Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1726 – 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 niraparib

Applicant: GSK Australia 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

The integrated codependent application requested:

- A Medicare Benefits Schedule (MBS) item for homologous recombination deficiency (HRD) testing of tumour tissue to determine eligibility for access to Pharmaceutical Benefits Scheme (PBS)-subsidised niraparib for maintenance treatment of patients with advanced (International Federation of Gynaecology and Obstetrics [FIGO] III-IV) high-grade epithelial ovarian cancer (HGEOC); and

- Expansion of the current PBS listing of niraparib for the maintenance treatment of HGEOC to include patients whose tumours are found to be HRD positive *BRCA* wild type (*BRCA*wt), in addition to the existing listing for patients whose tumours have a *BRCA* variant (*BRCA*m).

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 variants in the *BRCA1/2* genes) 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, 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 treatment benefit with niraparib. MSAC considered that the codependency was not strong as the key trial showed niraparib improved progression-free survival in both GI positive and GI negative patients, although in GI negative patients the magnitude of benefit may not have been clinically significant and there was no evidence for an improvement in overall survival. 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 PRIMA trial. MSAC considered that HRD testing (GI and *BRCA1/2* status) and subsequent treatment with niraparib

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 niraparib specifically 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 advised 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 item descriptor

Category 6 – Pathology Services   Group P7 - Genetics
MBS item XXXXX
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 *BRCA1/2* status, for access to PARP inhibitor therapy under the Pharmaceutical Benefits Scheme (PBS).   Evidence of homologous recombination deficiency must be derived through a test that has been validated against the Myriad MyChoice® HRD assay.   Applicable once per primary tumour diagnosis. Not applicable to a service to which 73295 or 73301 applies.   Fee: $3,000.00 Benefit: 75% = $2,250.00 85% = $2,906.80
Practice note: Validation against the Myriad MyChoice® HRD assay should use a score of 42 of greater as the threshold for HRD (genomic instability) positivity.

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 GlaxoSmithKline Australia Pty Ltd requesting MSAC consider Medicare Benefits Schedule (MBS) listing of testing of tumour tissue to detect homologous recombination deficiency (HRD) status in women with newly diagnosed advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. The test would determine whether the person was eligible for a medicine called niraparib as maintenance therapy, which at the same time was proposed to be funded on the Pharmaceutical Benefits Scheme (PBS).

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, MSAC considered that people with HRD-positive cancer are probably more likely to respond to treatment with niraparib than people who have HRD-negative cancer.

Niraparib comes from a family of medications called PARP inhibitors. Another PARP inhibitor called olaparib is already available on the PBS for people whose cancer has a variant in *BRCA1* or *BRCA2* (*BRCA*m), and another application also considered at this meeting proposed expanding olaparib access to all 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 broader understanding of HRD and HRD testing overall is still in development, and our understanding of HRD is likely to improve in future. Given some uncertainty remains around HRD testing, MSAC requested 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 including *BRCA* variant status in patients for access to PARP inhibitors including niraparib. 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 niraparib. 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 co-dependent application from GlaxoSmithKline Australia Pty Ltd (GSK) was 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 niraparib on the Pharmaceutical Benefits Scheme (PBS).

MSAC noted the similarity between this application and Application 1658.1[1] (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 olaparib in combination with bevacizumab on the PBS. Niraparib and olaparib are both poly (ADP-ribose) polymerase inhibitors (PARPi).

MSAC recalled it had not supported funding for HRD testing under 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.*"[2]

---

[1] MSAC application 1658.1 – available at: https://www1.health.gov.au/internet/msac/publishing.nsf/Content/1658.1-public
[2] 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 considered that HRD testing is complex testing. MSAC considered that a fee of less than $2,500 was likely to lead to out-of-pocket costs, and that a fee of $3,000 was reasonable given the cost and complexity of HRD testing.

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 niraparib but that it also supported application 1658.1 at this meeting. MSAC considered that generalising the MBS item for HRD testing to be for access to PBS-listed PARP inhibitors rather than niraparib alone was appropriate and would future-proof the listing. This decision reflected the similar nature of Application 1658.1 for another PARPi, olaparib, for the same patient population.

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 the item descriptor was proposed to state "Evidence of homologous recombination deficiency for patients that are not carriers of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant, must be derived through a validated test of tumour tissue to determine a genomic instability score." MSAC considered that this wording implied *BRCA* testing would take place before determining GI, which would not be the case as GI is part of HRD testing. MSAC considered that "pathogenic or likely pathogenic" was terminology specific to germline genetic variants, so would not be correct where testing also encompasses somatic variants. MSAC also advised that the descriptor wording should be changed from "cancer" to "carcinoma", as this is the correct terminology.

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 HRM™ HRD Solution. MSAC considered that the 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 PRIMA trial). MSAC considered the cutoff should be reflected in a practice note rather than the item descriptor, because the cutoffs may change in the future. 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 the applicant's pre-MSAC advice that numerous laboratories across Australia have accreditation for similar genomic methods, although no laboratory had yet received National Association of Testing Authorities (NATA) accreditation for the Illumina TSO 500 assay with HRD add-on. MSAC considered that there was therefore currently 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 (NPAAC)'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 1363[3]), 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 poster[4]. MSAC considered it was not necessary to wait until publication of the final findings, as there were people who could 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 the Weichert 2021a and 2022 studies reviewed by the commentary. MSAC considered that the concordance between the Myriad and Illumina assays of at least 90% was acceptable. MSAC considered it reasonable that very high concordance in HRD assays may be difficult to attain due to the homologous nature of tumour samples.

MSAC noted that the main safety issues were the implications of false positive and false negative test results, as these would affect treatment eligibility and could expose people to adverse events from medicines with uncertain treatment benefits. However, MSAC considered the assay itself had no safety issues.

MSAC noted that the key predictive clinical evidence was from the PRIMA trial, which used the NGS-based Myriad MyChoice® assay with a GI score threshold of ≥42 to determine HRD positivity. The data demonstrated that progression-free survival (PFS) benefit at the 2019 data cut-off for

---

[3] MSAC application 1363 PSD available at - http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1363-public
[4] Stires et al., 2022. Available at: https://friendsofcancerresearch.org/wp-content/uploads/AMP-Poster-FINAL.pdf

those treated with niraparib versus placebo appeared more pronounced in patients (hazard ratios [95% CIs]):

- with a *BRCA* variant (HR 0.40 [95% CI: 0.265, 0.618])
- who were HRD positive with no *BRCA* variant (HR 0.50 [95% CI: 0.31, 0.83]).

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 treatment benefit with niraparib. MSAC considered that the codependency was not strong as the key trial showed niraparib improved progression-free survival in both GI positive and GI negative patients, although in GI negative patients the magnitude of benefit may not have been clinically significant and there was no evidence for an improvement in overall survival.

MSAC noted ESC's concerns with the economic model in relation to the test:

- *BRCA*m and HRD-'not determined' (HRDnd) patients were not included in the model. In the base case replacement scenario, these groups of patients would be receiving testing at a higher cost, so replacing *BRCA* testing with HRD testing has cost-effectiveness implications for the *BRCA*m subgroup that were not modelled.
- The accuracy of HRD tests in establishing *BRCA*m status may be lower than that of dedicated *BRCA* testing. The model did not consider false positive rates separately for genomic instability score and *BRCA* variant status, and implied *BRCA*m results were always true positive.
- The economic model did not account for test failures.

MSAC noted the reported ICERs, and considered that testing at a fee of $3,000 was acceptably cost-effective.

MSAC noted that the financial impact to the MBS ranged from *$0 to <$10 million* in year 1 to *$0 to <$10 million* in year 6. MSAC noted that this budget impact relied on replacing testing using existing *BRCA* MBS items. MSAC considered the financial cost of testing to the MBS to be relatively low.

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 status as a biomarker remained incompletely understood, and HRD testing is in its early stages of development. However, MSAC considered that clinical utility of HRD status had been demonstrated, in an area of substantial clinical need – as outlined in the pre-MSAC response – and noted that there are now international guidelines and efforts to harmonise HRD testing.

MSAC considered that, beyond *BRCA*m, 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 niraparib 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 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 from relevant clinical trials.

4. Background

MSAC has not previously considered niraparib in combination with the requirement for HRD testing to allow access to treatment for ovarian cancer or for any other indication. HRD testing for patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer has previously been evaluated to determine eligibility for treatment with olaparib (application 1658, July 2022 MSAC meeting).

Currently there is no test available on the MBS to determine HRD status (which is based on both *BRCA* variant status and GI) in patients with HGEOC. Only testing for *BRCA* variant status, either through germline or tumour tissue testing, is available (MBS items 73301 and 73295).

Niraparib was initially approved by the TGA on 28 June 2019 and is currently registered for the maintenance treatment of patients with advanced high grade ovarian, fallopian tube or primary peritoneal cancer who have either completed first-line (1L) platinum-based chemotherapy (PBC) or are in response (complete or partial) to PBC.

Niraparib is currently PBS listed for the treatment of high grade advanced epithelial ovarian, fallopian tube or primary peritoneal cancer in patients with a (somatic or germline) class 4 or 5 *BRCA1/2* gene variant who are in response (partial or complete) to immediately preceding PBC. A maximum total niraparib treatment duration of 36 months applies.

Differing terminology has been used in submissions provided for the evaluation of different drugs and diagnostic tests associated with HRD for patients with HGEOC. For consistency, the terminology used in this commentary was aligned with terminology used in the first application for the treatment of patients with HRD positive *BRCA*wt HGEOC assessed by the PBAC and the MSAC (olaparib; item 6.07, July 2022 PBAC meeting and application 1658, July 2022 MSAC meeting). Therefore the terminology used in the commentary is different to the terminology used in the submission. Most notably, *BRCA*wt and HRD negative were used in the commentary, whereas non *BRCA*m and HRp, respectively, were used in the submission for these terms.

5. Prerequisites to implementation of any funding advice

The submission claimed that the proposed medical test, the Illumina TruSight Oncology 500 HRD test was commercialised in Australia in August 2022 and that completion of local validation and NATA accreditation is expected to occur at several Australian laboratories that are using the next-generation sequencing (NGS) TruSight™ Oncology 500 panel. The submission reported that the TruSight Oncology test is currently available at five major pathology laboratories in Australia that are participating in the MoST, ASPiRATION and PrOSPECT clinical trials. The commentary considered that it was unclear whether the Illumina TruSight Oncology 500 HRD is TGA registered (as no evidence of TGA registration was provided in the submission or found during the evaluation) and the expected timing of local validation and NATA accreditation was not provided in the submission. It also remained unclear whether the same five major pathology laboratories would conduct the HRD testing if it is listed on the MBS.

6.   Proposal for public funding

Table 2	Presentation of an existing, amended or newly proposed MBS item. Category 6 – Pathology services
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 determine eligibility with respect to homologous recombination deficiency (HRD) status for access to niraparib under the Pharmaceutical Benefits Scheme (PBS). Evidence of homologous recombination deficiency for patients that are not carriers of a *BRCA*1 or *BRCA*2 pathogenic or likely pathogenic variant, must be derived through a validated test of tumour tissue to determine a genomic instability score. Applicable once per primary tumour diagnosis Fee: $3000	

Source: Table 15, p55 of the submission

Notable differences between the proposed MBS items for niraparib and olaparib (p8, application 1658, Public Summary Document (PSD), July 2022 MSAC meeting) were:

- The proposed niraparib MBS item stated that evidence of HRD for patients who are not carriers of a *BRCA*1 or *BRCA*2 pathogenic or likely pathogenic variant, must be derived through a validated test of tumour tissue to determine a genomic instability score (GIS), whereas the details for determination of a GIS and use of a validated test were not specified in the proposed olaparib MBS item; and

- The proposed HRD test price was higher in this submission ($3,000) compared to the olaparib submission, application 1658 ($2,500).

While the proposed MBS item appears to be seeking to incorporate both an HRD test and a *BRCA*1/2 test to allow eligibility to niraparib to be determined based either HRD status or *BRCA*1/2 status, the commentary highlighted that the inclusion of a *BRCA*1/2 test was not specified in the proposed item. Additionally, as the proposed test incorporates *BRCA*1/2 testing, patients should not be able to undergo *BRCA* testing using the current MBS items in addition to the proposed test. The commentary therefore considered that it may be appropriate to include in the restriction wording "... to determine eligibility with respect to homologous recombination deficiency (HRD) status, including *BRCA*1/2 status, for access to niraparib under the Pharmaceutical Benefits Scheme (PBS)." and that the item is "Not applicable to a service to which 73301 or 73295 applies."

The commentary highlighted that the specification "carrier" in the context of germline variants may be considered somewhat ambiguous, as that term generally has the meaning in genetics of a person with one variant allele and one wild type one. The proposed MBS item specifically uses the term "carriers", however this may be misleading as the intended use appears to refer to patients who may have biallelic *BRCA*1 or *BRCA*2 variant status, rather than to patients specifically having one variant and one wild type allele. In being specific with the usage of "carriers", it may exclude pts with biallelic variants. The commentary considered that it was unclear if this was the intention.

The commentary considered the use of "pathogenic or likely pathogenic" to describe the *BRCA* variant may also be problematic as these are classes of germline variant, which equate to "tier I or II" of clinical significance in the somatic variant classification system. This use of the germline variant classification system in the proposed item technically means that only people with germline *BRCA*1/2 variants are included. The commentary considered if the intent was to include patients with somatic *BRCA*1/2 variants, then the wording should be revised.

As for olaparib (July 2022 MSAC meeting), the submission proposed HRD testing for all patients after a diagnosis of HGEOC, to allow the establishment of both *BRCA* variant status and GI status (GIS). Currently HRD status has not yet been satisfactorily defined by reference to a single test method, scoring algorithm and threshold (p1, application 1658, PSD, July 2022 MSAC meeting).

The proposed Illumina TruSight Oncology 500 HRD assay uses an NGS panel to capture both known and novel gene fusions, covering variants in 523 genes associated with tumorigenesis, including *BRCA1/2* and other genes encoding components of the homologous recombination repair (HRR) pathway. Inclusion of the Illumina TruSight Oncology 500 HRD assay in the NGS workflow involves ~25K genome-wide probes designed to assess for genomic scars across patients of a broad range of ethnicities. DNA enrichment with the HRD probes occurs on the same plate and at the same time as TruSight Oncology 500 enrichment. Biotinylated probes hybridize to regions of interest, which are pulled down using streptavidin-coated magnetic beads and eluted to enrich the library pool. The pooled TruSight Oncology 500 and HRD libraries are sequenced on the NextSeq 550, NextSeq 550Dx or NovaSeq 6000 System.

The submission stated that specimens for testing with Illumina TruSight Oncology 500 HRD are acquired from a biopsy or archived formalin-fixed paraffin embedded (FFPE) tissue sample collected at the time of ovarian cancer diagnosis (e.g. during laparoscopy prior to neoadjuvant chemotherapy) or primary debulking surgery (PDS). The commentary considered that it is unclear whether fresh tissue may also be used with the TruSight Oncology 500 HRD test. MSAC has previously considered fresh samples would be preferred for testing as sample quality is degraded both by the FFPE process and by prolonged storage (p5, application 1658 PSD, July 2022 MSAC meeting).

The submission proposed that the medical service for the requested HRD test should replace MBS item 73301 that is currently used to determine eligibility relating to *BRCA* status for access to niraparib (and olaparib) in patients with advanced ovarian cancer. The commentary noted that patients who only require *BRCA* testing (i.e. *BRCA*1/2 variant positive (*BRCA*m) and who are currently eligible for niraparib (and olaparib) under the current PBS-listed ovarian cancer indications) would be required to undergo fuller HRD testing and would therefore incur any additional out of pocket expenses associated with the fuller HRD test for no additional benefit and potentially have higher risks of misclassification and risk receiving suboptimal treatment.

The cost of the *BRCA* test (MBS item 73301) is currently listed as $1,200. MSAC previously advised (p1, Application No. 1618 MSAC PSD, MSAC meeting November 2021) that the fee for MBS items to test for germline or somatic variants in only the *BRCA*1 and *BRCA*2 genes should be reduced from $1,200 to $1,000 as the cost of this testing has decreased. Therefore, the cost of HRD testing is estimated to be $2,000 more than *BRCA* testing.

When considering application 1658 in July 2022, MSAC considered that the fee of $2,500 proposed for the HRD test was not sufficiently justified and seemed excessive for the costs of conducting the assay and the bioinformatics. MSAC noted the potential for patients to incur further out-of-pocket costs for this testing given the commercial tests sell for higher prices overseas (p3, MSAC application 1658, Public Summary Document, July 2022 MSAC meeting).

