation analysis by REDACTED provides appropriate certainty that the SOPHiA assay is concordant to the Myriad MyChoice® assay. The commentary considered that none of the specific MSAC concerns regarding the REDACTED validation study had been addressed.

The resubmission stated that the REDACTED has sourced additional samples and can provide additional concordance data for the SOPHiA Genetics HRD solution with Myriad MyChoice® CDx in Q4 2022. The commentary considered that it was unclear whether this would be simply the same study, with additional samples, or whether this would be a validation study that specifically addressed MSAC's concerns.

The pre-ESC response provided updated data that included new data from an additional 59 samples that have been added to the REDACTED validation study (Figure 1)

		SOPHIA HRD		
		Positive	Negative	
MyChoice GIS	Positive	TP 50	FN 9	59
	Negative	FP 7	TN 48	55
		57	57	114
		PPA=85% (Sensitivity)		
		NPA=87% (Specificity)		
		PPV=88%		
		OPA=86%		

		SOPHIA HRD		
		Positive	Negative	
MyChoice GIS	Positive	TP 59	FN 5	64
	Negative	FP 7	TN 48	55
		66	53	119
		PPA=92% (Sensitivity)		
		NPA=87% (Specificity)		
		PPV=89%		
		OPA=90%		

Figure 1 Updated REDACTED validation data for the ovarian samples

Note: a) Confusion Matrix for genomic instability alone, b) Confusion Matrix for genomic instability combined with *BRCA1/2* status, whereby a pathogenic variant overrides a negative or inconclusive genomic instability score.

Source: Figure 1, p3 of the pre-ESC response

Updated ESGO materials

The commentary noted that during the evaluation, a conference abstract from ESGO was identified with results of an assessment of concordance in ovarian cancer tumour samples (N=319) tested with SOPHiA DDM Dx HRD solution and Myriad MyChoice® CDx (Buisson et al 2022a). The results indicated a 'overall percentage agreement' of 90.48% (95% CI: 86.58, 93.33), between SOPHiA DDM Dx HRD and Myriad MyChoice® CDx status.

The abstract also noted that survival analysis was carried out for the subset of the cohort (206 samples) included in the PAOLA-1 clinical trial, to investigate differences in progression-free survival (PFS) in the olaparib and placebo arms of the study between patients, with HRD positive or non-positive tumours.

The median PFS time for patients with HRD positive tumours was 20.8 months higher in the olaparib arm (HR=0.44; 95% CI: 0.26, 0.76, P=0.003). No significant difference in PFS was observed between treatment arms in patients without HRD positive tumours (HR=0.92; 95% CI:

0.59, 1.43; P=0.69). The effect of the interaction between olaparib and HRD status on PFS, in the interim study, was similar for the two stratification methods (P=0.20).

The commentary noted that during the evaluation, the applicant also provided a poster presented at ESGO 2022 by the same authors (Buisson et al 2022b). The commentary highlighted that data presented varied slightly from the abstract (perhaps a consequence of further refining results between abstract submission and presentation. The pre-ESC response clarified that of the 206 samples processed, 10 did not have results using the Myriad assay, and one sample was classified as indeterminate using the SOPHiA assay and was therefore excluded. Therefore, in the poster it was decided to restrict the analysis to the 195 samples for which both assays' results were known.

The commentary noted that the poster presentation reported testing of 318 samples, of which 195 were from patients in the PAOLA-1 study. An overall agreement of 93.03% (95% CI: 89.48, 95.44%) between SOPHiA DDM Dx HRD and Myriad MyChoice® CDx was reported, concordance between tests is presented in Figure 2.

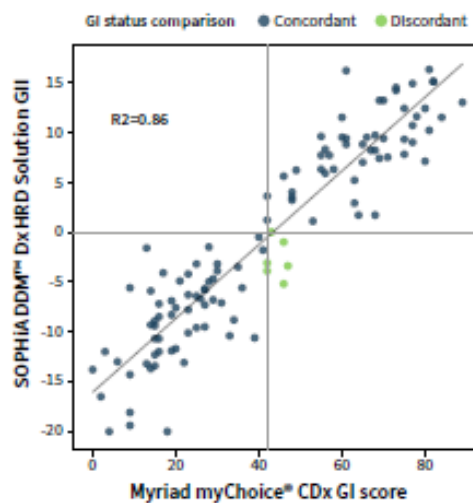


Figure 2 Concordance of GI index/score between SOPHiA DDM™ Dx HRD Solution and Myriad MyChoice® CDx (n = 116)

Source: ADAR Commentary Figure 1 adapted from Buisson 2022b
GI, genomic instability; GII, genomic integrity index.

The poster also reported progression free survival among the 195 patients enrolled in PAOLA-1 who tested HRD positive and negative according to the respective tests, see Figure 3. The commentary considered that it was not clear that the comparison of PFS among those who were GI positive or negative according to SOPHiA were comparable to those who were GI and BRCA positive or GI and BRCA negative according to Myriad MyChoice® CDx, respectively (noting that SOPHiA did not specify BRCA status). Importantly, the results for the population of interest, HRD positive/BRCAwt, were not reported for either test. The 1658.1 pre-ESC response clarified that GI+BRCA is interchangeable with HRD status for Myriad. The top two figures are therefore HRD positive patients (genomic instability positive including BRCAm) and the bottom two figures are HRD negative (genomic instability negative and BRCAwt)

