Australian Government

Department of Health

MSAC Application 1658:

Testing of tumour tissue to determine a positive homologous recombination deficiency status in patients newly diagnosed with advanced (FIGO Stage III-IV) high grade epithelial ovarian, fallopian tube or primary peritoneal cancer, for access to PBS olaparib

Second PASC consideration

Ratified
PICO Confirmation

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

PICO or PPICO rationale for therapeutic and investigative medical services only

Background

This PICO was initially considered by the PICO Advisory Subcommittee (PASC) in April 2021.

During this consideration, PASC expressed a preference to review the PICO Confirmation again after further consultation and before progressing the application as an integrated codependent submission or ADAR (applicant-developed assessment report). PASC considered that there were several outstanding issues for consultation including:

- The preferred definition of the eligible population, with consequences for the definition of the test interventions and the test comparators.
- The current and proposed clinical management algorithms. Specifically focusing on the role of bevacizumab and 'watch and wait'.
- The definition of several possible HRD testing methods that may become available as alternative options in Australia, but may be measuring different types of genomic aberrations. As such, these tests would seem unlikely to identify equivalent patients as being eligible or not for the proposed combination of medicines.
- The lack of full transparency regarding how HRD positivity is determined in the evidentiary standard test, including whether the nominated threshold HRD (GIS) score of 42 is performing as intended and what the consequences of this variation might be for predicting the size of the population eligible for the proposed combination of medicines and for predicting the variation in effectiveness of this combination.

Population

The patient population for whom public funding of the proposed medical service is intended includes patients with newly diagnosed advanced International Federation of Gynecology and Obstetrics (FIGO) Stage III-IV high grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

At its April 2021 meeting, PASC noted that the definition of the population for the proposed test is consistent with the population defined by the existing MBS listings to test patients with advanced, high-grade epithelial ovarian cancer to detect a somatic or germline *BRCA1/2* pathogenic variant to help determine eligibility for the existing PBS listing of olaparib monotherapy following response to first-line platinum-based chemotherapy.

The application proposed that first-line maintenance treatment with olaparib (to be used in combination with bevacizumab) on the PBS, be based on a positive homologous recombination deficiency (HRD) status in patients with no *BRCA1/2* pathogenic variant.

At its April 2021 meeting, PASC considered that, for this proposed population, the clinical assessment would need to address whether to rely on the intention-to-treat results of the pivotal PAOLA-1 trial or the results of any other relevant subgroup analysis of this trial for the estimates of

comparative effectiveness of the proposed maintenance with olaparib plus bevacizumab (see Table 2).

However, the applicant advised that HRD positive status would be defined as tumour *BRCA1/2* pathogenic variant positive and/or GIS positivity. See 'Rationale' for further discussion below. Briefly, the definition of 'HRD positive' suggested by the applicant (*BRCA1/2* pathogenic variant positive and/or GIS positivity) differs from the evidentiary standard in the key PAOLA-1 trial: having a pathogenic *BRCA1/2* variant OR an HRD (GIS) score ≥42 using the Myriad myChoice® HRD Plus assay (Myriad Genetic Laboratories); the applicant has indicated that this threshold is specific to this test. Moreover, the application advised that the Myriad myChoice® HRD Plus assay and a further commercial HRD approved test by Foundation Medicine® are available in Australia, however they are currently performed overseas and therefore ineligible for MBS funding.

The application advised that an HRD test (that includes a *BRCA1/2* and GIS test) was being developed by **REDACTED** *(the redacted text refers to an Australian pathology laboratory)*. The updated application (July 2021) further advised **REDACTED.** *(The redacted text refers to HRD test 2 which was proposed in the updated application. This second testing option is the Australian provision of a HRD assay which is similar to the HRD assay used in the pivotal PAOLA1 study (Myriad® myChoice HRD Plus assay). This test is not currently performed in Australia).* See further discussion under 'Intervention'.

Cancer Australia [2020] reported that:

- ovarian cancer was the tenth most commonly diagnosed type of cancer among females in Australia in 2015, with an estimated 1,532 new cases in 2020;
- the 5-year relative survival for ovarian cancer in Australia is low at 46% (2011-2015), which is primarily due to late-stage diagnosis; and
- ovarian cancer was the sixth leading cause of cancer related deaths for females in Australia in 2016 with 938 deaths. The report projected that it will remain the sixth most common cause of death from cancer among females in 2020 with an estimated 1,068 deaths.