7.   Population

The proposed MBS item descriptor is intended to allow testing of tumour tissue from patients with newly diagnosed advanced (NDA) HGEOC and would provide HRD status (both *BRCA* and GIS in parallel), with the base case presented by the submission assuming that testing occurs upfront following diagnosis of advanced HGEOC. The HRD testing will determine whether patients are eligible to receive treatment with niraparib, being those patients with HGEOC who are both HRD positive and *BRCA* wildtype (referred to as HRD positive *BRCA*wt herein) under the proposed PBS listing.

HRD is a phenotype that is characterised by the inability of a cell to effectively repair DNA double-strand breaks using the 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 PARP inhibitors and PBC, which target the destruction of cancer cells by working in concert with HRD through synthetic lethality (Stewart 2022).

HRD positive status was defined in the submission as having either tumour *BRCA*m or a composite GIS ≥42 measured using the Illumina TruSight Oncology 500 HRD assay. The appropriateness of the threshold is discussed later. The composite GIS is based on the sum of the measures of loss of heterozygosity (LOH), telomeric allelic Imbalance (TAI) and large-scale state transitions (LST), which are all measures of genomic scarring due to HRD and are observed as specific patterns of variants and structural aberrations of chromosomes, including rearrangements, gains and losses of DNA.

With cells that exhibit HRD generating identifiable patterns of variants and insertions/deletions in the genome, their expression in the form of mutation signatures or genomic scars can form the basis of clinical assays. Genomic scars of HRD consist of specific patterns of variants and structural aberrations of chromosomes, including rearrangements, gains and losses of DNA. This can be evaluated via the following metrics of genomic instability at the phenotypic level, that results from the loss of HRR capability (refer to Figure 1):

- LOH: deletion of one allele (copy loss LOH) or by deletion and simultaneous duplication of the remaining allele (copy neutral LOH), resulting in the loss of one of the two alleles at a heterozygous locus;
- TAI: the number of regions with allelic imbalance extending to the sub-telomere but not crossing the centromere; and
- LST: transition points between regions of abnormal DNA or between two different regions of abnormality.
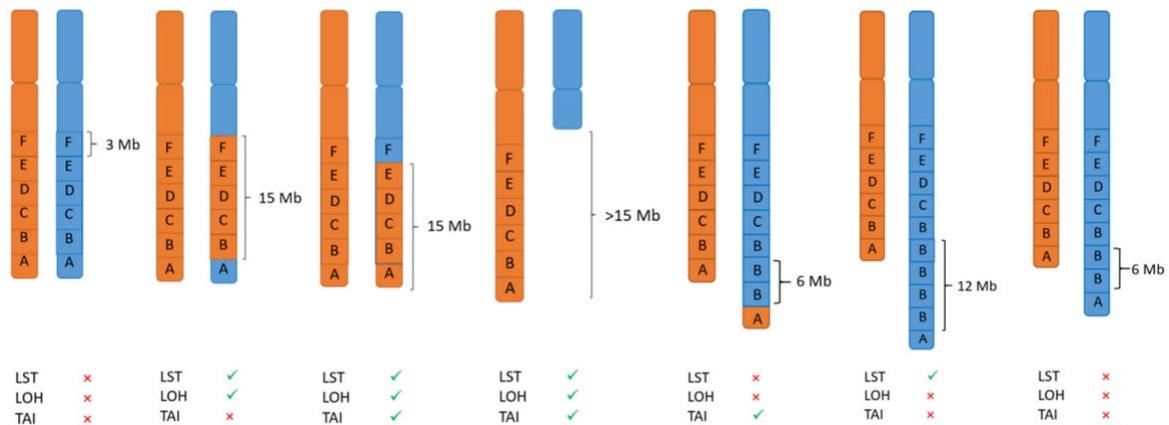
Figure 1   Examples of chromosomal alterations categorised by LOH, TAI and LST status
LOH = loss of heterozygosity; LST = large-scale state transition; TAI = telomeric allelic imbalance
Source: Figure 3, p30 of the submission

As HRD tests incorporating LOH, TAI and LST are designed to identify evidence of genomic scarring, they are an indirect measure of HRD function, and rather infer it from observing variants considered to be signature consequences of HRD. As genomic scars are permanent despite dynamic changes in homologous recombination function, the assessment of genomic instability can vary over time and may not represent the current HRD status of cancer cells. Reversion mutations are also a possibility.

The following patient testing scenarios were identified and were explored in the submission:

- Population #1 (Base case): HRD testing to determine *BRCA*1/2 variant status and GIS in parallel at diagnosis
- Population #2: HRD testing to occur sequentially following a negative *BRCA*1/2 test result at diagnosis

- <u>Population #3a:</u> HRD testing to determine *BRCA*1/2 variant and GIS in parallel, being deferred to the time of receipt of 1L platinum-based chemotherapy only
- <u>Population #3b:</u> HRD testing at the time of receipt of 1L platinum-based chemotherapy only, following determination of *BRCA* status at diagnosis.

The base case scenario was consistent with MSAC's previous view that a single combined test is preferred as it would be more efficient use of the sample for the pathology laboratory workflow, would more likely use the fresh tissue, which gives the best genetic test results, and would report both results faster than sequential testing. MSAC considered the logistics of sequential HRD testing would be complex (p5, application 1658, PSD, July 2022 MSAC meeting).

The submission proposed that testing of tumours to identify HRD (*BRCA* and GI) status should be applicable once per primary tumour diagnosis and that because of this restriction, repeat HRD testing was not expected to occur in practice. Consequently, the submission did not include any provision for HRD retesting. The submission proposed that patients who had a failed HRD test (i.e. homologous recombination not determined (HRnd)) may undergo germline *BRCA* (*gBRCA*) testing to determine eligibility for niraparib (or olaparib) under the existing PBS listing. However the commentary highlighted that no consideration of additional *gBRCA* testing in patients who were HRnd was included in the economic evaluation or financial estimates.

HRD testing expert advice

Following application 1658, MSAC had requested expert advice on the possible roles of the HRD biomarker and the means by which it is detected. Three experts provided the following advice:

<u>Definition of HRD:</u>

- While there is currently no precise definition of HRD, HRD can generally 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.

- HRD can be inferred from the 'causes' (e.g. deleterious alterations in *BRCA1* or *BRCA2*), the 'consequences' (e.g. genomic instability (GI) and structural chromosomal aberrations), or measured directly by 'functional' assays (e.g. RAD51 focus formation).

- Specifically, HRD in high-grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma can be inferred from:

    1. Deleterious germline or somatic variants in *BRCA1* or *BRCA2*, or in related genes, that are known to cause homologous recombination DNA repair deficiency; and

    2. Measures of GI, chromosomal aberrations, and other characteristic genomic features that reflect homologous recombination DNA repair deficiency with high specificity.

    Caveat: It should be noted that restoration of HR DNA repair, through mechanisms including *BRCA* reversion mutations, may contribute to discordance between HRD scores and clinical treatment response. However the mechanism of action of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors was based on the rationale of synthetic lethality in tumours with underlying HRD.

<u>How different definitions of thresholds will affect HRD positivity:</u>

- There is currently no uniformly accepted standard HRD test or test threshold. A good example being the Myriad MyChoice® CDx assay which has variable cut-offs depending on the PARP inhibitor used (veliparib uses a cut-off of 33 whereas olaparib has a cut-off of 42);

- HRD thresholds do not specifically rely on the presence or absence of *BRCAm* and should reflect whether genomic scarring is evident; and

- 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.

- Cut-offs 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.

- One of the experts also discussed the Friends' HRD Harmonization project[5], 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.

Different HRD test options in Australia:

- There are two test options that are becoming available in Australia, developed by SOPHiA and Illumina. The evidence thus far for the positive-predictive-values and negative-predictive-values for both the SOPHiA and Illumina assays are very similar and represent similar sensitivities and specificities to the Myriad My Choice assay as far as that can currently be judged.

- The SOPHiA assay is currently being assessed by the TGA prior to release in the Australian market and the Illumina assay is available but not yet submitted to the TGA.

- Test options that might become available in Australia could potentially be validated by the following approaches:

  o Demonstrating concordance with the MyChoice® HRD assay that has been used in clinical trials such as PAOLA-1.

  o Testing samples from PARP inhibitor clinical trials to directly assess association with response to treatment, in particular in *BRCAwt* cases.

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

Reporting HRD results:

- It is preferred that HRD results clearly state whether HRD is present or not and provide a score indicating whether the result is unequivocal in either direction. The HRR gene that carries a variant (with the type of variant and a clear definition of its effect) must accompany the HRD score. 'Expert 2' stated that "consideration would need to be given to the interpretation of variants 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 variants 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". The variant status of the main HRD genes would be useful to report. In addition to that, the report should include whether the variant is an inherited or a somatic pathogenic variant (although this can only be determined following testing non-tumour tissue such as blood). The majority of other HRD genes are not necessarily useful now, although as data accumulate they may become so. In the event no relevant 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.

---

[5] https://friendsofcancerresearch.org/wp-content/uploads/AMP-Poster-FINAL.pdf

- 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 stated that the breakdown of LOH, TAI and LST should also be presented.

8. Comparator

Currently tumour *BRCA* testing is funded under MBS item 73301 upon diagnosis of advanced ovarian cancer. This test was nominated by the submission as the main comparator (Populations #1 (base case) and #3a, parallel testing scenarios) 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 GI status.

For application 1658, the MSAC accepted the comparator for tumour HRD testing (i.e. combined *BRCA*1/2 testing with genomic instability testing) was tumour *BRCA*1/2 testing alone (i.e. MBS item 73301) (page 4, Application No. 1658, Public Summary Document, July 2022 MSAC meeting).

For the sequential testing scenarios (Populations #2 and #3b) the submission nominated no test as the comparator, as patients continue to receive *BRCA* testing but only those identified to be *BRCA*wt would then undergo HRD testing. HRD testing would not replace anything else.

A second MBS item is currently available for patients in whom tumour *BRCA* testing is not possible. MBS item 73295 allows for the detection of germline *BRCA*1 or *BRCA*2 pathogenic or likely pathogenic gene variants, in patients with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible, to determine eligibility for niraparib (or olaparib) under the PBS. The commentary considered that it is expected that this item will continue to be used if the proposed MBS item for HRD testing is funded and that MBS item 73295 is not an appropriate comparator.

The NGS-based Myriad MyChoice® HRD CDx assay was used to determine HRD status (including pathogenic *BRCA*m) in patients enrolled in the PRIMA study and was considered the clinical utility standard for *BRCA* testing in the submission.

The submission referenced several different Myriad HRD tests (i.e. Myriad MyChoice® HRD PLUS, Myriad MyChoice® CDx, Myriad MyChoice® PLUS research use only (RUO), and Myriad MyChoice). The commentary considered that there were uncertainties regarding the identification of which Myriad test was used in each trial or study, and despite the naming conventions being different, they were possibly referring to the same test in some instances. However, it was not always clear which test was being used during each study and this was a source of uncertainty. The submission identified 'bridging data' and claimed that it demonstrated that the different iterations of the MyChoice® test are concordant with regard to the determination of *BRCA* status, GIS and overall HRD status. The commentary considered that while these results indicated a high level of concordance between the various Myriad MyChoice® HRD tests, they demonstrated that the tests are not identical and it remains unclear whether they can be used interchangeably. During the evaluation of olaparib and HRD testing (application 1658) it was observed that Myriad MyChoice® HRD PLUS and Myriad MyChoice® CDx were both used to classify patients in the PAOLA-1 trial but the trial results were not identical, with potential for the two tests to have classified patients in the PAOLA-1 population differently, which may have had an impact on the interpretation of trial results as well as the resulting cost effectiveness (table 19, p38, application 1658, PSD, MSAC July 2022 meeting). The MSAC did not explicitly comment on this issue and the ESCs therefore accepted the applicant's arguments that it was reasonable to consider either the Myriad MyChoice® HRD test and the Myriad MyChoice® CDx test as the clinical utility standard (p53, Application No. 1658, Public Summary Document, July 2022 MSAC meeting). However, this was predicated on the fact that results using classification from both Myriad MyChoice® HRD and Myriad MyChoice® CDx being

presented for PAOLA-1 whereas only results from classification with Myriad MyChoice® CDx were presented for PRIMA.

The submission also included a supplementary trial that compared niraparib with standard medical management (SMM) (PRIME) in which HRD status was determined using the BGI assay. However the submission did not consider the BGI assay to be a clinical utility standard due to the limited details available regarding this trial and the assay. The commentary considered that while the BGI assay should be considered a clinical utility standard, the lack of information for this test and the PRIME study appears to restrict its usefulness in this context.

9.   Summary of public consultation input

In its consideration of MSAC Application 1658 in July 2022, MSAC had requested the Department seek targeted consultation from Australian and overseas experts on HRD testing and for this to also be included in its consideration of MSAC Application 1726. Responses were received from three Australian experts (summarised above).

Additional consultation feedback was received from one individual specialist and four organisations: the Royal College of Pathologists of Australasia (RCPA), Australian Genomics, Ovarian Cancer Australia, and Pink Hope. The input received was mixed in its support for HRD testing.

Advantages of the proposed testing were:
- It would allow for a greater proportion of patients with ovarian cancer access to maintenance therapy with PARP inhibitors that may improve overall survival and progression-free survival outcomes.
- 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 submission presented a linked evidence approach to support the contention that patients with HGEOC whose tumours are HRD positive *BRCA*wt who respond to PBC will derive benefit from maintenance treatment with niraparib.

The clinical evaluation of niraparib was based on two phase III randomised trials (PRIMA, PRIME), comparing niraparib versus SMM in women with NDA HGEOC who are in response (complete (CR) or partial (PR)) to PBC. A direct evidence approach could not be used as the methods used to test HRD status in PRIMA (Myriad MyChoice® CDx assay) and PRIME (BGI assay) were different to the test proposed for use in Australia (Illumina TruSight Oncology 500 HRD). Instead, the evidence presented included:

- Studies investigating the concordance of any Myriad MyChoice® HRD test with any other test to determine HRD status with the most relevant study identified comparing the Myriad MyChoice® PLUS assay with the Illumina TruSight Oncology 500 HRD RUO, (Weichert 2021a and 2022, with Weichert 2022 being an update of the study reported in Weichert 2021a); and

- Clinical trial data demonstrating the concordance of different iterations of the Myriad MyChoice® assay, as the version of the Myriad MyChoice® test used in the studies identified in the submission did not appear to be consistent and was not always known.

Table 3   Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (cross-sectional accuracy)	PRIMA (n=733) used Myriad MyChoice® CDx assay with a threshold of ≥42 to determine HRD positivity. PRIME (n=408) used the BGI assay. Nine studies were identified to address the concordance of any Myriad MyChoice® HRD test (i.e. one of Myriad MyChoice® PLUS, Myriad MyChoice® CDx, Myriad MyChoice® PLUS RUO or Myriad MyChoice) with any other test to determine HRD status. Of these, the study reported by Weichert (2021a and 2022) compared use of Myriad MyChoice® PLUS with the Illumina RUO TruSight Oncology 500. As the identified studies used various versions of the Myriad MyChoice® test, the submission provided 'bridging data', in order to demonstrate that that the different iterations of the MyChoice® test are highly concordant. No concordance information between the BGI assay and any of the Myriad MyChoice® assays were included.	RCT niraparib vs SMM for the 1L maintenance treatment of HGEOC ☐ k=2 n=1,141 Concordance of studies using Myriad MyChoice® versus any other HRD test ☐ k=9 n=1,246[a] Myriad MyChoice® concordance data ☐ k=6 n=1,442	The submission considered PRIMA and PRIME to have a low risk of bias, despite noting that certain risks of bias within the PRIME trial were considered unclear due to reporting limitations. The submission did not provide a risk of bias assessment for the concordance studies and the QUADAS-2 risk of bias tool was not presented in the submission. The risk of bias for Weichert 2021a and 2022 was considered high during evaluation, with limited study details being available. (Refer to Section 2A.3 of the commentary for further details.)