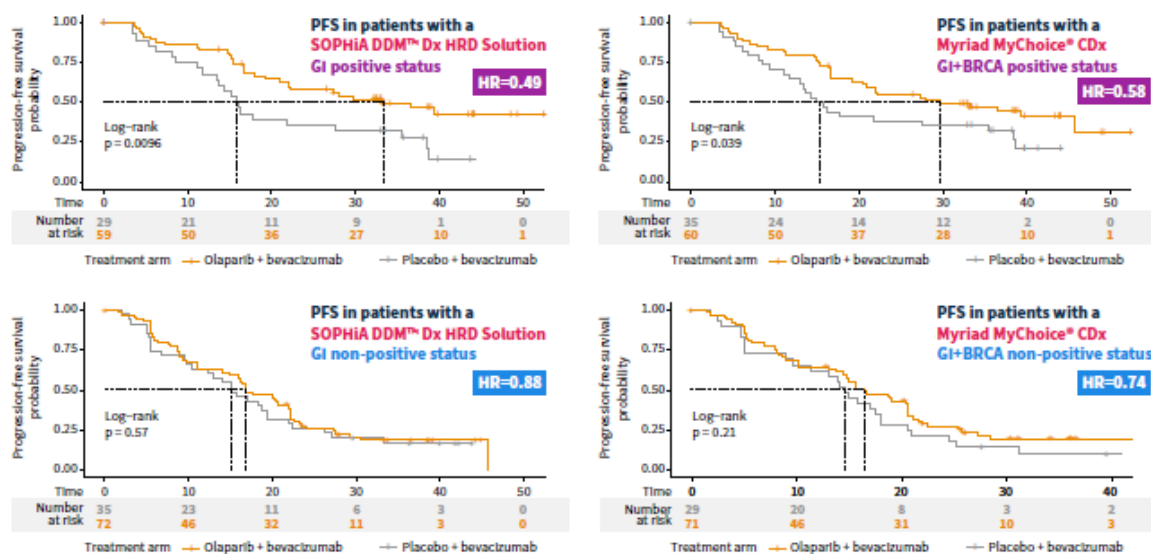


Figure 3 Progression-free survival in a PAOLA-1 sub-cohort of patients stratified according to SOPHiA DDM™ Dx HRD Solution GI status or Myriad MyChoice® CDx GI+BRCA status (n = 195)

Source: ADAR commentary Figure 2, adapted from Buisson 2022b

The authors concluded that “PFS validation metric was non-inferior with the SOPHiA DDM™ Dx HRD Solution compared to Myriad MyChoice® CDx on the subset of 195 PAOLA-1 samples with clinical response data”.

The commentary considered that while further details of the methods and results of the study(ies) are necessary, the concordance results described are consistent with MSAC’s consideration that the tests are not fully concordant. As such, a clearer description of consequences of discordant results (with regard to patient management, treatment effect, and costs) is necessary and has not been provided in the resubmission.

12.2 Provide a basis to demonstrate how the different definitions in this threshold of HRD positivity affects the ability to distinguish treatment effect variation

MSAC previously considered that a resubmission would need to 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)” (1658 Final PSD July 2022; p7).

In particular, 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)” (1658 Final PSD July 2022; p4).

MSAC also considered that, “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)” (1658 Final PSD July 2022; p4).

The resubmission claimed to have addressed these concerns in the following ways:

- 1) Demonstrating that acceptable definitions for HRD are available as per updated clinical guidelines and academic publications. The commentary considered that this was in reference to the molecular definitions presented above, which may not have addressed the MSAC concerns.
- 2) Providing the primary evidence that HRD is predictive of clinical response and outlines the updated DC03 data from the PAOLA-1 clinical trial.
- 3) Include the clinically relevant differentiation of HRD from HRRm: patients who harbour a HRRm in a non-*BRCA* gene will not automatically be considered HRD+. For example, a patient with a *BRCA*m will be classified as HRD+, however a patient with a non-*BRCA*m HRRm biomarker gene mutation would not be considered HRD+ on this basis alone, and HRD status would be considered on the basis of the GII score.
- 4) Outlining the link between HRD status and treatment effect, and demonstrating the clinical variation in the treatment effect of PARP inhibitors.
- 5) Demonstrating the need for patient access to HRD testing. MSAC has accepted that there was a high unmet need for effective treatment in this population (1658 Final PSD July 2022; p5).

The commentary considered that none of these approaches specifically addressed how differences in thresholds of HRD positivity affect the ability to detect treatment effect variation. However, the PAOLA-1 update did provide overall survival data in relevant subgroups (see below). The commentary considered the results for those with pathogenic variants in non-*BRCA* HRR genes, shown above, were also informative.

The commentary noted that importantly, the PAOLA-1 updated trial results (see below) only presented results for patients tested with Myriad MyChoice®, and treatment decisions based on a threshold of 42. Consequently, the commentary considered that this evidence could not inform discussion of changes in test thresholds.

Additionally, according to ‘Expert 1’ “HRD thresholds do not rely on the presence or absence of *BRCA*m and should reflect whether genomic scarring is evident”. Expert 2 stated that a confounding issue with the implementation of a numerical score is determining a robust cut-off between HR-deficient and HR-proficient, as the measures tend to be continuous in patient cohorts.

PAOLA-1 update:

Briefly, PAOLA-1 (N=806) was a randomised, double blind, placebo-controlled trial of olaparib plus bevacizumab versus placebo plus bevacizumab in patients with first line, newly diagnosed, high-grade serous or epithelial ovarian, primary peritoneal or fallopian tube cancer, FIGO stage IIIB to IV.

At the time of MSAC consideration of 1658, only data from data cut-off 2 (DC02) was available. The results of a final data cut (DC03) were presented in the resubmission.

Updated data from PAOLA-1 (DC-03 - Ray-Coquard 2022) sourced from slides at a presentation to ESMO in 2022 showed a statistically significant benefit in overall survival in the ITT population in the presence of substantial cross-over. The resubmission considered that such cross-over would not occur in clinical practice given that the PBS restriction prohibits sequential treatment with a PARP and considered that the OS benefit for patients on olaparib plus bevacizumab is expected to be greater than the trial data.

Table 5 presents a comparison in overall survival estimates in the two most recent data cuts from PAOLA-1. The resubmission noted that the HR for OS from DC03 has improved from 0.84 to 0.71 (95% CI 0.45-1.13) in the HRD+*BRCA*wt population.