The term 'ovarian cancer' is often used to include cancers in the fallopian tube/s and primary peritoneal cancer, as well ovarian cancer that encompasses a heterogeneous group of malignant tumours that may arise from germ cells, stromal tissue, or epithelial tissue within the ovary [Physician Data Query (PDQ) 2020]. The most common type of ovarian cancer is epithelial cancer, which is further classified into five main types: high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous carcinomas [PDQ 2020]. PDQ [2020] stated that approximately 80% of those with ovarian cancer have high-grade serous ovarian cancer (HGSOC), which the application noted is the most aggressive histological subtype. The application also stated that cancer of the fallopian tubes or primary peritoneal cancer frequently show similar serous features and is usually treated as for ovarian cancer.

The application stated that HGSOC is difficult to diagnose in its early stages as there are no effective tests for early detection, and symptoms tend to be vague and non-specific (e.g. bloating, fatigue and abdominal pain). Consequently, the majority of patients are diagnosed when their disease is advanced and widespread, with PDQ [2020] reporting 90% present with Stage III or IV disease.

Most patients diagnosed with ovarian cancer are treated with primary tumour debulking surgery (cytoreduction), followed by chemotherapy with the aim of eliminating detectable disease [Cancer Australia 2014]. Depending on the recommendations of the local multidisciplinary team, the patient may also receive neo-adjuvant chemotherapy prior to surgery. Primary cytoreduction aims to remove as much of the tumour as possible, to allow adjuvant treatment to be more effective.

Standard first-line treatment of advanced epithelial ovarian cancer is platinum-based chemotherapy [Cancer Australia 2014], however more than 70% of patients with advanced disease initially responding to first-line chemotherapy will relapse and require re-treatment within 3 years of diagnosis [Ledermann 2013].

Following surgery and first-line platinum-based chemotherapy; first-line maintenance therapy treatment options in newly diagnosed ovarian cancer include:

- 'watch and wait';

- bevacizumab (a vascular endothelial growth factor (VEGF) inhibitor). At the time of the April 2021 PASC consideration, bevacizumab was PBS listed for advanced FIGO Stage IIIB, IIIC or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer among patients:
  (i) who were suboptimally debulked (maximum diameter of any gross residual disease greater than 1 cm) only if the patient presented with Stage IIIB or Stage IIIC disease;
  (ii) who had a WHO performance status of 2 or less, and;
  (iii) whose condition must have been previously untreated.
  Bevacizumab would be started at the same time as platinum-based chemotherapy. PBS-subsidised doses of bevacizumab were not to exceed 7.5 mg/kg every three weeks and treatment must not have exceeded a lifetime total of 18 cycles. Treatment could only continue if the patient did not have progressive disease. The application stated that maintenance treatment with bevacizumab has become an established standard of care.

  As of 1 June 2021, bevacizumab is available on the PBS as an unrestricted benefit. From this date, Avastin® (the reference biological medicine) is no longer available and the biosimilar Mvasi® is the sole brand available on the PBS[1].

  The relevant Therapeutic Goods Administration (TGA)-approved indication for bevacizumab is:
  > MVASI (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

  Assuming that bevacizumab continues to only be used in the relevant TGA-approved indication, a greater proportion of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer now has access to treatment with bevacizumab as all patients with Stage IIIB and IIIC cancer are eligible for treatment (and not only those with suboptimally debulked disease) compared with its previous PBS restriction.

1 https://www1.health.gov.au/internet/main/publishing.nsf/Content/0CE13CDB4B59ACB0CA2580810077E68F/$File/Factsheet-biosimilar-bevacizumab-on-the-PBS.pdf

The TGA-approved dosage of bevacizumab for the treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer is:

15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of MVASI as single agent. It is recommended that MVASI treatment be continued for a total of 15 months therapy or until disease progression, whichever occurs earlier.

Assuming that bevacizumab is used according to the relevant TGA-approved dosage in this indication, the dose of bevacizumab per administration can be doubled and the total treatment duration can be extended compared with its previous PBS restriction.

Although not previously PBS listed for recurrent disease, bevacizumab is TGA-approved for both platinum-sensitive and platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Relevant dosages are as follows:

Platinum-sensitive

15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for 6 cycles (up to 8 cycles) followed by continued use of MVASI as a single agent until disease progression. Alternatively, 15 mg/kg of body weigh given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles (up to 10 cycles), followed by continued use of MVASI as single agent until disease progression.

Platinum-resistant

10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks. It is recommended that treatment be continued until disease progression.