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Prognostic evidence (longitudinal accuracy)	The prognostic evidence supplied was the PFS outcome data for the placebo arm of five PARP inhibitor maintenance RCTs (1L treatment: PRIMA, PAOLA-1 and VELIA; 2L treatment: NOVA and ARIEL3) and one study investigating PBC flat dosing versus intra patient dose escalation (SCOTROC4). Four RCTs used a Myriad MyChoice® assay and one study used the Foundation Medicine assay to identify patients with HRD tumours. The assay used was not reported in one study. The PARP inhibitor arm of these studies was not reported in the submission. PRIME was not included as part of the evidence to support longitudinal accuracy.	☐ k=6 n=1,510	Risk of bias assessment tool was not provided in submission. Five trials were randomised, double-blind and placebo controlled, and therefore may be considered to have low risk of bias. However, not all of the HRD subgroup analyses were planned and therefore subgroup results may have a high risk of selection bias. SCOTROC4 was not blinded and is therefore likely to have a high risk of bias.
Change in patient management	Not explicitly assessed. Patients designated as HRD positive *BRCA*wt using the proposed test would be eligible for niraparib treatment. Threshold for determining HRD positive status is discussed in section 1.1 of the commentary.	☐ k=0 n=0	-
Health outcomes (clinical utility) Predictive effect (treatment effect variation)	Based on PRIMA using primary endpoint PFS (investigator assessed). Analysis of PRIMA subgroups conducted (based on HRD and *BRCA* status, including HRD positive *BRCA*wt). PRIME was not included as part of the evidence to support predictive effect.	☐ k=1 n=733	The submission considered the risk of bias to be low however, given the high proportion of patients with unknown HRD status (15.1% of the total PRIMA population) and the fact that the HRD positive *BRCA*wt subgroup result was not part of the formal statistical analysis plan, the risk of bias may be high.

1L = first line; 2L = second line; *BRCA* = breast cancer gene; HGEOC = high grade epithelial ovarian cancer; HRD = homologous recombination deficiency; k=number of studies, n=number of patients; PBC = platinum-based chemotherapy; PFS = progression-free survival; RCT = randomised controlled trial; RUO = research use only; SMM = standard medical management; wt = wild type
Source: Constructed during evaluation
[a] Data not available for all studies.

The economic evaluation presented in the submission was based on the PRIMA trial. PRIME was not used to inform any part of the economic evaluation.

11. Comparative safety

Adverse events from testing

The submission stated that an ovarian biopsy is crucial in the diagnosis of ovarian cancer and the creation of a suitable treatment plan and that in most cases, an ovarian biopsy takes place during the removal of a tumour during a surgical procedure, such as laparotomy and laparoscopy, both of

which are conducted under general anaesthesia. The submission reported that doctors do not typically recommend stand-alone ovarian biopsies due to the potential risk of cancer cells breaking away from the primary tumour and spreading to the peritoneal cavity.

The submission claimed that in most cases there will be adequate material for both pathologic assessment and HRD profiling from the biopsies taken for diagnosis and that, as such, there is no additional risk to the patient due to biopsy because of the performing the HRD test. The commentary highlighted that the submission did not detail what would happen in clinical practice if the amount of tissue sample available proved to be inadequate for testing and this remains uncertain. While the proposed HRD test would involve using less tissue than conducting *BRCA* and GI testing one after the other, it is not clear if the combined HRD test would require more tissue than the currently used *BRCA* test.

Adverse events from changes in management

Safety data from the PRIMA trial for the safety population and HRD positive *BRCA*wt subgroup are presented in the table below. The PBAC has previously considered that niraparib was inferior to placebo in terms of safety in PRIMA due to more grade ≥3 treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and TEAEs leading to treatment discontinuation in the niraparib arm (Paragraph 6.37, Niraparib PSD, July 2021 PBAC meeting). The relative risks of experiencing any TEAE, experiencing a Grade ≥3 TEAE and experiencing a SAE in HRD positive *BRCA*wt patients who received niraparib compared to those who received placebo were similar to the corresponding relative risks in the overall safety population of PRIMA, with niraparib arm patients significantly more likely to experience a TEAE, a Grade ≥3 TEAE or a SAE compared to patients who received placebo.

Table 4   PRIMA trial TEAEs

	Niraparib N (%)	Placebo N (%)	Risk difference (95% CI)*b	Relative risk (95% CI)*b
Overall population (SAF), May 2019 DCO				
N	484	244	-	-
Mean treatment duration months (SD)	10.3 (6.6)	9.5 (5.9)	-	-
Any TEAE	478 (98.8)	224 (91.8)	**7.0 (3.4, 10.5)**	**1.08 (1.04, 1.12)**
Grade ≥ 3 TEAE	341 (70.5)	46 (18.9)	**51.6 (45.2, 58.0)**	**3.74 (2.86, 4.88)**
SAE	156 (32.2)	32 (13.1)	**19.1 (13.2, 25.1)**	**2.46 (1.74, 3.48)**
Any TEAE leading drug interruption	385 (79.5)	44 (18.0)	**61.5 (55.5, 67.5)**	**4.41 (3.36, 5.79)**
Any TEAE leading drug dose reduction	343 (70.9)	20 (8.2)	**62.7 (57.4, 68.0)**	**8.65 (5.66, 13.21)**
Any TEAE leading drug withdrawal	58 (12.0)	6 (2.5)	**9.5 (6.0, 13.0)**	**4.87 (2.13, 11.13)**
Any TEAE leading to death**	2 (0.4)	1 (0.4)	0.003 (-0.98, 0.99)	1.01 (0.09, 11.07)
***BRCA*wt HRD-positive population, May 2019 DCO**				
N	93 a	55 a	-	-
Mean treatment duration months (SD)	10.5 (6.8) a	10.2 (6.3) a	-	-
Any TEAE	93 (100.0) a	47 (85.5) a	**14.5 (7.5, 26.2)**	**1.17 (1.05, 1.31)**
Grade ≥ 3 TEAE	64 (68.8) a	12 (21.8) a	**47.0 (31.2, 59.9)**	**3.15 (1.88, 5.23)**
SAE	31 (33.3) a	8 (14.5) a	**18.8 (4.3, 3.2)**	**2.29 (1.14, 4.72)**
Any TEAE leading to death**	0 a	0 a	**NA**	**NA**

BRCA = breast cancer gene; DCO = data cut-off; HRD = homologous recombination deficiency; NR = not reported; SAE= serious adverse events; SAF = safety population; SD= standard deviation; TEAE = treatment emergent adverse event; wt = wild type
*Calculated during the evaluation
**One subject in the fixed starting dose cohort died from a serious AE related to intestinal perforation. Two other subjects in the PRIMA trial (one in the niraparib arm and one in the placebo arm) experienced TEAEs that led to death (pleural effusion and intentional overdose respectively), none of which were assessed as study treatment related.
Note: Blue shading indicates data previously seen by the PBAC.
Source: Table 70 of the submission (p147-8); Table 57 (p125) of the submission and Table 2.5.2 of the July 2021 niraparib PBAC commentary
a *Note: Results are derived from a post-hoc analysis conducted by the applicant specifically for the purposes of informing the MSAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.*
b *Note: Results are derived from post-hoc analyses conducted by the evaluation specifically for the purposes of informing the MSAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.*

The figure below presents individual TEAEs reported in ≥20% of patients in the overall safety population and in the individualised starting dose (ISD) population of PRIMA. In the overall population, thrombocytopenia (67.1%), anaemia (65.1%) and nausea (58.3%) were the most commonly reported TEAEs in niraparib patients, and abdominal pain (32.4%), fatigue (31.1%) and nausea (29.9%) were the most commonly reported TEAEs in placebo patients.
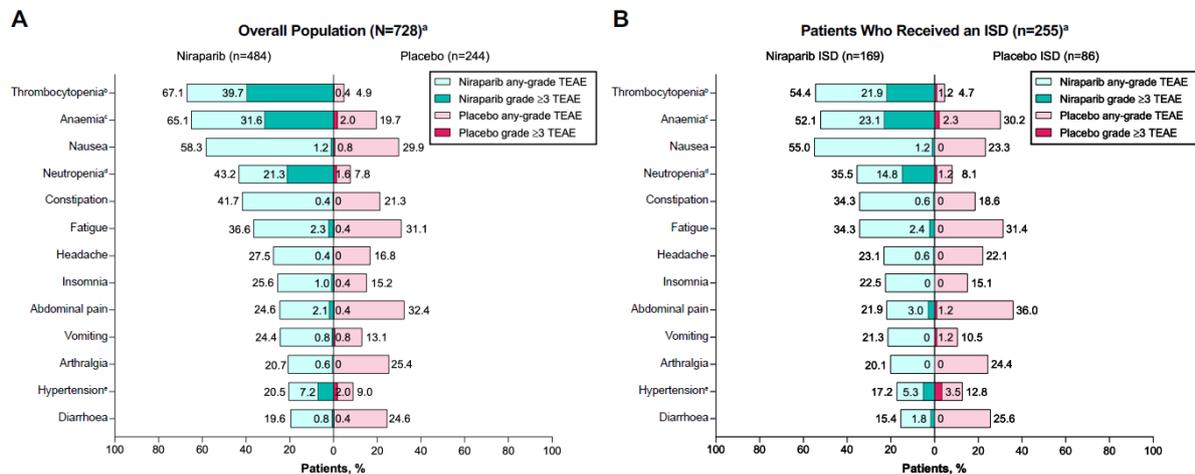
Figure 2   TEAEs reported in ≥20% of patients in PRIMA, November 2021 DCO
DCO = data cut-off; SAF = safety population; ISD = individualised-starting dose; TEAE = treatment
Source: Figure 34 (p150) of the submission

The submission claimed that the main safety concern associated with the proposed test was that a false test result may lead to inappropriate treatment allocation.

The submission stated that a false HRD test result would change the clinical management of a patient if their tumour was found to be HRD positive *BRCA*wt. In this scenario a false positive HRD would result in patients being eligible to receive 1L maintenance therapy with niraparib when they should receive bevacizumab or "watch and wait". The submission reasonably stated that while such patients would experience the same level of side effects as true positive HRD patients (but would not have experienced any bevacizumab-related adverse events if they had received the correct treatment), they may receive a reduced PFS benefit from niraparib. The submission also claimed that these patients were not necessarily forgoing a benefit by receiving maintenance with niraparib compared to not receiving niraparib as niraparib was associated with a PFS benefit versus SMM among HRD negative patients in PRIMA. The PBAC has previously considered the 3.5 months PFS benefit reported in PRIMA in HRD negative patients to be uncertain in the context of the uncertain OS (Paragraph 6.38, Niraparib PSD, March 2022 PBAC meeting).

The submission recognised that a false negative test result may also prevent a patient from potentially benefitting from a targeted therapy. These patients would be forgoing niraparib maintenance therapy for bevacizumab or "watch and wait" and would be monitored to detect disease progression but would likely progress more quickly than true positive patients receiving niraparib.

The commentary considered that there are additional scenarios in which patients could receive incorrect treatment due to false test results arising from the implementation of HRD testing. Patients could receive incorrect treatment if the proposed test returned a *BRCA* test result that was inaccurate. If a patient has a false *BRCA*m result but a correct HRD negative result, they would be eligible to receive niraparib when they should receive bevacizumab or watch and wait. If a patient has a false *BRCA*wt result but a correct HRD negative result, they would receive bevacizumab or SMM when they should be eligible for a PARP inhibitor and there would be benefits foregone due to them not receiving a PARP inhibitor.

12. Comparative effectiveness

Effectiveness (based on linked evidence)

As there was no direct evidence from the test population to health outcomes, the assessment framework presented in the submission involved a stepwise approach. The table below provides a summary of the data available to inform the comparisons of PARP inhibitor efficacy in biomarker positive and negative patients.

Table 5   Data availability to inform comparisons

Proposed test vs no test	HRD positive *BRCA*wt subgroup versus ITT analysis of PRIMA	
Proposed test vs alternative test	Weichert (2021a and 2022) compared use Myriad MyChoice® PLUS with the Illumina RUO TruSight Oncology 500 HRD	
	Proposed drug	**Comparator drug**
Biomarker test positive	PRIMA	PRIMA
Biomarker test negative	PRIMA	PRIMA

HRD = homologous recombination deficiency; ITT = intention to treat; RUO = research use only
Source: Constructed during evaluation

In the PRIMA trial, tumour samples were centrally tested using the clinical trial assay version of the Myriad MyChoice® CDx HRD test. The Myriad MyChoice® CDx test is an NGS-based assay for homologous recombination that quantitates genomic instability of the tumour and, in parallel, detects and classifies variants in *BRCA*1 and *BRCA*2. Three algorithms were used to determine the GIS, which is an algorithmic measurement of LOH, TAI and LST. The HRD GI score represents a continuum of genomic instability accumulated over time in the tumour and is presented as a score between zero (low) and 100 (high). For PRIMA, HRD was defined by tumour *BRCA* variant or a composite GIS of greater than or equal to 42. Based on the test results provided, tumours were classified as HRD positive, HRD negative (homologous recombination proficient), or inconclusive/not done.

MSAC has previously considered the appropriateness of the threshold of 42 to determine HRD using the Myriad MyChoice® CDx test (pp6-7, 9, 22-25, application 1658, PSD, MSAC July 2022 meeting). Briefly, the applicability of the threshold defining HRD positivity remains uncertain because:

- The threshold of 42 used in PRIMA was established by Telli 2016 to obtain a sensitivity of at least 95% in the training set of known *BRCA*1/2-deficient (*BRCA*m) tumours (i.e. not using samples from the requested patient population);

- The threshold was derived using a mix of breast and ovarian cancer samples (Telli 2016) and alternative thresholds have been proposed (e.g. Takaya 2020 proposed a threshold of 63 based on an analysis conducted specifically using HGSOC samples); and

- Takaya 2020 also reported that HRD cases caused by genetic HRD such as germline and somatic *BRCA*1/2 variants had better prognosis than those caused by epigenetic changes and those caused by undetermined reasons (p-0.0002), suggesting that the cause of HRD has a significant impact on prognosis and possibly treatment response.

The commentary considered that the submission had not provided any further explanation as to why a cut-off of 42 should be used in the requested HRD positive *BRCA*wt population and it is not apparent what threshold should be used in this population. Previously, 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) (p4, application 1658, Public Summary Document, July 2022 MSAC meeting). MSAC also noted that the way the Myriad MyChoice® HRD test works is also secret (a "black box" algorithm) and the lack

of transparency may hinder quality assurance. (p2, application 1658, Public Summary Document, July 2022 MSAC meeting).

Weichert (2021a and 2022) reported details of the same study that compared the Myriad MyChoice® HRD test with the RUO version of the Illumina TruSight Oncology 500 HRD test. The submission stated that this was the only study identified that compared the clinical utility standard HRD test with an HRD test known to be available in the Australian setting. The commentary considered it was unclear if the RUO version of the Illumina TruSight Oncology 500 HRD test would be the same as the version that would be used in Australia or if (and in what ways) it differs.

The commentary considered that there was limited information available regarding the Weichert 2021a and 2022 study, with only data from two abstracts available. The commentary considered the study was likely associated with a high degree of bias as there were no details available to describe the sample selection or their source (other than ovarian cancer tissue samples were used), it was unclear if the index test results were interpreted without knowledge of the results of the reference standard, and different numbers of samples were tested with the Illumina and Myriad assays, respectively.

The submission claimed that the reports of studies presented in the submission did not always specify which iteration of the Myriad MyChoice® test was used but that, based on the bridging data presented in the manufacturer technical specifications and the FDA Summary on safety and effectiveness, the different Myriad MyChoice® tests are highly concordant. The submission stated that as such, the Myriad MyChoice® test used was considered representative of (or a proxy for) the evidentiary standard test in all the identified studies. As noted above in the advice to MSAC, the commentary considered there were potential issues associated with this assumption that could affect the cost effectiveness of the test and intervention.

The table below provides a summary of the reference standards for accuracy of biomarker detection and validity of the biomarkers, the details of which are discussed below.

Table 6   Reference standards to determine the accuracy and prognostic validity of genetic testing

Type of test information	Reference standard
Accuracy of biomarker detection (cross-sectional accuracy)	*BRCA* testing using DNA from fresh tissue using NGS technology
Prognostic validity of biomarker (longitudinal accuracy)	Response to PARP inhibitor in terms of PFS and OS in patients who are HRD positive *BRCA*wt compared with the complement of patients (i.e. patients who are HRD positive *BRCA*m and HRD negative)
Predictive validity of biomarker (longitudinal accuracy)	

BRCA = Breast cancer gene; HRD = Homologous recombination deficiency; NGS = Next-generation sequencing
Source: Constructed during evaluation

Previously, MSAC noted that all commercial molecular pathology service providers for *BRCA*m testing in Australia currently conduct *BRCA* testing using DNA from fresh tissue using NGS technology (p20, application 1658, PSD, July 2022 MSAC meeting). This was defined as the reference standard for *BRCA* testing in Application 1658. MSAC noted that for Application 1658, the submission stated that current literature and recommendations indicate that NGS platforms are widely accepted and utilised for detecting *BRCA*m (Wu 2017) and it was therefore considered the gold standard in that submission. Similarly, in the current application (1726), *BRCA* testing using DNA from fresh tissue using NGS technology should be considered the reference standard.

The commentary highlighted that the Illumina TruSight Oncology 500 HRD assay operates on an NGS platform however the specifications and workflow process provided in the submission appear to indicate that the input specimen is required to be FFPE and not fresh tissue. The submission stated that the overall time from receipt of the FFPE specimen by the pathology laboratory to reporting will involve a 4-week turnaround time, which also suggests that FFPE specimens will be used in clinical practice, as well as having been used in the concordance studies. However, fresh tissue is currently used for the reference standard and was considered preferable by MSAC (p5, Application 1658, Public Summary Document, July 2022 MSAC meeting).