Table 5 Comparison of OS in DC02 and DC03 in PAOLA-1

	DC02			DC03		
	Ola + beva	Pbo + beva	HR (95% CI)	Ola + beva	Pbo + beva	HR (95% CI)
HRD positive <i>BRCAwt</i>						
Median OS	NR	45.8	0.84 (0.46,1.52)	NR	52.0	0.71 (0.45,1.13)
Events, n/N (%)	30/97 (30.9)	19/55 (34.5)		44 (45.4%)	32 (58.2%)	
HRD positive						
Median OS	NR	NR	0.70 (0.47,1.04)	75.2	57.3	0.62 (0.45,0.85)
Events, n/N (%)	61/255 (23.9)	42/132 (31.8)		93 (36.5%)	69 (52.3%)	

Source: Table 2, p9 of the resubmission.

Beva = bevacizumab CI = confidence interval; HR = hazard ratio; NR = not reached; Ola = Olaparib; OS = overall survival; Pbo = Placebo; wt = wild type

The PBAC (Olaparib PSD July 2022, paragraph 6.10) previously noted that the submission claimed that the risk of bias for the PAOLA-1 trial was considered low. The PBAC considered this was reasonable when considering the ITT population, however the use of what were effectively post hoc HRD subgroups (as they were determined post randomisation nearly three years after enrolment began) introduced a high risk of selection bias.

The commentary noted that the updated DC03 results showed an improved point estimate of HR for HRD positive *BRCAwt* subgroup than the DC02 results (0.84 versus 0.71), but the confidence intervals remained wide, and also crossed 1, indicating statistically non-significant results. The commentary considered that this may be expected given the smaller sample size of the subgroup compared to other subgroups and likely being underpowered.

For the HRD positive subgroup (irrespective of BRCA status) the HR improved from 0.70 (0.47, 1.04) in DC02 to 0.62 (0.45, 0.85) in the subgroup.

The commentary noted that the ESMO presentation (Ray-Coquard 2022) provided with the resubmission also showed that the HR for OS in the ITT population in DC03 was 0.92 (CI: 0.76, 1.12; p value = 0.4118). This compared with a DC02 estimate of 0.93 (95% CI: 0.74, 1.18).

A comparison of the PFS results in DC02 and DC03 are presented in Table 6; DC03 results are shaded in grey. Of note was that only updated DC03 results (in terms of hazard ratios) were presented for the HRD positive subgroup. The commentary considered that this limited the usefulness of these PFS results.

Table 6 Comparison of all available results reported for PFS in data cut-off 1, 2 and 3 for PAOLA-1 patients

	Ola + beva	Pbo + beva	HR (95% CI)
Full analysis set (FAS)			
Data cut-off 1			
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)			
Data cut-off 1			
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)	
Data cut-off 2			
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)	
Data cut-off 3			
Median PFS	30.0 months	16.6 months	Not calculated
Events; n/N (%)	58/97 (59.8)	46/55 (83.6)	
HRD positive tumours (includes <i>BRC</i>Am)			
Data cut-off 1			
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)	
Data cut-off 2			
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)	
Data cut-off 3			
Median PFS	46.8	17.6	0.41 (0.32, 0.54)
Events; n/N (%)	136/255 (53.3)	104/132 (78.8)	
HRD negative tumours			
Data cut-off 1			
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)	
Data cut-off 3			
Median PFS	16.6 months	16.2 months	Not calculated
Events; n/N (%)	167/192 (87.0)	74/85 (87.1)	
Tumour <i>BRC</i>Am			
Data cut-off 1			
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			
Data cut-off 1			
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			
Data cut-off 1			
Median PFS	NR	NR	0.71 (0.46, 1.10)
Events; n/N (%)	NR/90	NR/52	
All HRD tested population (82% of the overall PAOLA-1 population)			
Data cut-off 2			
Median PFS	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)	

Source: Table 6, p16 of July 2022 Olaparib PBAC Minutes, Table 3, p10 of the resubmission and Table 9, p36 of the resubmission. Beva = bevacizumab CI = confidence interval; HR = hazard ratio; NC = not calculated; NR = not reported; Ola = Olaparib; Pbo = Placebo; PFS = progression free survival.

The resubmission considered that while patients with *BRC*Am derive the greatest benefit from this treatment, the PAOLA-1 study demonstrated patients who are HRD+*BRC*Awt will also derive

clinically meaningful benefit from treatment with PARP inhibitors, updated data from DC03 of the PAOLA-1, stratified by HRD status show an improvement in OS.

The commentary considered that this claim may be reasonable given the positive overall survival updates, but must be considered with caution considering the nature of post-hoc subgroup analyses.

Regarding the variation in treatment effect by subgroup, the commentary noted that the trends in treatment effect by *BRCA* and HRD subgroup were generally consistent between the PFS results previously considered by the PBAC and MSAC and the updated OS results.

Specifically, the PBAC (Olaparib PSD July 2022, paragraph 7.7) noted that from data cut off (DCO) 1 that the PFS HR for the HRD positive subgroup (including *BRCAm*) was similar to that for the *BRCAm* subgroup (0.33; 95% CI 0.25, 0.45 vs 0.28; 95% CI 0.19, 0.42), while the PFS HR for the proposed PBS population (HRD positive *BRCAwt* subgroup) was less favourable (PFS HR 0.43; 95% CI 0.28, 0.66). In contrast, treatment with olaparib plus bevacizumab did not result in any benefit in terms of PFS in patients with HRD negative tumours (HR 1.00; 95% CI 0.75, 1.35) compared with bevacizumab alone.

Similarly, the OS results indicated a higher hazard ratio that crossed 1.00 in the HRD positive *BRCAwt* subgroup (0.71 :0.45,1.13), although this was not statistically significant. Compared to the HR for the HRD positive subgroup (0.62: 0.45,0.85), which was statistically significant.