Comparative accuracy/test performance

Concordance with HRD evidentiary standard

A summary of the HRD concordance outcomes of the nine studies identified to address the concordance with the HRD evidentiary standard is presented in Table 7. While the Myriad MyChoice® CDx assay was the evidentiary standard, the concordance of all Myriad MyChoice® assays was investigated.

The concordance varied in the six studies that reported comparisons on overall HRD (Weichert 2022 and 2021a; Buisson 2022; Li 2022; Loverix 2022; Ranghiero 2022; Saranti 2022). The positive percentage agreement (PPA) in the studies ranged from to 91.3% to 100%; the negative percentage agreement (NPA) ranged from 81.2% to 100% and the overall percentage agreement (OPA) ranged from 87% to 100%.

Three studies (Weichert 2022 and 2021a; Loverix 2022; Ranghiero 2022) reported comparisons specifically on the *BRCA* testing element of the HRD tests. The PPA was 92.9%, 95%, and 100%, the NPA was 98.6%, 99.6% and 100% and the OPA was 96.9%, 98%, 100% in the Weichert, Loverix and Ranghiero studies, respectively.

Five studies (Weichert 2022 and 2021a; Loverix 2022; Mills 2020; Timms 2020 and Weichert 2021b) reported comparisons specifically on measures of GI and found that concordance varied considerably. The submission observed that concordance was highest in studies where the GIS was based on a composite of LOH, TAI and LST (Weichert 2022 and 2021a; Loverix 2022; Weichert 2021b). In these studies, the PPA was 95.1%, 88% and 88%, the NPA was 97.1%, 86% and 75% and the OPA was 96.1%, 87% and 81.6%, respectively. Whereas, in the three studies (Mills 2020; Timms 202; Weichert 2021b) that compared a single measure of genomic instability (LOH) with the composite GIS element of the MyChoice® HRD test, the composite MyChoice® GIS (TAI, LST as well as LOH) determined a higher prevalence of positivity.

The submission claimed that the results from the study reported by Weichert (2022 and 2021a) were the most relevant to the Australian treatment setting as it compared the Myriad MyChoice® HRD test with the RUO version of the Illumina TruSight Oncology 500 HRD test. As such, the submission considered the performance of the TruSight Oncology 500 HRD test in this study to be the best evidence available to reflect HRD testing in clinical practice scenario as proposed in the submission.

Comparison between the RUO Illumina TruSight Oncology HRD 500 and Myriad MyChoice® HRD tests showed that overall HRD status, *BRCA* analysis, and HRD GIS detection results were > 90% concordant; HRD GIS was highly correlated (r > 0.98); and prevalence estimates were similar. However, as the concordance was not perfect, the commentary considered false positive or false negative *BRCA* and HRD results will have some implications for patients (as described above), resulting in some patients receiving the incorrect treatment. Further, as previously noted, the commentary considered the RUO tests used in Weichert 2022 and 2021a may differ from the commercial test available in Australia, and the Myriad MyChoice® HRD in Weichert (2021a and 2022) may differ to the Myriad MyChoice® CDx used in PRIMA, which adds to the uncertainty.

Table 7   Summary of outcomes of HRD test concordance studies

Author/year Myriad MyChoice® test	Definition of HRD positivity	Comparator test	Comparator HRD test element & definition of positivity	PPA [95%CI]	NPA [95%CI]	OPA [95%CI]	HRD prevalence (MyChoice)	HRD prevalence (comparator test)
Studies comparing Myriad MyChoice® (any version) with test known to be commercialised the Australian setting								
Weichert 2022/2021a[a] MyChoice® Plus	*BRCA*m	Illumina RUO TSO 500	*BRCA*m	92.9 (83.0-97.2)	98.6 (95.0-99.6)	96.9 (93.5-98.6)	25.5%	27.6%
	GIS ≥42		GIS ≥42	95.1 (89.1-97.9)	97.1 (91.9-99.0)	96.1 (92.6-98.0)	-	-
	HRD (*BRCA*m /GIS ≥42)		*BRCA*m / GIS ≥42	95.2 (89.2-97.9)	96.8 (91.0-98.9)	96.0 (92.2-97.9)	49.2%	51.2%
Weichert 2021a[a] MyChoice® Plus	*BRCA*m	Illumina RUO TSO 500	*BRCA*m	92.9 (83.0-97.2)	98.6 (95.0-99.6)	96.9 (93.5-98.6)	25.5%	27.6%
	GIS ≥42		GIS ≥42	91.3 (84.2-95.3)	98.0 (93.1-99.5)	94.6 (90.6-97.0)	-	-
	HRD (*BRCA*m /GIS ≥42)		HRD (*BRCA*m / GIS ≥42)	92.3 (85.6-96.1)	96.7 (90.7-98.9)	94.3 (90.1-96.8)	49.2%	51.0%
Studies comparing Myriad MyChoice® (any version) with other tests approved or in development for commercial/clinical use elsewhere								
Buisson 2022[b] MyChoice® CDx	HRD	Sofia Genetics SA GII	HRD based on GII [e]	91.7%	95.5%	93.5% [h]	*51.8%*	49.6%
Li 2022[c] MyChoice® CDx	HRD (*BRCA*m /GIS ≥42)	ACTHRD test	*BRCA*m & genomic wide LOH & 22 HRR genes	100%	90.91%	97.1% [h]	24/36 (66.7%)	25/35 (71.4%)
Loverix 2022 MyChoice® Plus RUO	*BRCA*m	Leuven HRD test	*BRCA*m	95%	99.6%	98%	32.3%	31.4%
	GIS ≥42		GIS (LOH + TAI + LST) ≥56	88%	86%	87%	19.4%	22.9%
	HRD (*BRCA*m /GIS ≥42)		HRD (*BRCA*m + GIS ≥56)	94%	86%	91%	51.7%	54.3%
Ranghiero 2022 MyChoice® CDx	*BRCA*m	Amoy Dx Focus Panel (In house)	*BRCA*m	100%	100%	100%	NR	NR
	HRD (*BRCA*m /GIS ≥42*)		HRD (*BRCA*m & GSS > 50)	100%	81.2%	87.8%	NR	NR
Scaranti 2022 MyChoice® CDx	HRD (*BRCA*m /GIS ≥42)	HRD One test	*BRCA*m and/or HRD-One genomic scar score ≥2.0	NR	NR	94.74%	NR	NR
Other studies comparing Myriad MyChoice								
Mills 2020 MyChoice	GIS≥42	LOH score	Score ≥8	86.70%	NR	NR	NR	NR
		%LOH	LOH≥16%	67.71% [f]	NR	NR	NR	NR
	GIS≥33	LOH score	Score ≥8	NR	NR	NR	NR	NR
		% LOH	LOH≥16%	53.45% [f]	NR	NR	NR	NR
Timms 2020 MyChoice® CDx	GIS≥42	%LOH	LOH≥16%	67.7% [g*]	NR	NR	NR	NR
				80.88% [g*]	NR	NR	NR	NR
		11 gene panel	Pathogenic variant in ≥1 genes	53.06% [g*]	NR	NR	NR	NR
	GIS≥33	%LOH	LOH≥16%	53.5% [g] [*]	NR	NR	NR	NR
				60.61% [g*]	NR	NR	NR	NR
		11 gene panel	Pathogenic variant in ≥1 gene	38.57% [g*]	NR	NR	NR	NR
Weichert 2021b[d]	GIS≥42	Foundation	LOH [e]	67.6%	85.7%	77.0%	NR	NR

Author/year Myriad MyChoice® test	Definition of HRD positivity	Comparator test	Comparator HRD test element & definition of positivity	PPA [95%CI]	NPA [95%CI]	OPA [95%CI]	HRD prevalence (MyChoice)	HRD prevalence (comparator test)
MyChoice® CDx		One CDx						
		AmoyDx HRD	GIS [e]	92.0%	52.1%	72.4%	NR	NR
		Focus	GIS [e]	88.0%	75.0%	81.6%	NR	NR

AUROC = Area Under the Curve Receiver Operating Characteristic; *BRCA* = BReast CAncer gene; FP = false positive; FN = false negative; GII = genomic integrity index; GIS = genomic instability score; HRD = homologous recombination repair deficiency; HRR = homologous recombination repair; LOH = loss of heterozygosity; LST = large-scale state transitions; NGS = next generation sequencing; NPA = negative percentage agreement; NR = not reported; OPA = overall percentage agreement; PPA = positive percentage agreement; RUO = research use only; TAI = telomeric allelic imbalance; TN = true negative; TP = true positive; TSO = TruSight Oncology.

[a] Analytic sensitivity and specificity of the Illumina-derived HRD GIS to classify HRD GIS (cut-off, 42) were evaluated using AUROC. AUROCS were 0.995 and 0.992, for all samples and non *BRCA*m respectively.

[b] Unclear if GII was compared to overall MyChoice® *BRCA* or MyChoice® GIS element

[c] Threshold for HRD positivity based on non-*BRCA* measures (gene panel and/ or LOH not stated).

[d] All tumour samples were non-*BRCA*m status

[e] Manufacturer recommended thresholds

[f] Entire cohort

[g] Clinical trial cohort

[h] Buisson 2022 TP: 66, FP: 3, FN: 6, TN: 64; Li 2022 TP: 24, FP: 1, FN: 0, TN: 10

Figure in italics amended during commentary.

*Details unable to be independently verified.

Source: Table 35, p82 of the submission

Concordance with *BRCA* evidentiary standard

To address the concordance and discordance of the proposed test compared with current tumour *BRCA* testing to determine *BRCA* variant status, the submission provided linked evidence as follows:

- Data previously considered by MSAC (Application 1554), which established concordance of germline and tumour *BRCA* testing;

- Data from Hodgson 2021, which provided concordance between germline *BRCA* (*gBRCA*) variant status classified with the *BRCA*nalysis CLIA test (which appears to have used Sanger sequencing) and tumour *BRCA* (*tBRCA*) status classified with Myriad MyChoice® Dx (the *BRCA* test element of the Myriad MyChoice® HRD test);

- Data from Weichert 2022, Loverix 2022, Ranghiero 2022 and Hodgson 2018, which compared *tBRCA* variant classification of different HRD tests; and

- Data comparing concordance between the Illumina TruSight Oncology 500 and TruSight Oncology 500 HRD at detection of small variants and copy-number variants across all genes (i.e. not specific for *BRCA*).

No evidence comparing the concordance of *BRCA* testing with the proposed Illumina TruSight Oncology 500 HRD test with NGS testing was provided. The MSAC has previously considered that NGS was more accurate than Sanger sequencing for *BRCA* testing (p3, Application 1554, Public Summary Document, November 2019 MSAC meeting), though the commentary acknowledged that both Sanger sequencing and NGS were generally accepted as 'gold standard' tests (p11, Application 1554, Public Summary Document, November 2019 MSAC meeting). It was unclear if comparison with the *BRCA*nalysis CLIA test in Hodgson 2021 was sufficient to establish linked concordance with NGS testing, the nominated reference standard for *BRCA* testing.

The submission presented data from the PSD for MSAC Application 1554 that summarised the evidence for the concordance of tumour NGS *BRCA* testing with germline *BRCA* testing (table 6, p13, application 1554, MSAC November 2019 meeting). The application 1554 PSD also stated that "somatic *BRCA* testing is now shown to have high analytical sensitivity and specificity, from indirect evidence" and "(a)s NGS is a highly accurate methodology, the diagnostic yield of the tumour NGS *BRCA* test is likely to be equivalent to the prevalence of germline plus somatic variants in (high grade serous ovarian cancer) HGSOC" (pp 13 and 19, application 1554, Public summary Document, November 2019 MSAC meeting).

The Hodgson 2021 study included a concordance analysis of *gBRCA*m status (*BRCA*nalysis CLIA test) and *tBRCA* status (MyChoice® Dx, i.e., the *BRCA* test element of the MyChoice® HRD test). Of the 295 enrolled patients, 289 had a *gBRCA*m confirmed centrally and *tBRCA*m status was evaluable in 241 patients. This implies that 54/295 (18.3%) of patients did not have a *tBRCA* result from the use of the MyChoice® Dx, which was substantially higher than 6/295 (2.0%) with *BRCA*nalysis CLIA. There was 98.3% and 100% concordance between tumour and germline testing for *BRCA*1m and *BRCA*2m, respectively, and 98.3% concordance overall. All discordant results (n=4) were false negatives from the MyChoice® Dx test. All samples were centrally determined to be *BRCA*m rather than being a mix of *BRCA*wt and *BRCA*m, and as such, the specificity of the MyChoice® Dx could not be determined. Therefore, Hodgson 2021 may not represent a complete concordance study.

Concordance data between different *tBRCA* tests that use NGS technology to detect variants in *BRCA*1 or *BRCA*2 genes are presented in the table below. The submission claimed that high concordance between the tests was expected with respect to the *tBRCA* status determination and that this may contrast with the genomic instability element of the HRD tests, which can use different measures of genomic scarring (i.e., LOH, TAI and LST) and use different cut-offs to determine HRD in *BRCA*wt patients (e.g., GIS threshold of 33 or 42).

Table 8 *BRCA* status concordance between Myriad MyChoice® and other NGS-based *BRCA* tests

Author / year	MyChoice® reference test	MyChoice® HRD test element & definition of positivity	Comparator test	Comparator HRD test element & definition of positivity	PPA [95%CI]	NPA [95%CI]	OPA [95%CI]	*BRCA*m prevalence (MyChoice)	*BRCA*m prevalence (comparator test)
Weichert 2022	Myriad MyChoice® Plus	t*BRCA*m	NGS assay, based on Illumina's RUO TSO 500	t*BRCA*m	92.9% (83.0-97.2)	98.6% (95.0-99.6)	96.9% (93.5-98.6)	25.5%	27.6%
Loverix 2022	Myriad MyChoice® Plus RUO assay	t*BRCA*m	Leuven HRD test	t*BRCA*m	95%	99.6%	98%	32.3%	31.4%
Ranghiero 2022	(Central) Myriad MyChoice® CDx	t*BRCA*m	(In house testing) Amoy Dx Focus Panel	t*BRCA*m	100%	100%	100%	NR	NR
Hodgson 2018	MyChoice® RUO assay	t*BRCA*m	Foundation Medicine T5 panel	t*BRCA*m	97.2%	100%	98.5% TP: 106 FP: 0 FN: 3 TN: 84	56.5%	54.9%

BRCA = BReast CAncer gene; CI = confidence interval; FN = false negative; FP = false positive; HRD = homologous recombination repair deficiency; NGS = next generation sequencing; OPA = overall percentage agreement; NPA = negative percentage agreement; PPA = positive percentage agreement; RUO = research use only; t*BRCA*m = tumour *BRCA* variant; TN = True negative; TP = true positive; TSO = TruSight Oncology.

Data in the table below were provided in the submission to demonstrate concordance between the *BRCA* elements of Illumina's TruSight Oncology 500 HRD and TruSight Oncology 500 tests. The submission acknowledged that this data is not specific to *BRCA* genes, but claimed that it demonstrated the addition of HRD testing to the NGS-based tumour *BRCA* assay was unlikely to impact the identification of *BRCA* variants. It is unclear if this concordance data may be directly applied to *BRCA*m detection.

Table 9 Concordance between TruSight Oncology 500 and TruSight Oncology 500 HRD by variant type

Variant	PPA	NPA	OPA
Small variants	99.43%	99.99%	99.99%
CNVs	96.79%	99.65%	99.4%
MSI	NR	NR	100%

CI = confidence interval; CNV = copy-number variants; MSI = microsatellite instability; NPA = negative percent agreement; OPA = overall percent agreement; PPA = positive percent agreement
Sources: Table 41, p93 of the submission

The submission claimed that overall, data from MSAC application 1554, published literature (Weichert 2022 and 2021a, Loverix 2022, Ranghiero 2022, Hodgson 2018 and Hodgson 2021) and product data sheets (Illumina TruSight Oncology 500 HRD) demonstrated that tests in development for HRD testing and current tumour *BRCA* testing methods are highly concordant with respect to identifying *BRCA* variants in patients with HGEOC.

The submission has suggested that as the TruSight Oncology 500 uses NGS technology, it is therefore aligned to current clinical practice. However, as the data in Table MSAC.8 was not specific to *BRCA*m testing, it is of limited use to address concordance with the *BRCA* evidentiary standard. While data from Weichert 2022 demonstrated high concordance of the *BRCA* status determined by Myriad MyChoice® PLUS compared with the RUO Illumina TruSight Oncology HRD 500, it was not perfect and there will be patients who would be misclassified compared to existing testing and reduce the applicability of PRIMA. Further, it remains uncertain if the MyChoice® Plus is the same HRD test as used in PRIMA (MyChoice® CDx) and if the Illumina RUO version is the same as the Illumina TruSight Oncology 500 HRD assay proposed for use in clinical practice.

Prognostic evidence

The submission acknowledged that, because the treatment of ovarian cancer with PARP inhibitor therapies and companion testing for HRD are relatively new, the differentiation of HRD status as being prognostic as opposed to predictive of the outcomes with PBC in NDA HGEOC is difficult.

In the submission, the evidence of the presence or absence of a prognostic effect of the biomarkers, as identified by the proposed HRD test, was based on:

- Efficacy outcomes of patients in the control arms of three randomised controlled trials (RCTs) (PRIMA: PFS; VELIA: PFS; PAOLA-1: PFS and overall survival [OS]) that combined biomarker testing for HRD and the use of PARP inhibitor maintenance therapy in patients with platinum sensitive advanced ovarian cancer in the 1L treatment setting;
- PFS outcomes of patients in the control arms of two RCTs (NOVA and ARIEL3) that combined biomarker testing for HRD and the use of PARP inhibitor maintenance therapy in patients with platinum sensitive relapsed advanced ovarian cancer in second or later line setting; and
- One study (Stronach 2018) that evaluated associations between HRD status and PFS and OS outcomes following 1L carboplatin monotherapy, in patients with ovarian tumours enrolled in the SCOTROC4 clinical trial.

Control arms of the first-line PARP inhibitor trials (PRIMA, PAOLA-1 and VELIA)

MSAC has previously considered the results from PRIMA (as Gonzalez-Martin 2019), PAOLA-1 and VELIA in application 1658 (Table 17, pp34-35, application 1658, PSD, MSAC meeting July 2022). The PALOA-1 trial was fully evaluated, however only PRIMA and VELIA were only briefly evaluated.

The submission claimed that based on median PFS from PRIMA and VELIA, it appears that HRD negative status is associated with poorer PFS outcomes than HRD positive status, leading to a tendency to suggest that HRD positive *BRCA*m status may be associated with better outcomes than HRD positive *BRCA*wt. However, in PAOLA-1 where the control arm received bevacizumab maintenance therapy, the median PFS for the HRD negative and HRD positive *BRCA*wt patients were similar (16.2 months and 16.6 months, respectively), whereas HRD positive *BRCA*m patients exhibited better PFS outcomes (median PFS = 21.7 months). Long-term OS data was also available from PAOLA-1, with median survival longest in *BRCA*m patients (53.8 months), followed by HRD positive *BRCA*wt patients (44.2 months), and poorer survival experienced by HRD negative patients (32.3 months). Refer to Table 10 for details.

However, the submission claimed that there were key differences across the trials which likely contributed to differences in PFS outcomes between the placebo arms. VELIA used a different HRD threshold ($\geq$33) and therefore the conclusion may not be applicable to the proposed PBS population.

Of the three RCTs identified, only PAOLA-1 reported OS data that was considered mature, with the PBAC previously considering the PRIMA May 2019 data cut-off (DCO) ITT OS data to be immature (Paragraph 7.9, Niraparib PSD, July 2021 PBAC meeting). MSAC has previously noted that data on comparative clinical effectiveness from the PAOLA-1 trial showed improved PFS but no improvement in OS in the ITT population, the HRD-positive subgroup and the HRD-positive *BRCA*wt subgroup (p6, Application 1658, Public Summary Document, July 2022 MSAC meeting). MSAC has previously considered that there was uncertainty about whether the treatment effect is predicted by the combination of *BRCA*1/2 status and genomic instability, compared with either *BRCA*1/2 status or genomic instability alone. MSAC noted that response to platinum-based chemotherapy itself is a predictor of response to PARP inhibitors (p6, Application 1658, Public Summary Document, July 2022 MSAC meeting).

Control arms of the second-line PARP inhibitor trials (NOVA and ARIEL3)

MSAC has previously considered the results from NOVA (as Mirza 2016) and ARIEL3 (as Coleman 2017) (Table 17, pp34-35, application 1658, PSD, MSAC meeting July 2022).

In the NOVA and ARIEL3 trials, patients received at least two prior lines of PBC, and placebo maintenance therapy was received alone in the comparator arm. The submission claimed that based on the median PFS for the placebo arms of these studies (Table 11), there was no clear indication that HRD positive-*BRCA*wt status was associated with better outcomes than HRD negative status in platinum sensitive relapsed ovarian cancer. The submission stated that in the NOVA study there was a suggestion that *BRCA*m was associated with better PFS outcomes than HRD positive-*BRCA*wt and HRD negative status in platinum sensitive relapsed OC, however, the same was not observed in the ARIEL3 study. However as these were second (and later) line trials, they have limited applicability to the current submission.

Table 10   PFS by HRD status in patients receiving placebo in the randomised controlled trials of PARP inhibitor maintenance therapy in HGEOC: 1L studies

Trial	Primary therapy	Time of randomisation	Biomarker use (test detail)	Analysis group based on HRD status	Number of patients in placebo arm (n)	Median PFS in the placebo arm: months (95% CI)
Advanced platinum sensitive HGSOC cancers-first-line setting						
PRIMA (NCT02655016) Gonzalez-Martin 2019	CR/PR after 1L PBC Stage III patients must have residual disease after primary debulking surgery	Randomisation within 12 weeks after completion of the last dose of PBC PFS was from start of maintenance	MyChoice® HRD (Myriad Genetics): t*BRCA*; GIS ≥42 (genomic scar)	All patients	246	8.2 (7.3,8.5)
				HRD+ (GIS-high or t*BRCA*m)	126	10.4 (8.1,12.1)
				HRD+ (t*BRCA*m)	71	10.9 (8.0,19.4)
				HRD+ (GIS-high and t*BRCA*wt)	55	8.2 (6.7, 16.8)
				HRD- (GIS-low and t*BRCA*wt)	80	5.4 (4.0,7.3)
				HRDnd/unk	40	8.3 (5.7,12.5)
PAOLA-1 (NCT02477644) Ray-Coquard 2019	CR/PR after chemotherapy + bevacizumab (CA125/imaging/physical exam) during first line chemo/before randomisation ECOG PS 0 or 1	Randomisation within 9 weeks after completion of the last dose of PBC PFS was from start of maintenance	MyChoice® HRD (Myriad Genetics): t*BRCA*; GIS ≥42 (genomic scar)	All patients	269	16.6
				HRD+ (GIS-high and/or t*BRCA*m)	132	17.7
				HRD+ (t*BRCA*m)	80	21.7
				HRD+ (GIS-high and *BRCA*wt))	55	16.6
				HRD-p (GIS-low and *BRCA*wt)	85	16.2
				HRDnd/unk	52	~14.5
VELIA (NCT02470585) Coleman 2019	None specified	Randomisation was prior to receiving chemotherapy plus placebo. Patients who remained progression free after chemo, received maintenance or placebo PFS was taken from start of chemotherapy	*BRCA*nalysis test (Myriad Genetics): g*BRCA* MyChoice® HRD (Myriad Genetics): t*BRCA*; GIS ≥33 (genomic scar)	All patients	375	17.3 (15.1,19.1)
				HRD+ (GIS-high or *BRCA*m)	207	20.5 (17.8, 22.8)
				HRD+ (*BRCA*m)	92	22.0 (17.8, 29.1)
				HRD+ (GIS-high and *BRCA*wt))	115	19.8 (16.8, 22.6)
				HRD- (GIS-low and *BRCA*wt)	124	11.5 (10.1, 14.9)
				HRDnd/unk	44	Not reported

1L = first-line; *BRCA* = BReast CAncer gene; CA = cancer antigen; CI = confidence interval; CR = complete response; ECOG = Eastern cooperative oncology group; g = germline; GIS = genomic instability score; HGSOC = high grade serous ovarian cancer; HRD+ = homologous recombination repair deficient; HRD- = homologous recombination repair proficient; m = variant; nd = not determined; PBC = platinum-based chemotherapy; PFS = progression-free survival; PR = partial response; PS = performance status; t = tumour; unk = unknown; wt = wild type.
Blue shaded cells indicate data previously considered by MSAC
Source: Table 24, p65 of the submission

Table 11   **PFS by HRD status in patients receiving placebo in randomised controlled trials of PARP inhibitor maintenance therapy in platinum sensitive HGSOC: 2L studies**

Trial	Platinum sensitivity	Time of randomisation	Biomarker use (test detail)	Analysis group based on HRD status	Number of patients in placebo arm (n)	Median PFS in the placebo arm: months (95% CI)
Advanced platinum sensitive HGSOC relapse - (at least 2 previous lines of platinum-based chemotherapy)						
NOVA[1] (NCT01847274) Mirza 2016	Radiologic CR/PR to last and penultimate PBC; and disease progression more than 6 months after completion of the last round of PBC Low disease burden (<2 cm size) CA125<ULN or decreased by 90% during lats Pt - based regimen PFS was from start of maintenance	Randomisation within 8 weeks after completion of the last dose of PBC PFS was taken from start of chemotherapy;	*BRCA*analysis test (Myriad Genetics): g*BRCA* MyChoice® HRD (Myriad Genetics): t*BRCA*; GIS ≥42 (genomic scar)	All patients	181	Not reported
				HRD+ (g*BRCA*m)	65	5.5 (3.8 ,7.2)
				All g*BRCA*wt	116	3.9 (3.7, 5.5)
				HRD+ (GIS-high or s*BRCA*m)	56	3.8 (3.5, 5.7)
				HRD+ (GIS-high)	44	3.7 (3.3, 5.6)
				HRD+ (t*BRCA*m)	12	11.0 (2.0, NE)
				HRD- (GIS-low)	42	3.8 (3.7, 5.6)
				HRDnd	18	7.3 (1.9, NE)
ARIEL3[2] (NCT01968213) Coleman 2017	Radiological disease progression more than 6 months after the last dose of the penultimate PBC CR/PR to last PBC; responses must have been maintained through completion of chemotherapy and during the interval period between completion of chemotherapy and entry into the trial CA125 normalisation; PS 0 to 1	Randomisation within 8 weeks after completion of the last dose of PBC PFS was taken from start of chemotherapy;	Foundation Medicine T5 NGS assay: g/s*BRCA*; LOH (genomic scar); variants in 28 HRR genes LOH high: ≥16%)	All patients	189	5.4 (5.3, 5.5)
				HRD+ (g/s*BRCA*m or LOH-high)	118	5.4 (5.1, 5.6)
				HRD+ (g/s *BRCA*m)	66	5.4 (3.4, 6.7)
				HRD+ (LOH-high and *BRCA*wt	52	5.6 (2.9, 8.2)
				HRD- (LOH-low and *BRCA*wt)	54	5.3 (2.8, 8.2)
				HRDnd	17	Not reported

BRCA = BReast CAncer gene; CA = cancer antigen; CI = confidence interval; CR = complete response; g = germline; GIS = genomic instability score; HGSOC = high grade serous ovarian cancer; HRD = homologous recombination repair deficient; HRp = homologous recombination repair proficient; HRR = homologous recombination repair; LOH = loss of heterozygosity; m = variant; nd = not determined; NE = not estimable; NGS = next generation sequencing; PBC = platinum-based chemotherapy; PD = progressive disease; PFS = progression-free survival; PR = partial response; PS = performance status; s = somatic; t = tumour; ULN = upper limit of normal; unk = unknown; wt = wild type.
Blue shaded cells indicate data previously considered by MSAC
Sources: Source: Table 25, p69 the submission

Stronach 2018

Stronach 2018 evaluated the impact of ovarian tumour HRD status on PFS and OS for the overall study cohort and the subset with HGSOC for patients enrolled in the SCOTROC4 RCT (refer to Table 12). Tumours were considered HRD positive if they had a HRD score ≥42, based on TAI, LST, and LOH biomarkers or a tumour *BRCA* variant, and HRD negative if they had a HRD score <42 and wild-type *BRCA*1/2, however the name of the HRD test was not reported.

The submission claimed that Stronach 2018 provided evidence for the predictive impact of HRD – identifying patients with ovarian cancer who have an improved response to PBC, and that it illustrates the prognostic impact of the HRD biomarker – showing improved OS in this treatment setting. The submission claimed that while the outcomes of HRD positive *BRCA*wt patients were not considered in isolation, it could be surmised from the data that HRD status based on genomic instability alone was also predictive of response to chemotherapy and also prognostic in terms of OS. As for PARP inhibitor response, the commentary considered there may be uncertainty about whether the treatment effect is predicted by the combination of *BRCA*1/2 status and genomic instability, compared with either *BRCA*1/2 status or genomic instability alone.

Table 12   PFS and OS by HRD status and t*BRCA* variant status, in the SCOTROC overall trial HGSOC sub-cohorts treated with carboplatin as 1L single agent chemotherapy

	N	PFS Events	Median Months PFS (95% CI)	OS Events	Median Months OS (95% CI)
Overall trial cohort (N=250)					
HRD Status					
HRD positive	74	41	18.9 (13.91-22.26)	23	48.53 (30.48-NA)
HRD negative	175	119	11.57 (9.34-14.93)	73	28.11 (23.47-NA)
t*BRCA* Variant Status					
Mutant	34	19	19.92 (14.99-NA)	12	48.53 (27.52-NA)
Wild Type	216	141	12 (10.52-15.45)	84	30.74 (24.99-NA)
HGSOC sub-cohort (*N*=179)					
HRD Status					
HRD positive	65	39	16.47 (12.46-20.45)	21	48.53 (29.42-NA)
HRD negative	115	90	9.47 (8.81-12.00)	55	23.47 (19.69-28.11)
t*BRCA* Variant Status					
Mutant	29	18	18.90 (13.91-33.63)	11	48.53 (27.52-NA)
Wild Type	150	111	11.01 (9.11-13.05)	65	25.81 (21.70-34.32)

HGSOC = high-grade serous ovarian cancer; HRD = homologous recombination deficiency; PFS = progression-free survival; OS = overall survival; t*BRCA* = tumour breast cancer gene
Source: Table 26, p71 of the submission

Overall, the submission (p62) stated that evidence across several clinical trials indicated that HRD status has a predictive effect on patient outcomes in current standard practice in NDA HGEOC (i.e. 1L PBC) and that across PRIMA, PAOLA-1, VELIA, SCOTROC4 and GOG-0218 HRD positive patients consistently experienced better outcomes when treated with 1L PBC than HRD negative patients, irrespective of *BRCA* status.

The submission (p62) noted that predictive effects for 1L PBC in NDA HGEOC did not appear to translate to 2L PBC in platinum sensitive relapsed (PSR) HGEOC, based on data from NOVA and ARIEL3 and that this is likely a function of patient selection, with platinum-sensitivity to prior PBC being a larger driver of outcomes to subsequent PBC than HRD status.

The commentary noted that the same five 1L and 2L PARP inhibitor RCTs were identified in the olaparib Application No. 1658 codependent submission (p34, Application 1658, Public Summary Document, July 2022 MSAC meeting). In Application 1658, MSAC found that the magnitude of PFS results across studies varied widely. HRD positive *BRCA*wt patients had PFS durations of 3.8 months (Mirza 2016 - NOVA) to 19.8 months (VELIA study), and the studies were also inconsistent in suggesting whether there was a difference in PFS between HRD positive *BRCA*wt and HRD negative patients, with PAOLA-1, Coleman 2017 and Mirza 2016 suggesting no difference but

Gonzalez-Martin 2019 and the VELIA study suggesting longer median PFS in HRD positive *BRCA*wt patents compared to HRD negative patients. The commentary considered that ideally, investigation of prognostic validity of the requested biomarker would require demonstration of the prognostic validity of tumours being HRD positive *BRCA*wt vs its complement (HRD positive *BRCA*m plus HRD negative). While no evidence was available specifically for the complement population (for Application 1658), the commentary considered that there was evidence to support the prognostic effect of patients with HGEOC having HRD positive *BRCA*wt tumours vs a HRD negative population based on PFS results as demonstrated by González-Martín 2019.

Application No. 1658 also identified the population-based cohort studies Hjortkjaer 2019 and Lecuelle 2021 that reported OS results by HRR variant, *BRCA*ness phenotypes and germline *BRCA* status. MSAC previously found that the relevance of these subgroups to the requested population (HRD positive *BRCA*wt) was unclear (p34, Application 1658, Public Summary Document, July 2022 MSAC meeting).