Overall, the commentary considered that the updated PAOLA-1 results did not specifically address the concerns raised by MSAC with regard to the test's ability to differentiate between patients who benefit from treatment. However, the generally positive OS results may suggest (acknowledging the post-hoc nature of the subgroup analyses) that patients, using a Myriad MyChoice® test set at a threshold of 42, may benefit from olaparib combination treatment.

The commentary considered that while the HR in subgroup of interest, *BRCAwt* HRD positive patients was not statistically significant, this should be viewed in the context of substantial post-progression cross over and a small sample size. The PBAC considered that cross-over to second line PARPi treatment may have impacted the interpretation of updated OS data and that mature data from the SOLO1 study (olaparib monotherapy in first line setting) provided reassurance that the observed PFS benefit in PAOLA-1 will likely translate into an overall survival benefit in the long-term (Olaparib PSD July 2022, paragraph 7.8).

However, the commentary considered that these results do not clearly demonstrate the Myriad MyChoice®'s accuracy in discerning patients who will benefit from olaparib treatment, outside of the fact that the subgroup analyses suggest that patients in this subgroup benefit from treatment.

Further results from PAOLA-1 that the commentary considered are of interest were those reported in Pujade-Lauraine (2021), a poster presentation at the SGO Virtual Annual Meeting on Women's Cancer 2021, provided by the applicant during the evaluation. Pujade-Lauraine (2021) reported further analysis of PAOLA-1 samples using HRR mutation gene panels. The authors explored mutations in genes involved in HRR beyond *BRCAm* as a predictive biomarker in PAOLA 1.

Given this was a conference presentation, limited information regarding the methods were reported. The commentary noted that it appeared that samples from the 804 patients randomised in the PAOLA-1 trial had their DNA samples analysed by various HRR gene panels; the applicant is requested to confirm this.

Pujade-Lauraine (2021) reported that HRD by genomic instability score and non-BRCA HRRm are not interchangeable. Use of a predefined gene panel including 13 genes (*ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*) identified that 54 patients in the PAOLA-1 trial had mutations in these specific genes. The commentary noted that mutations in these genes were also not associated with being classified as HRD positive (defined as a score ≥ 42 by Myriad MyChoice[®]), see Figure 4.

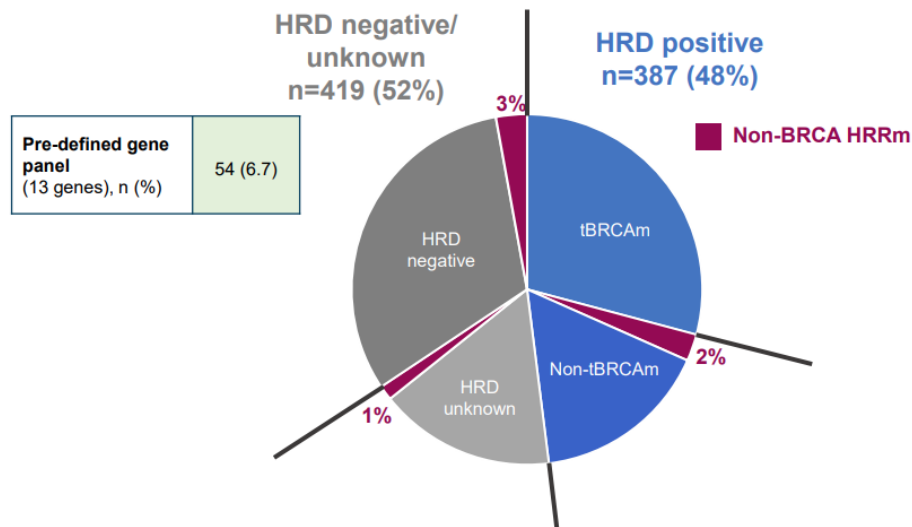


Figure 4 Proportion of patients with non-BRCA HRRm and whether they were HRD positive, negative or unknown, in the PAOLA-1 trial

Source: ADAR Commentary figure 3 adapted from Slide 9 of Pujade-Lauraine 2021

The authors also reported that only five (*BLM, BRIP1, RAD51C, PALB2* and *RAD51D*) of 18 genes investigated had a median GIS ≥ 42 according to Myriad MyChoice[®].

Pujade-Lauraine (2021) reported the PFS results for patients enrolled in PAOLA-1, see Table 7 and Figure 5.

Table 7 PFS by HRD status in patients with a *BRCA*m and non-*BRCA* HRRm

Patients with:	N	PFS HR (95% CI)
HRD positive (including <i>BRCA</i> m)	387	0.33 (0.25, 0.45)
HRD positive (excluding <i>BRCA</i> m)	152	0.43 (0.28, 0.66)
HRRm according to 'pre-defined HRR gene panel' (13 genes: <i>ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L</i>)	54	0.95 (0.49, 1.94)
HRRm according to 'expanded HRR gene panel' (18 genes: pre-defined panel + <i>BLM, FANCA, FANCI, FANCM, NBN</i>)	72	1.01 (0.55, 1.95)
HRRm according to 'restricted gene panel' (5 genes: <i>BLM, BRIP1, PALB2, RAD51C, RAD51D</i>)	30	Not calculated
Gene panel used in Study 19 ¹¹ (26 genes ^a)	79	0.92 (0.51, 1.73)
Gene panel used in ARIEL 3 ¹² (19 genes ^a)	61	1.35 (0.65, 3.14)
Gene panel used in NOVA ¹³ (11 genes ^a)	44	1.83 (0.76, 5.43)

Source: ADAR Commentary Table 1 adapted from Slide 6 of Pujade-Lauraine 2021

^a genes included in the analyses were not reported

Pujade-Lauraine 2021 stated that non-*BRCA* HRRm was not predictive of improved PFS, regardless of gene panel in first-line ovarian cancer.