Predictive evidence

The PRIMA trial provided the pivotal clinical data used to support the use of niraparib versus SMM for the treatment of patients with HGEOC, with PBS listing requested specifically in the subpopulation of patients whose tumours are HRD positive *BRCA*wt. The clinical utility standard (as per the definition in the MSAC Guidelines) for determining HRD and *BRCA* status was the Myriad MyChoice® HRD CDx assay, as was used in PRIMA with a threshold of ≥42 determining HRD positivity.

Patients in PRIMA were stratified by the use of neoadjuvant chemotherapy (yes or no), best response to platinum therapy (complete or partial response), and homologous recombination deficiency test status (positive or negative/not determined). However, they were not stratified by *BRCA* status. As such, the HRD positive *BRCA*wt and the complementary HRD negative *BRCA*wt subgroups were partially non-randomised between treatment arms which could lead to higher risk of selection bias. PRIMA was powered to test for a PFS HR of 0.5 and 0.65 for niraparib versus placebo in the HRD positive and ITT populations, respectively.

PRIMA allowed the comparison of PFS in patients who were classified as HRD positive *BRCA*wt, HRD positive, HRD negative, tumour *BRCA*m, tumour *BRCA*wt and for the full analysis set. A summary of the PFS results assessed by blinded independent committee review (BICR) at the 17 May 2019 data cut off and investigator assessed (INV) PFS at an ad hoc 17 November 2021 data cut off is presented in the tables below.

Table 13   PFS by BICR in PRIMA by subgroup, 17/5/2019 data cut off

	Niraparib	Placebo	PFS per BICR
ITT			
Median PFS (95%CI)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)	**0.62 (0.502, 0.755)**
Events, n/N(%)	232/487 (47.6)	155/246 (63.0)	
HRD positive *BRCA*wt			
Median PFS (95%CI)	19.6 (13.6, NE)	8.2 (6.7, 16.8)	**0.50 (0.305, 0.831)**
Events, n/N(%)	32/95 (33.7)	33/55 (60.0)	
***BRCA*m**			
Median PFS (95%CI)	22.1 (19.3, NE)	10.9 (8.0, 19.4)	**0.40 (0.265, 0.618)**
Events, n/N(%)	49/152 (32.2)	40/71 (56.3)	
HRD negative*			
Median PFS (95%CI)	8.1 (5.7, 9.4)	5.4 (4.0, 7.3)	**0.68 (0.492, 0.944)**
Events, n/N(%)	111/169 (65.7)	56/80 (70.0)	
HRnd			
Median PFS (95%CI)	11.0 (7.4, 13.9)	8.3 (5.7, 12.5)	0.85 (0.509, 1.432)
Events, n/N(%)	40/71 (56.3)	26/40 (65.0)	

Source: Table 64 (p135) and Table 75 (p155) of the submission
BICR = blinded independent central review; *BRCA*m = *BRCA* variant; CI = confidence interval; HR = homologous repair; HRD = homologous repair deficiency; nd = not determined; NE = not evaluable; NR = not reported; PFS = progression free survival wt= wild type
Bold text indicates statistically significant differences between treatment groups
*HRD negative status was defined in the PRIMA trial as a GIS score <42 and not possessing a deleterious or suspected deleterious *BRCA* variant.

Table 14   INV PFS in PRIMA by subgroup, 17/11/21 data cut off

	Niraparib	Placebo	INV PFS
ITT			
Median PFS (95%CI)	13.8 (11.9, 16.3)	8.2 (7.6, 9.8)	**0.66 (0.556, 0.792)**
Events, n/N(%)	332/487 (68.2)	199/246 (80.9)	
HRD positive *BRCA*wt			
Median PFS (95%CI)	19.4 (12.5, 33.5)	10.4 (7.0, 13.7)	**0.66 (0.437, 0.999)**
Events, n/N(%)	54/95 (56.8)	43/55 (78.2)	
***BRCA*m**			
Median PFS (95%CI)	31.5 (19.3, 51.8)	11.5 (8.4, 16.6)	**0.45 (0.322, 0.641)**
Events, n/N(%)	83/152 (54.6)	55/71 (77.5)	
HRD negative			
Median PFS (95%CI)	8.4 (NR)	5.4 (NR)	**0.65 (0.49, 0.87)**
Events, n/N(%)	NR	NR	
HRnd			
Median PFS (95%CI)	NR	NR	NR
Events, n/N(%)	NR	NR	

Source: Table 64 (p135) and Table 76 (p155) of the submission
*BRCA*m = *BRCA* variant; CI = confidence interval; HR = homologous repair; HRD = homologous deficiency repair; INV = investigator assessed nd = not determined; NR = not reported; PFS = progression free survival wt= wild type
Bold text indicates statistically significant differences between treatment groups

The commentary considered it was unclear whether PRIMA supported the predictive value of HRD positive *BRCA*wt as niraparib appeared to be effective in patients irrespective of HRD positivity. No tests for interaction were provided in the submission. PRIMA reported that patients randomised to niraparib had statistically significant (i.e. upper 95% confidence interval of HR was less than 1.0) PFS benefits compared to patients randomised to placebo irrespective of whether they were HRD positive *BRCA*wt or HRD negative, though neither subgroup analyses were part of the formal statistical plan and results should be considered exploratory. In fact, in the ad hoc November 2021 data cut, HRD negative patients reported a numerically better PFS HR (0.65, 95% CI 0.49, 0.87) compared to HRD positive *BRCA*wt patients (PFS HR = 0.66, 95%CI 0.437, 0.999), with the upper 95% CI for the HRD positive *BRCA*wt patients almost reaching one (and not being statistically significant). The improvement in median PFS however was better in HRD positive *BRCA*wt patients (9.0 months) than in the HRD negative population (3.0 months), and the improvement of 3.0 months was likely less clinically significant than the improvement of 9.0 months.

The PBAC has previously noted the uncertain clinical benefit for niraparib in patients with HRD negative HGEOC. The PBAC considered that in the HRD negative or not determined subgroup the PFS benefit was small and may not be clinically meaningful. The PBAC noted that no OS benefit was demonstrated (paragraphs 6.36 and 7.17, niraparib, Public Summary Document, July 2021 PBAC meeting).

The commentary considered the ITT results in PRIMA (statistically significantly in favour of PARP inhibitor treatment compared to placebo) differed to PAOLA-1 (no statistically significant difference between PARP inhibitor + bevacizumab compared to bevacizumab alone) despite there being similar proportion of *BRCA*m and HRD positive patients (though the use of bevacizumab in PAOLA-1 may confound any comparison of hazard ratios across trials).

Results from other genes of interest in HRR were not reported in PRIMA. The commentary highlighted that in PAOLA-1, HRD positive patients with a variant in HRR genes other than *BRCA* treated with olaparib + bevacizumab also reported longer median PFS (28.1 months, n=18) than patients treated with bevacizumab alone (17.7 months, n=7) but in HRD negative patients with variant in HRR genes other than *BRCA*, the median PFS for patients treated with olaparib + bevacizumab (16.1 months, n=33) was similar to patients treated with bevacizumab alone

(16.6 months, n=14). [6] The commentary considered that caution needs to be exercised when interpreting these results with regards to any application to niraparib as sample size in these specific subgroups were extremely small, and PAOLA-1 had a different active treatment (olaparib + bevacizumab) and comparator (bevacizumab) than PRIMA (niraparib and placebo, respectively).

The OS results available for PRIMA were not yet mature (41% maturity for the overall population based on data cut-off 17/5/2019) and therefore did not allow demonstration of the predictive validity of HRD positive *BRCA*wt status. Final OS analyses results are expected in 2024 when approximately 440 deaths have occurred in the ITT population, corresponding to 60% data maturity.

Change in management in practice

The submission proposed the test population (patients with NDA HGEOC undergoing maintenance treatment following response to 1L PBC) undergo HRD testing (using the Illumina TruSight Oncology 500 HRD) to determine GIS and *BRCA* status at diagnosis (base case). As shown in the figure below, patients whose tumours are found to be HRD positive *BRCA*wt HGEOC and are in response to 1L PBC (CR/PR) would be eligible for niraparib under the proposed PBS-listing.

The proposed use of HRD testing would result in a change in clinical practice as ovarian cancer patients currently undergo *BRCA*1 and *BRCA*2 variant testing. The submission proposed the MBS item for tumour HRD testing replace the currently used item for somatic *BRCA* testing (MBS item 73301). Currently, these patients would be eligible to receive niraparib if they were found to be HRD positive *BRCA*wt, whereas the submission details that these patients currently receive SMM.
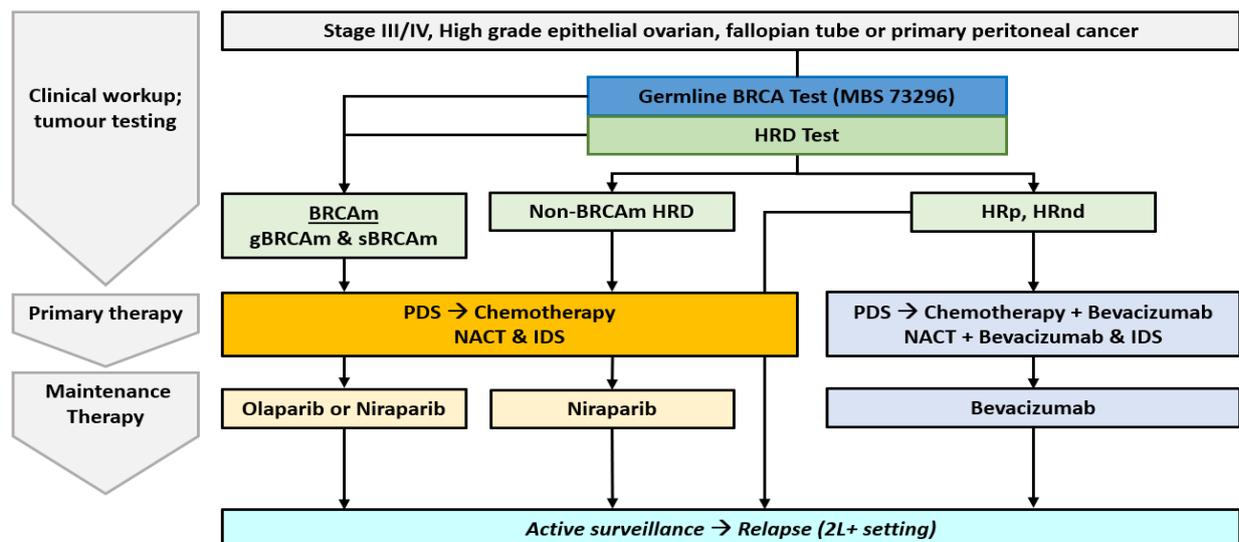
Figure 3   Proposed treatment algorithm presented in the submission

*BRCA*m = *BRCA* gene variant; g = germline; HRD = homologous recombinant deficient; HRnd = homologous recombinant not determined; HRp = homologous recombinant proficient; NACT = neoadjuvant chemotherapy; IDS = interval debulking surgery; PDS = primary debulking surgery; s = somatic

Notes: (1) Platinum-based chemotherapy is recommended as adjuvant therapy post-PDS and as neoadjuvant therapy prior to IDS and adjuvant therapy post-IDS. Following completion of platinum-based chemotherapy, patients are required to be in response (i.e. CR/PR) in order to transition to maintenance PARP inhibitors; (2) The submission incorrectly listed the germline *BRCA* test as MBS item number 73296, instead of the correct item number of 73295.

Source: Figure 10, p50 of the submission

Note: diagram does not reflect MSAC's advice that the appropriate terminology was "ovarian, fallopian tube or primary peritoneal carcinoma", rather than "epithelial ovarian, fallopian tube or primary peritoneal cancer".

---

[6] Pujade-Lauraine E, Brown J, Barnicle A et al. 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 Volume 162, Supplement 1, August 2021, Pages S26-S27

Claim of codependence

The submission did not explicitly state that there was a biological rationale for targeting HRD positive *BRCA*wt HGEOC. While the codependency between HRD status and PARP inhibitors has not previously been accepted by MSAC and PBAC, they have both accepted that variation in the size of the treatment effect of PARP inhibitors is predicted by *BRCA*1/2 status as one HRD biomarker (paragraph 6.45, olaparib PSD, July 2022 PBAC meeting).

13. Economic evaluation

The submission presented a modelled economic evaluation (cost effectiveness analysis (CEA)) based on subgroup results from PRIMA, a direct randomised trial comparing niraparib versus SMM for the maintenance treatment of patients with high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (CR/PR) to 1L PBC.

The economic model compared the proposed scenario where all patients undergo HRD testing versus the comparator/current scenario where patients receive *BRCA* testing only, using a stepped economic evaluation. A diagnostic testing component was added prior to model entry for the allocation of test costs and patient outcomes. Concordance between the proposed HRD test and the clinical utility standard was informed by Weichert (2021a and 2022), using the RUO Illumina TruSight Oncology HRD test as a proxy for the proposed commercial Illumina TruSight Oncology HRD test and the Myriad MyChoice® HRD PLUS test as a proxy for the clinical utility standard of Myriad MyChoice® CDx. Concordance data was used to allocate maintenance therapy costs and outcomes as a function of treatment (niraparib or SMM) and biomarker status (HRD and/or *BRCA*m).

The economic model allowed consideration of the four proposed test populations (including parallel or sequential *BRCA* and GIS testing, and testing occurring either at diagnosis or delayed until PBC treatment), as discussed above. The model base case scenario of HRD testing to determine *BRCA*1/2 variant and GIS in parallel at diagnosis is shown in the figure below.
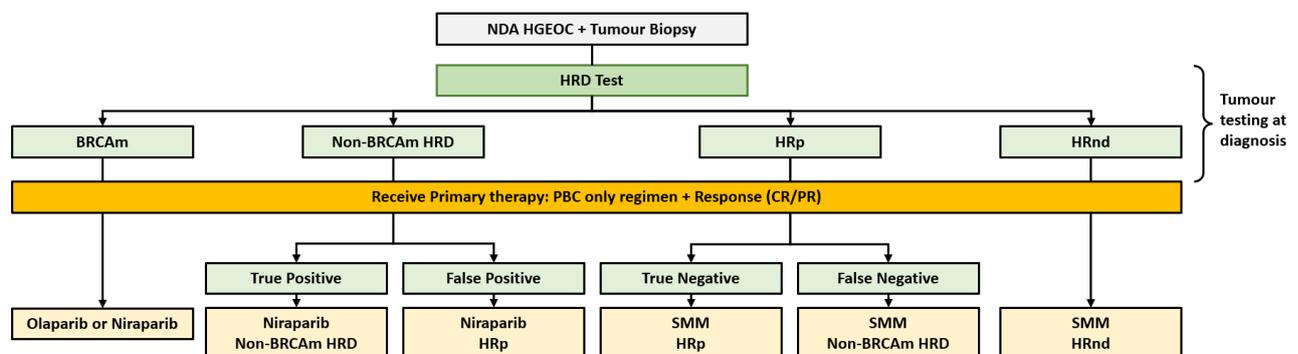
Figure 4   Tumour testing at diagnosis and outcomes in proposed clinical practice (Population #1: parallel – base case)

*BRCA*m = breast cancer gene variant; CP = complete response; HGEOC = high-grade epithelial ovarian cancer; HRnd = homologous recombination not determined; HRD = homologous recombination deficient; HRp = homologous recombination proficient; ND = not determined; NDA = newly diagnosed advanced; PBC = platinum-based chemotherapy; PR = partial response; SMM = standard medical management.
* The diagnostic accuracy of HRD testing was assessed based on concordance between Illumina TSO 500 assay and Myriad MyChoice.
Source: Figure 41, p177 of the submission