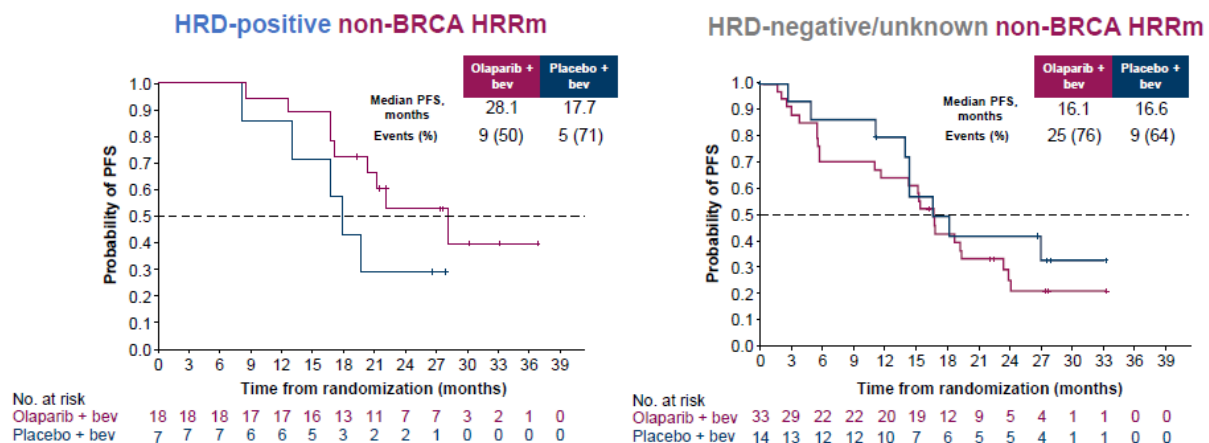


Figure 5 PFS by HRD status in patients with a non-*BRCA* HRRm (expanded panel)

Source: ADAR Commentary figure 4 adapted from Slide 13 of Pujade-Lauraine 2021

The authors reported that even among a small non-*BRCA* HRRm population, HRD by genomic instability testing appeared to be predictive of a PFS benefit with olaparib + bevacizumab

¹¹ Hodgson DR, et al. 2018 Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the *BRCA* genes. *Br J Cancer*. Nov;119(11):1401-1409. doi: 10.1038/s41416-018-0274-8. Epub 2018 Oct 24. PMID: 30353044; PMCID: PMC6265286.

¹² Coleman RL, and ARIEL3 investigators. 2017 Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. Oct 28;390(10106):1949-1961. doi: 10.1016/S0140-6736(17)32440-6. Epub 2017 Sep 12. Erratum in: *Lancet*. 2017 Oct 28;390(10106):1948. PMID: 28916367; PMCID: PMC5901715.

¹³ Mirza et al. ASCO 2019 (abstract 5568)

maintenance vs placebo + bevacizumab. While acknowledging the limitation of small subgroup sizes, Pujade-Lauraine (2021) concluded that:

- non-*BRCA* HRRm, in contrast to HRD (genomic instability), was not predictive of PFS benefit with olaparib + bevacizumab vs placebo + bevacizumab as first line maintenance regardless of HRR gene panel used in the PAOLA 1 study;
- non-*BRCA* HRR gene panels captured a small proportion of patients with newly diagnosed HGOC (3.7-9.8%) compared with genomic instability excluding *BRCAm* (19%); and
- beyond *BRCAm*, non-*BRCA* HRRm and HRD (genomic instability) are not interchangeable and should not be considered as substitutes for each other in clinical practice for first line maintenance in ovarian cancer.

13. Economic evaluation

The commentary noted that the resubmission to MSAC did not provide an economic evaluation, however the early re-entry submission considered by the PBAC at its November 2022 meeting provided an updated economic evaluation.

The incremental cost-effectiveness ratio in the updated economic evaluation increased to \$55,000 to < \$75,000 per quality adjusted life year gained (QALY) from \$45,000 to < \$55,000 /QALY in the July 2022 submission, see Table 8.

Table 8 Comparison of economic evaluation between resubmission and July 2022

Increment	July 2022 submission	November 2022 resubmission
Cost (\$)	REDACTED	REDACTED
LY (discounted)	0.52	0.40
QALY (discounted)	0.46	0.36
Cost effectiveness ratio (\$/QALY)	REDACTED ¹	REDACTED ²

Source: Table 6, p12 of the olaparib November 2022 PBAC minutes

Assumes 1.2% false negative and 2.5% false positive

The REDACTED values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

The commentary considered that the difference in incremental cost was due to the reduced olaparib price, and the difference in life years and QALYs was primarily due to the reduction in the assumed cure fraction for olaparib (changed from 38.6% to 30%). The change in the utility value applied in the post-progression health state (changed from 0.544 to 0.577) and change in the *BRCA* testing cost (from \$1200 to \$1000) both had a minimal impact on the ICER.

The commentary considered that notable changes to the model included:

- Cure fractions;
- Method of extrapolation; and
- Updated costs (increased palliative costs and decreased olaparib and *BRCA* testing costs in the comparator arm).

Key sensitivity analyses showed the model was sensitive to changes in the cure fraction in either arm. When the cure fraction for olaparib + bevacizumab was changed from 30% to 25.45%, the ICER increased by 16.8% to \$55,000 to < \$75,000 /QALY. Using the Weibull function for the extrapolation of bevacizumab monotherapy PFS (which decreased the cure fraction to 17.4%) increased the ICER by 45.5% to \$75,000 to < \$95,000 /QALY. Removal of the PFS point of

truncation from the model only had a small impact on the model, resulting in a 4.8% increase in the ICER \$55,000 to < \$75,000/QALY).

Although for 1658 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 and that costs and outcomes associated with inconclusive test results were omitted from the initial analysis, the commentary noted that these were not addressed in the updated analysis.

14. Financial/budgetary impacts

This resubmission to MSAC did not provide an assessment of the financial/budgetary impacts, however the early re-entry submission considered by the PBAC at its November 2022 meeting provided updated estimates.

Although the updated net cost to the MBS appeared to decrease in the November 2022 resubmission compared with the estimates in the July 2022 submission; the commentary noted that there were errors in the calculation of costs of testing for both HRD and BRCA in that 80% of the scheduled fees were applied rather than the fee minus the greatest permissible gap (\$93.20 as at November 2022). The commentary considered that the costs to the MBS should remain the same as those estimated in the July 2022 submission given the (i) number of patients tested remains unchanged; and (ii) the costs of the tests remain largely unchanged.

Net costs to the MBS estimated in the July 2022 submission ranged from \$1.5 million in Year 1 to \$1.6 million in Year 6.

15. Other relevant information

None.

16. Committee-in-confidence information

Table 8 Names of experts from whom HRD testing advice was sought by MSAC (in order of surname by alphabetical order)

Expert	Organisation
██████████	██████████
██████████	██████████
██████████	██████████

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- There is currently no practical definition of homologous recombination deficiency (HRD) or genomic instability (GI) that can be applied to HRD tests to help harmonise tests and define thresholds for HRD-positivity. The ESC considered that the findings of the Friends of Cancer Research HRD Harmonisation project could be used to identify the most appropriate tests for determining eligibility for niraparib and other PARP inhibitors. The findings are due to be reported in approximately the second quarter of 2023.
- While a brand-specific approach was proposed by the commentary, it was difficult to determine how the brands of HRD tests available in Australia could be described by the proposed item descriptor wording “a validated test”. It was unclear how the harmonisation of different brands of HRD test and thresholds could be achieved in implementation. HRD testing may not be available in Australia. It appears that no brand of HRD test has completed the regulatory processes required for implementation.
- Non-*BRCA* HRR genes appear to not be predictive of treatment effect. There is expert consensus that HRR gene variant results may still be useful to report as they may provide other clinically relevant information.

Economic issues:

- The appropriate fee for HRD testing is uncertain. MSAC previously considered the proposed fee of \$2500 may be high and insufficiently justified. However, the Royal College of Pathologists Australasia considered the proposed fee may not be sufficient to cover the laboratory costs of HRD testing. HRD testing may be more complex than whole exome/genome sequencing. This may result in patients incurring out-of-pocket expenses.
- The ICERs are high and sensitive to the prevalence of HRD positive results – but this also varied depending on the assay and Genomic Index Score (GIS) thresholds used. The costs of failed tests (about 13% of all tests), the consequences for patients and any possible follow-up costs were not considered in the economic evaluation or financial impact.

Financial issues:

- The placement of the proposed test in the clinical management algorithm affects the MBS costs. ESC considered it more practical to perform HRD testing early in the management pathway due to the quality deterioration issues of the samples over time.
- The population is relatively small, resulting in a modest impact on the MBS. Reporting of non-*BRCA* HRR genes may require consideration of germline cascade testing thereby increasing the financial impact by ~\$30,000 per year.

ESC discussion

ESC noted that this application from AstraZeneca was for listing of a new Medicare Benefits Schedule (MBS) item for a test to detect positive homologous recombination deficiency (HRD) status in tumour material from a patient diagnosed with advanced (FIGOIII-IV), high-grade serous or high-grade epithelial ovarian cancer (HGEOC), fallopian tube cancer or primary peritoneal cancer, including *BRCA1* or *BRCA2* pathogenic or likely pathogenic gene variants, to determine if requirements are fulfilled for access to olaparib in combination with bevacizumab, under the Pharmaceutical Benefits Scheme (PBS). ESC noted that, at its November 2022 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) deferred its decision to list olaparib, and

that “the PBAC was of a mind to recommend olaparib pending MSAC consideration of HRD testing” in March 2023.

MSAC did not support public funding of Application 1658 at its [July 2022 meeting and requested that any resubmission address several matters related to HRD testing \(refer to background\)](#).

HRD occurs when cells cannot effectively repair double-stranded breaks in DNA using the homologous recombination repair (HRR) pathway. ESC recalled that HRD can be assessed using different pathology testing methods. The focus of the submission was HRD status as defined by genomic instability (GI).

ESC noted the similarities between this Application 1658.1 and [Application 1726](#).

The submission proposed the SOPHiA DDM Homologous Recombination Deficiency test (SOPHiA assay) to determine GI and *BRCA* status. ESC noted that the REDACTED is validating the SOPHiA assay. ESC noted that the SOPHiA HRD assay (used in the REDACTED validation study) assesses tumour samples for *BRCA1/2* variants and pathogenic variants in several other HRR genes, while also estimating GI via a Genomic Integrity Index (GII). ESC noted that the Illumina TruSight Oncology 500 (TS500) HRD test may be another test option that could be implemented.

ESC also noted that the SOPHiA assay is currently being considered by Therapeutic Goods Administration (TGA) and the National Association of Testing Authorities (NATA). ESC noted the Department’s advice that MSAC may not be able to support public funding without a test that meets the relevant regulatory requirements for implementation on the MBS. ESC considered that further consultation with TGA/NATA is required about the timeline for the accreditation and regulatory process for the test. ESC noted the pre-ESC response stated that the NATA and TGA assessment has started and that the REDACTED are awaiting next steps regarding validation as an ‘in-house’ in vitro diagnostic (IVD) medical device.

ESC noted that the resubmission did not include an updated MBS item descriptor. ESC noted the commentary’s comment that the MBS descriptor could use a test-specific approach, but there is currently no assay with direct trial evidence (clinical utility standard), such as Myriad’s MyChoice® CDx, available in Australia to test HRD status. The applicant suggested in their pre-ESC response that “TGA [Therapeutic Goods Administration] approved IVD [in vitro diagnostic] companion diagnostic test” or the “SOPHiA DDM™ Homologous Recombination Deficiency test” could be used in the MBS item descriptor. ESC considered that a test-agnostic approach would be preferred. ESC noted that the application did not sufficiently describe the SOPHiA assay, and it could not determine whether the assay was a panel test or whole-genome sequencing (WGS). ESC considered that the requestors and frequency of testing in the descriptor were appropriate. ESC advised that the test would not normally require hospital treatment or accommodation.