Based on the concordance from Weichert, the proportion of patients treated with niraparib are illustrated in Figure 5. The figure shows that 94.43% (21.3%/22.6%) of all patients treated with niraparib were considered to be true HRD positive *BRCA*wt and 5.57% (1.3%/22.6%) were false positives who were actually HRD negative patients.

```
┌─────────────────────┐                    ┌─────────────────────┐
│   BRCAm (25.3%)     │                    │  Non-BRCAm (74.7%)  │
└──────────┬──────────┘                    └──────────┬──────────┘
           │                                          │
           │              ┌───────────────────────────┼───────────────────────────┐
           │              │                           │                           │
           │    ┌─────────▼─────────┐      ┌─────────▼─────────┐      ┌─────────▼─────────┐
           │    │   HRD (23.7%)     │      │   HRp (39.3%)     │      │   HRnd (11.7%)    │
           │    └─────────┬─────────┘      └─────────┬─────────┘      └─────────┬─────────┘
           │              │                          │                          │
┌──────────▼──────────┐  │                          │                          │
│ Olaparib or Niraparib│ ┌▼──────────────────┐ ┌───▼───────────────┐ ┌────────▼──────────┐
│      (25.3%)        │ │ Niraparib vs SMM   │ │ Niraparib vs SMM  │ │    SMM (11.7%)    │
│                     │ │     (21.3%)        │ │      (1.3%)       │ │                   │
│   No Change in      │ │                    │ │                   │ │   No Change in    │
│    Outcomes         │ │ True positive:     │ │ False positive:   │ │    Outcomes       │
└─────────────────────┘ │ Change in Outcomes │ │ Change in Outcomes│ └───────────────────┘
                        ├────────────────────┤ ├───────────────────┤
                        │   SMM (2.4%)       │ │   SMM (38.0%)     │
                        │                    │ │                   │
                        │ False negative:    │ │ True negative:    │
                        │ No Change in       │ │ No Change in      │
                        │ Outcomes           │ │ Outcomes          │
                        └────────────────────┘ └───────────────────┘
```
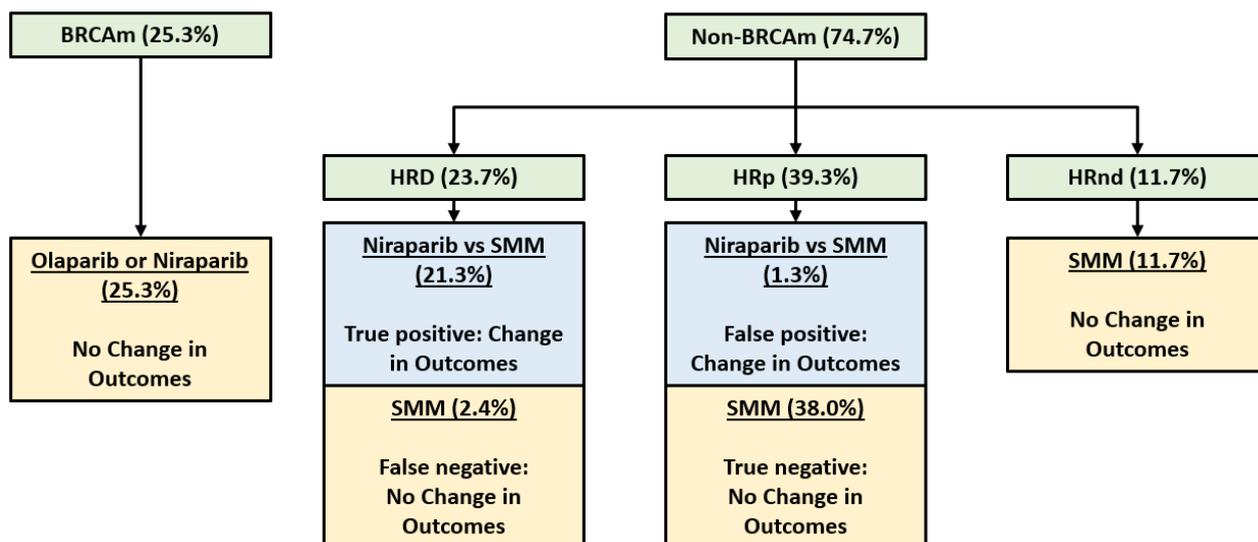
Figure 5   **Clinical outcomes (blue shaded boxes) and proportions of patients modelled in the economic evaluation – parallel testing base case**

*BRCA*m = *BRCA* variant; HRD = homologous recombination deficient; HRnd = homologous recombination not determined; HRp = homologous recombination proficient; SMM = standard medical management

Source: Figure 49, p194 of the submission

Previously, the PBAC considered that in the *BRCA*wt population there may be patients who do not receive any clinically meaningful benefit from treatment with niraparib (paragraph 7.7, niraparib, Public Summary Document, March 2022 PBAC meeting). The PBAC considered that in the HRD negative or not determined subgroup the PFS benefit was small and may not be clinically meaningful. Additionally, the PBAC noted that no OS benefit was demonstrated (paragraph 6.36, niraparib, Public Summary Document, July 2021 PBAC meeting). As such, it was unclear that a base case that assumed clinical benefit in the HRD negative cohort was reasonable.

The submission stated that clinical outcomes and treatment exposure associated with *BRCA*m and HRnd patients were not included in the model as HRD testing was not expected to impact the use of PARP inhibitors in these patients. The Commentary considered this was inappropriate as the submission proposed that *BRCA*m patients who currently undergo *BRCA* testing alone (currently associated with a cost of $1,200, although MSAC advised that this should be reduced to $1,000, p1, Application No. 1618 MSAC PSD, MSAC meeting November 2021) would instead need to undergo HRD (GIS and *BRCA*) testing at an increased cost of $3,000. As the submission proposed the replacement of tumour *BRCA*m testing, MBS item 73301, with HRD testing, the commentary considered acceptable cost-effectiveness of HRD testing should be demonstrated for the *BRCA*m cohort in addition to the HRD positive *BRCA*wt cohort. However, the incremental cost and outcomes in the *BRCA*m cohort were not considered in the submission. Further, though false results were considered for HRD they were not considered separately for GIS and *BRCA* results. All categorisation of *BRCA*m or *BRCA*wt were inappropriately assumed to be true positives. *(Refer to Economic Evaluation – Joint ESC advice to PBAC)*

The submission claimed that as the proposed MBS item limits HRD testing to once per primary tumour diagnosis, repeat testing is not expected to occur in practice and therefore was not included in the model. However, the commentary highlighted that the cost of subsequent germline *BRCA* testing in patients in whom HRD testing was inconclusive was inappropriately not considered in the submission, which may underestimate the cost of testing in the proposed scenario.

The submission included a 'without diagnostic testing scenario' for the economic analysis, which assumed the HRD and *BRCA* status of all patients was already known in clinical practice. The commentary considered that this was implausible as this implied 'free and perfect testing' as opposed to 'without diagnostic testing'.

The commentary considered the model also inappropriately applied half cycle correction to the cost of niraparib, which underestimated the total cost of treatment. The base case was respecified during the commentary to include a *BRCA* test cost of $1,000 and to update subsequent anti-cancer treatments include to current prices (PBS ex-manufacturer prices dated 1/11/2022) and to remove half cycle correction from the cost of niraparib. The respecified base case ICER was *$55,000 to <$75,000*/QALY, which was an increase of 4.95% compared to the base case ICER presented in the submission (*$55,000 to <$75,000*/QALY). The respecified base case ICERs for the trial-based analysis and the modelled analysis are presented below.

Table 15   Results of the base case economic evaluation from clinical study data

Component	Niraparib (proposed scenario)	SMM (current scenario)	Increment
Modelled cost per QALY versus SMM (20 years), with diagnostic testing			
Discounted costs	*$Redacted*	*$44,154*	*$Redacted[1]*
Discounted LYG	6.2065	5.3203	0.8863
Discounted QALYs	4.5369	3.8075	0.7294
		Incremental cost per LY gained	*$Redacted[2]*
		Incremental cost per QALY gained	*$Redacted[2]*

ICER = incremental cost effectiveness ratio; ISD = PFLY = progression-free life year; QALY = quality adjusted life year; SMM = standard medical management.
Figures in italics calculated from the respecified base case model.
Source: Table 146, p267 of the submission and Zejula (niraparib) 1L HRD_non*BRCA*m CUA.xls.
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*
[2] *$55,000 to < $75,000*

The economic evaluation results for the alternate population testing scenarios explored in the model are provided in Table 16. Parallel testing post initiation of PBC led to the largest change in the ICER (- 4.55%) compared to the base case of parallel HRD testing at diagnosis.

Table 16   Economic evaluation results for additional diagnostic testing scenarios (alternate testing populations; base case parallel testing at diagnosis

Scenario	Cost	QALYs	ICER	% difference to base case
Parallel testing (Population#1, base case)	$ Redacted	0.7294	$ Redacted[1]	-
Sequential testing at diagnosis (Population #2)	$ Redacted	0.7323	$ Redacted[1]	+1.39%
Parallel testing post initiation of PBC (Population #3a)	$ Redacted	0.7294	$ Redacted[1]	-4.55%
Sequential testing post initiation of PBC (Population #3b)	$ Redacted	0.7323	$ Redacted[1]	-1.84%

Source: Table 154, p274 of the submission and Zejula (niraparib) 1L HRD_non*BRCA*m CUA.xls.
PBC = platinum-based chemotherapy; QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*

The scenarios in which all patients were either HRD positive or HRD negative were explored, as summarised in Table 17. The commentary highlighted that the incremental QALY gain from niraparib in the HRD positive *BRCA*wt population was around double that of the HRD negative, though the incremental costs were lower due to patients remaining on treatment for a shorter period of time. Importantly, the ICER in the HRD negative population was not substantially worse than the base case, which was a result of the statistically significant PFS benefit (and therefore OS benefit) from PRIMA being used in the model.

Table 17   Economic evaluation results for additional population scenarios

Scenario	Cost	QALYs	ICER	% difference to base case
Base case (94.4% HRD positive *BRCA*wt)	$Redacted	0.7294	$Redacted[1]	-
All patients HRD positive *BRCA*wt [a]	$Redacted	0.7510	$Redacted[2]	-24.1%
All patients HRD negative [a]	$Redacted	0.3630	$Redacted[1]	+9.7%

Source: Zejula (niraparib) 1L HRD_non*BRCA*m CUA.xls "CUA results" sheet
HRD = homologous recombination deficient; PBC = platinum-based chemotherapy; QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio
[a] *These analyses do not include testing costs.*
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$45,000 to < $55,000*

Results of the key univariate sensitivity analyses that relate to diagnostic accuracy and testing costs are summarised in the table below, further sensitivity analyses are shown in Table PBAC 15.

Table 18   Key univariate sensitivity analysis around economic model

Model variable	Incr. cost	Incr. QALYs	IC per QALY	% difference
Base case (respecified: BRCAm test = $1,000; chemotherapy costs updated, no half cycle correction)	**$Redacted**	**0.7294**	**$Redacted[1]**	**-**
Base case presented in submission	$ Redacted	0.7294	$Redacted[1]	-4.95%
Diagnostic accuracy: PPV = 97.5%; NPV = 94.0% [c]				
PPV = 100%; NPV = 100%	*$Redacted*	*0.7510*	*$Redacted[1]*	*-2.5%*
PPV = 95%; NPV = 95%	*$Redacted*	*0.7181*	*$Redacted[1]*	*0.3%*
PPV = 90%; NPV = 90%	*$Redacted*	*0.6838*	*$Redacted[1]*	*3.4%*
PPV = 85%; NPV = 85%	*$Redacted*	*0.6481*	*$Redacted[1]*	*7.1%*
Cost of proposed HRD test: Base case $3,000				
$2,500	*$Redacted*	0.7294	$Redacted[1]	-5.80%
$2,000	*$Redacted*	0.7294	$Redacted[1]	-11.59%

Source: Table 154, p275 of the submission and Zejula (niraparib) 1L HRD_non*BRCA*m CUA.xls. *Values for diagnostic accuracy were revised in the PSCR (p9)*
*BRCA*m = breast cancer gene variant; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficient; ISD = individualised starting dose; IC = incremental cost; ITT = intention-to-treat; NPV = negative predictive value; OS = overall survival; PFS = progression-free survival; PPV = positive predictive value; QALY = quality adjusted life year; SMM = standard medical management; TTD = time to treatment discontinuation; tx = treatment
[c] Method of calculating these figures could not be replicated during evaluation as PPV and NPV values did not appear to have been used in the model. Numbers as per submission presented.
Details in italics calculated during commentary.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*

A scenario in which all patients were eligible and treated with niraparib in the absence of HRD testing was also considered during the evaluation, and this actually led to a lower ICER than the proposed base case (-15%), as the high cost of testing was not incurred and both HRD positive *BRCA*wt and HRD negative patients were assumed to benefit from niraparib (based on PRIMA results). However, assuming no niraparib benefit in the HRD negative population increased the ICER by 49%.

Table 19   Multivariate sensitivity analyses around assumptions of HRD negative patients and testing

Scenario	Incr. cost	Incr. QALYs	IC per QALY	% difference
Base case (respecified: *BRCA*m test = $1,000; chemotherapy costs updated, no half cycle correction)	**$Redacted**	**0.7294**	**$Redacted[1]**	**-**
No difference in OS or PFS between the treatment arms for HRD negative patients	$Redacted	0.7087	$Redacted[1]	+2.66%
'No testing' scenario (HRD test cost = $0 and % treated with niraparib = 100%) [a]	$Redacted	0.5088	$Redacted[1]	-15.02%
No difference in OS or PFS between the treatment arms for HRD negative patients and 'no testing' scenario [b]	$Redacted	0.2774	$Redacted[2]	+48.69%

Source: calculated during submission using Zejula (niraparib) 1L HRD_non*BRCA*m CUA.xls.
[a] ratio of HRD positive *BRCA*wt (94.43%) to HRD negative (5.57%) unchanged from base case
[b] ratio of HRD positive *BRCA*wt (37.59%) to HRD negative (62.41%) reflects prevalence
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000
[2] $95,000 to < $115,000

14.   Financial/budgetary impacts

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

The submission financial estimates included the cost of *BRCA* testing of $1,200. As the MSAC has previously stated that the cost of *BRCA* testing should be reduced to $1,000, financial estimates assuming an MBS fee of $1,000 for *BRCA* testing was included during the evaluation. Additionally, the treatment duration assumed was changed during the evaluation to reflect no half cycle correction.

The 1 November 2022 Greatest Permissible Gap (GPG) is $93.20, which means that out-of-hospital *BRCA* testing (and HRD testing if implemented) will attract a benefit that is greater than 85% of the MBS fee so that patients do not incur a gap fee greater than $93.20 (which occurs for MBS fees of $621.50 or more). As the cost of *BRCA* testing has decreased, the commentary considered that 85% of the MBS fee may be sufficient to cover the test with no out-of-pocket payments (e.g. private laboratories are listing a fee of $400 for non-Medicare rebated *BRCA* tests)[7]. Therefore patients may incur out-of-pocket costs for HRD testing that they would not incur for *BRCA* testing alone. Patients may incur further out-of-pocket costs for HRD testing if pathology providers charge a fee higher than the proposed fee of $3,000 as this would not be covered by the GPG.

---

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

Table 20   Estimated use and financial implications of listing HRD test and niraparib

	2023	2024	2025	2026	2027	2028
Estimated extent of use of HRD test						
Incidence of epithelial ovarian, fallopian tube and primary peritoneal cancer	1,731	1,758	1,786	1,813	1,841	1,868
% with high-grade disease	93.63%					
% with advanced disease	81.81%					
% with viable tissue sample for testing	67.5%	70.0%	72.5%	75.0%	77.5%	80.0%
NDA HGEOC patients receiving HRD test (MBS)	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Patients treated with niraparib	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]
Number of tests in application 1658	*1,131*	*1,152*	*1,174*	*1,195*	*1,218*	*1,240*
Estimated financial implications of the proposed test to the MBS						
Total testing cost [a]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost to MBS (85% rebate)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost to MBS (GPG) [b]	*$Redacted[3]*	*$Redacted[3]*	*$Redacted[3]*	*$Redacted[3]*	*$Redacted[3]*	*$Redacted[3]*
Estimated financial implications for other MBS items						
Blood count [c]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Additional cost of blood count (85% rebate)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
t*BRCA* test not used	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Cost offset of t*BRCA* tests not used (85% rebate)	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]
Cost offset of t*BRCA* tests not used (GPG)	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]	Redacted[4]
Net financial implications						
Net cost to MBS (85% rebate for all items)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Net cost to MBS (GPG for HRD and *BRCA* test)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Net cost to MBS application 1658	$1,710,895	$1,772,642	$1,805,525	$1,839,017	$1,873,131	$1,907,878

Source: Tables 186 and 187, p295, Table 195 and 199, p299-300 of the submission worksheet "2a. Patients - incident" ,"5. Impact – net" "7. Net changes – MBS", Zejula (niraparib) 1L BIM Oct 22".xlsx worksheet, Table 26, p47, application 1658, PSD, MSAC July 2022 meeting
a Assumed cost to the MBS of $3000 per test, i.e. 100% of the proposed fee.
b 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). Rebate per HRD test set to $2,906.80 and rebate per BRCA test set to $906.80.
c MBS item 65070, schedule fee $16.95. Assume 15.35 tests in year one and 4 tests each year, applied pro-rata
EOC = epithelial ovarian cancer; GPG = greatest permissible gap; HGEOC = high-grade epithelial ovarian cancer; HRD = homologous recombination deficiency; NDA = newly diagnosed advanced; tBRCA = tumour breast cancer susceptibility gene variant
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] < 500
[3] $0 to < $10 million
[4] net cost saving

The commentary highlighted that the number of tests was lower than estimated in application 1658, primarily due to this submission assuming only 67.5%-80% of patients will have a viable sample for testing, whereas in application 1658 the proportion of patients who would undergo testing was consistent with *BRCA*m testing in the olaparib July 2020 submission (95%, para 6.47,

olaparib PSD, July 2020 PBAC meeting). Despite this, as the cost per test is higher in this submission, the net cost to MBS was similar to application 1658.