ESC noted that, if MBS item 73301 were replaced with the proposed MBS item, clinicians would not be able to request only *BRCA1/2* testing in this population; HRD testing would be required in all instances, which may result in additional out-of-pocket costs for patients. ESC noted that the Royal College of Pathologists of Australasia (RCPA) was not supportive and considered that the proposed fee of \$2500 was not sufficient to cover the laboratory costs of HRD testing, meaning possible out-of-pocket expenses for patients. The RCPA also noted that the concordance results for the different HRD tests are acceptable for *BRCA* testing but not for GI. ESC agreed with the RCPA’s concern that the fee was too low and noted that the MyChoice® assay costs the equivalent of AU\$REDACTED

ESC considered that this might result in large out-of-pocket costs to patients. ESC also noted that, due to the small population size, there would be no economies of scale associated with testing costs. ESC noted the commentary stated that fees for MBS items for whole-exome sequencing (WES) or WGS analysis of germline variants range between \$2,100 and \$2,900, but

ESC considered HRD testing to be more complex than germline testing and therefore queried whether it is appropriate to benchmark this to existing tests.

ESC noted that following MSAC's consideration of application 1658, the Department had received expert consultation input from three HRD experts on the possible definitions of the HRD biomarker and how it is detected by testing, for MSAC to better judge whether the definition of HRD has been sufficiently established for the purpose requested and by the means proposed.

ESC noted that the three HRD experts and the submission defined HRD as a phenotype that is characterised by the inability of a cell to effectively repair DNA double-strand breaks using the HRR pathway. ESC considered that this definition was consistent with guidelines and the definition provided by the applicant. However, ESC considered that this definition was conceptual, rather than a practical definition that could be applied to HRD tests to help harmonise tests and define thresholds for HRD-positivity.

The experts advised that HRD can be inferred from the 'causes' (e.g. deleterious alterations in *BRCA1* or *BRCA2* genes), or the 'consequences' (e.g. GI and structural chromosomal aberrations), or measured directly by 'functional' assays (e.g. RAD51 foci formation). In patients with HGEOC, ESC considered that HRD can be inferred from i) deleterious germline or somatic variants in *BRCA1* or *BRCA2*, or in other genes in which aberrations cause homologous recombination repair deficiency; and/or ii) measures of GI, chromosomal aberrations, and other characteristic genomic features that reflect homologous recombination DNA repair deficiency.

ESC noted that the HRD experts all advised there is no uniformly accepted 'gold standard' HRD test or threshold to determine HRD or threshold to determine which patients benefit from PARP inhibitors. ESC concluded from the HRD experts' advice that HRD thresholds do not rely on the presence or absence of *BRCAm* and should reflect whether genomic scarring is evident. The experts advised that measures of HRD (or homologous recombination proficiency) tend to be continuous, making it difficult to determine a robust cut-off. ESC noted that the Myriad MyChoice® HRD test had two different thresholds for different PARP inhibitors.

ESC noted that two of the experts advised that the tests and thresholds used could be those that have been demonstrated in clinical trials or validation studies to determine which patients would benefit from PARP inhibitors. ESC noted that experts acknowledged that these tests may not correctly identify all patients who may benefit from PARP inhibitors. One expert suggested that once the Friends of Cancer Research HRD Harmonisation project reports its findings in approximately the second quarter of 2023, funding of HRD tests in Australia could potentially be reduced to the best performing tests. One expert suggested other possibilities for validating tests that may become available in Australia include testing samples from PARP inhibitor trials to assess association with response to treatment especially for *BRCAt* cases and determining the ability of the HRD test to predict platinum sensitivity as a surrogate given it is highly associated with response to PARP inhibitors.

Regarding preferred methods of HRD results reporting, the resubmission indicated that pathogenic variants in non-*BRCAm* HRR genes would not be reported in the HRD test reports provided to clinicians. Through the Department's targeted consultation with experts, ESC noted that clinicians prefer reporting of pathogenic variants in non-*BRCAm* HRR genes. One expert stated that the HRR genes that carries a mutation (with the type of mutation and a clear definition of its effect) must accompany the HRD score. Additionally, the experts considered that the variant status of the main HRR genes would be useful to report. While acknowledging that the majority of other HRR genes are not necessarily useful now, as data accumulates they may become so. Experts also expressed that, in the event no pathogenic variant has been revealed, this must be reported as well such that there is accumulating knowledge pointing towards more cryptic events that may be associated with HRD. Thus, ESC considered that there is consensus

that HRR gene variant results may be useful to report, and that including information about clinical significance of HRR gene variants should be considered. Pre- and post-test genetic counselling may also be beneficial.

ESC considered that potential safety issues associated with HRD testing and treatment with olaparib were important for consumers. ESC considered that the implications of false positive and false negative test results were important as this would have implications for treatment eligibility and the potential for people to be exposed to adverse events from medicines with uncertain treatment benefits. ESC considered the potential for out-of-pocket costs and uncertainty related to whether a test would be available for MBS implementation are also key issues for consumers. ESC noted that the Ovarian Cancer Australia website discusses the use of olaparib in women with ovarian cancer, but does not mention the requirement for testing to access the drug. ESC noted that the members of the organisation were surveyed and queried if the survey results were available.

ESC noted the response from the National Pathology Accreditation Advisory Council stating that the tests need to be validated and reviewed by the TGA and the National Association of Testing Authorities (NATA). The “black box” nature of the assay is difficult to assess as part of a quality assurance program.