The cost to MBS for each of the proposed testing populations is presented below. The commentary noted that Population 2 had the highest total cost as all patients were assumed to use *BRCA* testing, therefore there was no associated offset. Population 3a was associated with the lowest cost of testing overall, but may not be viable in practice, particularly as the turnaround time of HRD testing was estimated to be four weeks and may represent an unacceptable delay in initiating treatment.

Table 21   Financial estimates for different testing population scenarios

	2023	2024	2025	2026	2027	2028
Population 1: (Base case): HRD testing to determine *BRCA*1/2 variant and GIS in parallel at diagnosis						
Number of HRD tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Cost to MBS	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]
Population 2: HRD testing to occur sequentially following a negative *BRCA*1/2 test result at diagnosis						
Number of HRD tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Cost to MBS	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]
Population 3a: HRD testing to determine *BRCA*1/2 variant and GIS in parallel, being deferred to the time of receipt of 1L platinum-based chemotherapy only						
Number of HRD tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Cost to MBS	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]
Population 3b: HRD testing at the time of receipt of 1L platinum-based chemotherapy only, following determination of *BRCA* status at diagnosis.						
Number of HRD tests	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Cost to MBS	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]	$Redacted[2]

Source: Table 202, p306 of the submission
The redacted values correspond to the following ranges:
[1] *500 to < 5,000*
[2] *$0 to < $10 million*

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:
- The codependency between niraparib treatment benefit and homologous recombination deficiency (HRD) status defined by genomic instability (GI) for *BRCA*-negative patients was not strong. The key PRIMA trial demonstrated a progression-free survival benefit (PFS) benefit for both HRD-positive and HRD-negative patients. Point estimates for PFS benefit from the PRIMA trial and other PARP-inhibitor trials in ovarian cancer show somewhat consistent evidence of treatment effect modification between HRD status and PFS with PARP inhibitors. However, these trials have a high risk of bias as the results were from subgroups that were not prespecified and therefore not powered to show differences in outcomes. An application without explicit codependency could still be considered by MSAC, and this may obviate the need to define a threshold for HRD positivity.
- There is currently no practical definition of HRD or GI that can be applied to HRD tests to help harmonise tests and define thresholds for HRD-positivity. The ESCs 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 which brand of HRD test that is 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.

Economic issues:

- The appropriate fee for HRD testing was uncertain. The proposed fee of $3,000 may be high and insufficiently justified. Patients may be charged out-of-pocket costs for HRD testing, though this would be mitigated by the Greatest Permissible Gap.
- The value of funding HRD testing depended on whether the codependency between HRD (GI) and response to niraparib was accepted due to the relatively high cost of the test, the incremental cost-effectiveness ratios (ICERs) with and without HRD testing area similar. However, the incremental cost-effectiveness ratio (ICER) was highly uncertain due the underlying uncertainty in the modelled PFS and overall survival outcomes. Additionally, the economic model did not consider the accuracy of the proposed HRD (GI) tests for identifying *BRCA* status and HRD status separately, the implications of a higher cost test for cost-effectiveness in *BRCA*m and HRD not determined groups, or the impact of test failures.

Financial issues:

- The cost of HRD testing to the MBS may have been underestimated, because the proportion of patients with viable tissue and therefore the number of estimated HRD tests was lower than that estimated under comparable previous applications.

ESC discussion

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

The HRD occurs where cells cannot effectively repair double-stranded breaks in DNA using the homologous recombination repair (HRR) pathway. The ESCs recalled that HRD can be assessed using by different methods. The focus of the submission was HRD status as defined by genomic instability (GI). The submission proposed the Illumina TruSight Oncology 500 (TS500) HRD test to determine GI and *BRCA* status.

The key predictive evidence was from the PRIMA trial, which used the next-generation sequencing (NGS)-based Myriad MyChoice® HRD CDx assay with a GI score threshold of ≥42 to determine HRD positivity. The ESCs noted that this application is being considered at the same meeting as MSAC Application 1658.1, which requested a similar MBS listing to determine treatment eligibility for treatment with olaparib. ESC recalled that MSAC had previously considered the evidence in the submission for Application 1658 was not sufficient to ascertain the clinical validity of HRD tests broadly for predicting benefits of poly (ADP-ribose) polymerase (PARP) inhibitor treatment in patients with these cancers, especially when removing *BRCA* alteration status (*BRCA*m) as the basis for defining the cancer as being HRD-positive.

The ESCs 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 the means by which it is detected by testing, in order for MSAC to better judge whether the definition of HRD has been sufficiently established for the purpose requested and by the means proposed.

The ESCs noted that the three 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 homologous recombination repair (HRR) pathway. The ESCs considered that this definition was

consistent with guidelines and the definition provided by the applicant. However, the ESCs 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, the ESCs 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.

The ESCs 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. The ESCs concluded from the HRD experts' advice that HRD thresholds do not rely on the presence or absence of *BRCA*m 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. The ESCs noted that the Myriad MyChoice® HRD test had two different thresholds for different PARP inhibitors.

The ESCs noted that two of the experts advised that the thresholds used could be those that have been demonstrated in clinical trials or validation studies to determine the patients who would benefit from PARP inhibitors. The ESCs noted that experts acknowledged that these tests may not correctly identify some patients who may benefit form 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 *BRCA*wt 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.

The proposed MBS item descriptor was brand-agnostic, which the ESCs considered was consistent with the Department's general preference for method-agnostic MBS item descriptors where possible. The commentary had suggested a brand-specific approach similar to that recently supported by MSAC for the EndoPredict® gene expression profiling test for patients with breast cancer (Application 1408.1, MSAC Public Summary Document [PSD], pp3-4). However, the ESCs queried whether this approach was appropriate given no brand of HRD test is yet available in Australia.

The ESCs considered that potential safety issues were important for consumers. The ESCs 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. The ESCs 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.

The ESCs 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). The ESCs noted the applicant's pre-ESC response stated an application has not yet been lodged with the TGA for the Illumina TSO 500 HRD assay, though six Australian laboratories are currently accredited to run this assay. However, the TGA advised that it was currently a research use only device and ██████████████████████████████████████. The

ESCs 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. The ESCs considered that further consultation with TGA/NATA is required about the timeline for the accreditation and regulatory process for the test. The ESCs considered that if MSAC were to support a brand-specific MBS item descriptor for the Myriad MyChoice® HRD test as the clinical utility standard for HRD testing, then the item descriptor may need to specify not only Myriad MyChoice® HRD test but also other brands of HRD test that have been successfully validated against it.

The ESCs noted that the proposed item descriptor stated to determine eligibility with respect to HRD status for access to PBS-listed niraparib. ESC considered that HRD status includes *BRCA1/2* variant status, and suggested MSAC consider clarifying that both HRD status and *BRCA1/2* variant status are to be determined in the item descriptor.

The ESCs noted the ADAR indicated the proposed MBS item should replace existing MBS items 73295 and 73301, which provide for testing of *BRCA* germline variants in germline and tumour tissue samples respectively for access to PBS-funded PARP inhibitor treatment. ESC noted that the MSAC Executive had in April 2022 supported expanding these items to replace 'olaparib' with 'PARP inhibitor', and this was implemented in September 2022. The ESCs considered that the proposed item should not replace 73295 because 73295 is for germline testing, and could not replace 73301 unless the proposed new item provides for access to all PARP inhibitors. The ESCs considered that if this application was supported by MSAC, a new MBS item may need to implemented for GI testing that is separate and additional to 73295 and 73301 rather than replacing them. The ESCs proposed clarifying in the item descriptor that this testing is separate to that provided under items 73295 and 73301.

The ESCs noted that the proposed frequency restriction of once per primary tumour diagnosis would not be enforceable through the Medicare payment system, and would instead be monitored by compliance post-implementation. ESC considered the proposed service would not normally need hospital treatment or accommodation.

The ESCs noted that the proposed MBS item descriptor used germline variant terminology in referring to "carriers of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant", which it considered implies only germline variants are being tested for. The ESCs considered that because the proposed testing also includes somatic variants it may be more appropriate for the item descriptor to be reworded to clarify that somatic variants are also included.

ESC's suggested revisions to the proposed MBS item descriptor are below.

Table 22   ESC's suggested revisions to the proposed MBS item descriptor

Category 6 – Pathology services
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 determine eligibility with respect to homologous recombination deficiency (HRD) status, *including BRCA1/2* status, for access to niraparib under the Pharmaceutical Benefits Scheme (PBS).   Evidence of homologous recombination deficiency for patients that ~~are not carriers of~~ do not have a relevant *BRCA*1 or *BRCA*2 ~~pathogenic or likely pathogenic~~ variant, must be derived through a validated test of tumour tissue to determine a genomic instability score.   Applicable once per primary tumour diagnosis. Not applicable to a service to which 73295 or 73301 applies.   Fee: $3000   Benefit: 75% = $2,250.00   85% = $2,906.80

ESC's additions are shown in underlined green text, and deletions in strikethrough text.
85% benefit reflects the 1 November 2022 Greatest Permissible Gap (GPG) of $93.20. All out-of-hospital Medicare services that have an MBS fee of $621.50 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).
Source: ESC

The ESCs noted the proposed MBS fee for HRD testing was $3,000, which was higher than the $2,500 proposed for HRD testing in application 1658. ESC recalled that MSAC had previously advised a fee of $2,500 seemed excessive for the costs of conducting the assay and the bioinformatics, however that consultation input suggested the Illumina TS500 NGS panel test without the HRD component is around this cost, therefore the add-on to assess GI will cost at least another $1,000. The ESCs noted the Greatest Permissible Gap (GPG) limits out-of-pocket (OOP) costs, this would not cover amounts greater than the MBS fee that providers may charge.

ESC noted NPAAC had also raised concerns around there being no 'gold standard' for HRD testing, and that the concordance of commercially available and in house in vitro devices (IVDs) against the evidentiary standard and each other is unclear. NPAAC advised HRD assays would need to be validated using the NPAAC in house IVD standard, and the data reviewed by the TGA and the National Association of Testing Authorities (NATA). NPAAC noted there is no external quality assurance (EQA) program, so a sample exchange program would need to be developed for this. The ESCs noted that the Department had sought advice from the TGA in January 2023 the TS500 HRD assay is a research use only device. ESC requested the Department seek advice from the TGA about the regulatory status of the test to inform MSAC's consideration.

On comparative safety, the ESCs noted some adverse events had been reported from collection of a tumour sample, though an additional sample would not usually be required for the patient to receive HRD testing. However the ESCs raised concerns with the high rate of test failure (15% in the PRIMA trial), and queried whether there was an increased risk of adverse events given the high test failure rate. The ESCs considered the main safety concerns were around the clinical consequences of misclassification, especially for false positive or negative results, and noted that a false positive result would get the same chance of quite significant adverse events as in the PRIMA trial but perhaps for less clinical benefit.

The ESCs noted that the submission did not provide a risk of bias assessments for the concordance studies for cross-sectional accuracy and performance of the tests nor the QUADAS-2 risk of bias tool, and the commentary considered the risk of bias for Weichert 2021a and 2022 was high. ESC noted the concordance evidence was primarily based on conference abstracts, so may be of lower quality – however, it did suggest concordance across all HRD assays. ESC noted the prevalence of HRD was a little higher for other tests (such as the Illumina RUO TSO 500) than for the Myriad MyChoice® HRD test.

The ESCs considered that it was uncertain whether the evidence demonstrated a codependency exists between HRD status and niraparib treatment benefit (i.e., treatment effect variation), and

it is therefore unclear whether HRD testing was clinically justified. The ESCs noted the hazard ratio (HR) for progression-free survival (PFS) from the PRIMA trial for HRD+ patients (Myriad MyChoice® test GI ≥42) was 0.50 (95% CI: 0.31, 0.83), but also 0.68 (0.40, 0.94) for HRD- patients. A test for interaction was not reported. The ESCs noted the evidence for treatment effect variation included a high proportion of patients with unknown HRD status (15.1% of the total PRIMA population), and that the analysis of the HRD+ and *BRCA* wildtype (*BRCA*wt) patient subgroup was considered exploratory and not pre-specified in the formal statistical analysis plan. The ESCs considered that the risk of bias may be high in the evidence for a predictive effect. The ESCs considered the point estimates indicate there may be more effect in HRD+ than HRD- patients, though there was also some statistical evidence of benefit from treatment in the HRD- subgroup. The ESCs noted that the point estimate for patients with unknown HRD status appeared worse. The ESCs considered this result could not be reliably interpreted as it was based on small patient numbers.

The ESCs considered the clinical trials showed some consistency in terms of direction of the hazard ratios for the effects of various PARP inhibitors on PFS across the HRD+ versus HRD- groups, suggesting there may be treatment effect variation, however ESC considered that this clinical trial evidence had a high risk of bias. The ESCs considered the exclusion of PRIME from the primary evidence was reasonable.

However, the ESCs also considered that some evidence did support the existence of treatment effect modification: the PRIMA analysis (May 2019) showed median PFS was smaller for HRD- or HRD not determined (HRDnd) patients, than for *BRCA*wt and HRD+ patients. Though the ad hoc analysis in November 2021 showed almost no evidence for effect modification on PFS, with analysis of *BRCA*wt patients showing HRs of 0.66 for HRD+ patients versus 0.65 for HRD- patients. The ESCs also noted that although there was no statistical evidence of a benefit on overall survival (OS), the PRIMA trial point estimates did show an effect of niraparib with HR = 0.70 (0.44, 1.11)[8] but considered that the results were immature. ESC considered that an effect on PFS may not translate well to OS.

ESC considered the test component of this application in comparison to that in MSAC application 1658 and 1685.1, and noted that the differences are primarily in how the HRD positivity is defined, with the Illumina and Myriad tests using three features (LOH, TAI and LSTs), whereas the SOPHiA assay proposed in 1658 determines GI based mainly on LOH though including some deletions and insertions. ESC also noted differences in eligibility criteria between the two trials.

The ESCs noted that the comparator had used a fee of $1,000 for *BRCA* testing in line with MSAC's previous advice, however this testing was still listed on the MBS at a fee of $1,200. The ESCs noted the economic model included being parallel to existing testing in the base case, and scenarios were proposed for sequential testing (after a negative *BRCA1/2* result) at diagnosis, parallel testing post-platinum-based chemotherapy (PBC) initiation, and sequential testing post-PBC initiation. ESC recalled MSAC had previously accepted an approach in line with the base case, and that single tests were preferable as they avoided the complex logistics of re-testing. ESC noted the modelling had not addressed whether the proposed scenarios would differ in terms of germline testing where a tumour test was not successful.

---

[8] Note that the OS results for the HRD positive *BRCA*wt subgroup from the May 2019 DCO are derived from a post-hoc analysis conducted by the applicant specifically for the purposes of informing the MSAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.

The ESCs had some concerns with the economic model in relation to the test. *BRCA*m and HRD not determined (HRDnd) patients were not included in the model yet, in the base case replacement scenario, these groups of patients would be receiving testing at a higher cost – so replacing *BRCA* testing with HRD testing has cost-effectiveness implications for the *BRCA*m subgroup that were not modelled. The ESCs were also concerned that the accuracy of HRD tests in establishing *BRCA*m status may be lower than that of dedicated *BRCA* testing. The model did not consider false positive rates separately for GIS and *BRCA* variant status, and implied *BRCA*m results were always true positive. The ESCs noted the base case was re-specified during the commentary to apply a *BRCA* test cost of $1,000 in line with MSAC's advice, update subsequent cancer treatment prices, remove an incorrect half cycle correction from the cost of niraparib (which had underestimated the cost of treatment). The ESCs considered that the respecified base case amended some issues, and noted this resulted in a 5% increase in the ICER. The ESCs reiterated that the justification to incur the cost of the HRD test is unclear if niraparib benefit is accepted for all HRD status groups. Furthermore, the economic model did not account for test failures. MSAC's previous advice (PSD for 1658) was that HRD testing generally requires more and higher quality tumour tissue. MSAC had advised that tumour tissue deteriorates over time, and this may increase the likelihood of inconclusive or failed tests compared with tumour *BRCA* testing only.

The ESCs noted the utilisation estimates included a substantially lower proportion of samples with viable tissue (67.5%-80%) than the 95% assumed in the olaparib July 2020 submission and in previous MSAC application 1554 in July 2020, and this had resulted in a lower estimated number of HRD tests in this assessment. The ESCs considered the number of MBS-funded services may have been underestimated. The ESCs noted the choice of testing scenario affected the service utilisation estimates and had implications for the financial cost to the MBS.

16.   Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17.   Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: <u>visit the MSAC website</u>