The RCPA advocated waiting for more data from the Friends of Cancer Research HRD Harmonization Project. ESC noted that findings from this project should be available in the second quarter of 2023, and that accreditation of HRD tests in Australia could be reduced to those best performing tests as shown by this project. ESC noted the RCPA’s advice that more cost-effective in-house testing is likely to be available soon.

The data available suggested that the positive predictive values (PPVs) and negative predictive values (NPVs) for both the SOPHiA and Illumina assays were similar, and represented similar sensitivities and specificities to the Myriad MyChoice® assay. ESC noted that a new concordance study from the PAOLA-1 trial compared the SOPHiA assay with the Myriad MyChoice® CDx assay. This study suggested that the two tests performed similarly (HRD positive 51.8% for MyChoice® vs 49.6% for SOPHiA). ESC also noted the pre-ESC response that this study also provided evidence that the SOPHiA assay predicts treatment response. The study found no differences in the effect modification with the two different assays. However, these results were from a conference abstract only, so ESC could not evaluate the study nor risk of bias status. In the pre-ESC response updated data from an additional 59 ovarian cancer samples added to the REDACTED validation study were presented. Updated concordance analysis of Myriad and SOPHiA for HRR + GI showed a positive, negative and overall per cent agreement of 92%, 87% and 90%, respectively. ESC considered that, overall, the current resubmission did not address MSAC’s previous concerns.

ESC noted that the evidence used to support the clinical claim had largely not changed from the original application. ESC noted that a direct evidence approach was not possible, and that the application proposes using the SOPHiA assay; however, the pivotal PAOLA-1 trial from which the clinical evidence was derived used the Myriad MyChoice® HRD plus and CDx assays. Therefore, a linked evidence approach was used, assuming equivalence between SOPHiA, the Myriad MyChoice® assays and NGS testing, but ESC noted that there were no studies comparing the SOPHiA assay to NGS BRCA testing (fresh tissue), and that there is limited evidence comparing the SOPHiA assay to the MyChoice® CDx assay. ESC considered that while most of the direct evidence was for the Myriad MyChoice® HRD test (as used in the pivotal trial) or a version of it, this test is not currently registered with the Therapeutic Goods Administration (TGA) for inclusion in the Australian Register of Therapeutic Goods (ARTG).

ESC also noted the following results from the PAOLA-1 trial:

- non-*BRCA* HRRm, in contrast to HRD (GI), was not predictive of PFS (progression free survival) benefit with olaparib + bevacizumab vs placebo + bevacizumab as first-line maintenance, regardless of which *HRR* gene panel was used
- non-*BRCA* HRR gene panels captured a small proportion of patients with non-*BRCA* HRR variants (3.7–9.8%) compared with HRD (GI) excluding *BRCAm* (19%). Tumours with non-*BRCA* HRR variants included both HRD (GI) positive or negative tumours.
- beyond *BRCAm*, non-*BRCA* HRRm and HRD (GI) are not interchangeable and should not be considered as substitutes for each other in clinical practice for first-line maintenance in ovarian cancer.
- ESC noted that the pre-ESC response accepted that HRR genes may provide beneficial prognostic information, but do not appear to predict response to PARP inhibitors (Pujade-Lauraine 2021¹⁴).

ESC considered that there are reasonable explanations for these results, as not all mutations will result in an unequivocal loss of function and some mutations may result in partial activity but not be sufficient to be associated with HRD.

ESC noted evidence in the original application of olaparib and bevacizumab treatment having benefit in the HRD positive group on progression free survival (PFS), and no benefit on PFS in the HRD negative group. ESC also noted that the updated overall survival results (final data cut-off at 5 years) suggested olaparib combination therapy in the subgroup of interest (*BRCAwt*, HRD positive) may have an overall survival benefit, but the results were not statistically significant. The resubmission considered that, given the high crossover in the trial, the results underestimated the likely treatment effect. ESC agreed with the commentary's observation that the overall survival results were generally encouraging and consistent with PBAC considerations of olaparib + bevacizumab based on PFS results in the original submission, but that these results do not address any of the issues raised by MSAC in July 2022.

ESC also noted that tissue quality for HRD testing needs to be of higher quality than for *BRCA1/2* testing. Of all samples, 13% fail testing and what happens to these patients afterwards is uncertain (i.e. whether they are retested or treated as HRD negative and proceed with bevacizumab monotherapy). ESC noted that this has not been considered in the economic evaluation or the financial impact. ESC noted the pre-ESC response that provided new agreement data on the GIS of the SOPHiA HRD test vs the MyChoice® test, showing that there would be a negligible change to the ICER (increasing from \$55,000 to < \$75,000 to \$55,000 to < \$75,000) when the positive percent agreement and negative percent agreement are based on the updated meta-analysis of 5 cohorts.

ESC noted that the test's placement in the clinical management algorithm affected the MBS costs; options include to replace the *BRCA1/2* test with the HRD testing up front, or to test *BRCA1/2* first and only perform testing on *BRCAwt* results. ESC considered it more practical to perform the HRD testing first, as the quality and age of the tissue deteriorates, and the population is relatively small (1,131 per year).

ESC noted that the budget impact to the MBS ranged from \$1,710,895 in year 1 to \$1,907,878 in year 6, but that the overall costs to the health budget were substantial (about \$20 million to <

¹⁴ Pujade-Lauraine E 2021. [LBA33 maintenance olaparib rechallenge in patients \(pts\) with ovarian carcinoma \(OC\) previously treated with a PARP inhibitor \(PARPi\): Phase IIIb OReO/ENGOT Ov-38 trial](#). *Annals of Oncology* 32(S5): S1308–09.

\$30 million) due to the cost of the drugs. ESC noted that a renegotiated drug price could positively affect the economic evaluation and overall budget impact.

ESC also noted that there is a potential cost relating to reporting HRD genes in cascade testing (additional germline test of \$400), and that this would also result in an additional budget impact of \$30,000 per year.

18. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

19. Further information on MSAC

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