- olaparib (a poly-adenosine 5' diphosphoribose polymerase (PARP) inhibitor) is PBS listed for high grade Stage III/IV epithelial ovarian, fallopian tube or primary peritoneal cancer in patients who:
  (i) have a class 4 or 5 *BRCA1* or *BRCA2* gene mutation (evidence of a *BRCA1* or *BRCA2* gene mutation must be derived through germline or somatic mutation testing); and
  (ii) are in partial or complete response to the immediately preceding platinum-based chemotherapy regimen prior to commencing treatment with this drug for this condition (a response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

  PBS-subsidised olaparib must be used as monotherapy (the sole PBS-subsidised therapy for this condition) and must not have previously received PBS-subsidised treatment with this drug for this condition. Treatment can only continue if the patient has not developed disease progression while receiving treatment with this drug for this condition and treatment must not exceed a total of 24 months of combined non-PBS-subsidised and PBS-subsidised treatment for patients who are in complete response.

Olaparib is also PBS listed as second-line treatment for use among patients who have high grade epithelial ovarian, fallopian tube or primary peritoneal cancer where:

- the condition must be associated with a class 4 or 5 *BRCA1* or *BRCA2* gene mutation (must be derived through germline or somatic mutation testing);
- the condition must be platinum sensitive (defined as disease progression greater than 6 months after completion of the penultimate platinum regimen);
- patient must have received at least two previous platinum-containing regimens;
- patient must have relapsed following a previous platinum-containing regimen;
- patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen (assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines); and
- the treatment must be maintenance therapy.

PBS-subsidised olaparib must be used as monotherapy (the sole PBS-subsidised therapy for this condition) and patients must not have previously received PBS-subsidised treatment with this drug for this condition (i.e. if patients were treated with olaparib in the first-line maintenance setting, they cannot be treated with olaparib in the second-line setting). Treatment can only continue if the patient has not developed disease progression while receiving treatment with this drug for this condition.

High-grade epithelial ovarian cancer, in addition to being a VEGF responsive tumour, has a high prevalence of homologous recombination deficiency (HRD). Approximately 50% of epithelial ovarian carcinomas are estimated to exhibit defective DNA repair by HRD [Konstantinopoulos 2015]. Germline *BRCA1* and *BRCA2* pathogenic variants are the most well-known HRD aetiology, others include somatic *BRCA1* or *BRCA2* pathogenic variants and germline and somatic pathogenic variants in other genes related to HRD [Bonadio 2018]. The application stated that *BRCA1/2* pathogenic variants "contribute to 29% of the HRD positive pathway" and non-*BRCA1/2* HRD variants "are thought to contribute 6% to 27% of genetic risk". The application cited no reference for the former estimate and cited Norquist [2016] and Walsh [2011] for the latter estimates. These estimates could not be independently verified. Should the integrated codependent submission or ADAR rely on these estimates, the source (or how they were derived) must also be clearly articulated. Prognosis is known to vary with *BRCA1/2* status, as *BRCA1/2* wild-type patients (i.e. those patients with no *BRCA1/2* pathogenic variants) have significantly worse progression-free and overall survival than patients with a pathogenic variant in *BRCA1/2* [Xu 2017]. However, the application identifies at least three populations relevant for estimating prognostic variation: (a) *BRCA1/2* positive (by definition HRD positive); (b) *BRCA1/2* negative and HRD positive (including GIS positive); and (c) *BRCA1/2* negative and HRD negative (including GIS negative).

The application cited Bindra [2004], Bindra [2005], Bindra [2007], Glazer [2013] and Kaplan [2019] as providing pre-clinical data suggesting a potential clinical synergistic benefit may be achieved when combining VEGF and PARP inhibitors, as there have been multiple observations around the impact of hypoxia on cell stress, including the DNA damage response and specifically inhibition of HRD. The application contended that this provides a strong rationale for targeted treatment with PARP inhibitors such as olaparib, in this patient population.

HRD testing is proposed as a means of determining which patients would be eligible for receiving the codependent drug, olaparib, in combination with bevacizumab as maintenance therapy after first-line treatment with platinum-based chemotherapy plus bevacizumab. The PAOLA-1 trial provides

supporting evidence in patients with FIGO Stage III-IV high grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Prespecified subgroup analyses from this trial suggest that an HRD positive status (defined using the Myriad myChoice® HRD Plus assay as having a pathogenic *BRCA1/2* variant OR an HRD (GIS) score ≥42) is a marker for improved efficacy with combination olaparib and bevacizumab compared with bevacizumab monotherapy.

The applicant has indicated that the following TGA indication was approved on 10 March 2021 (https://www.tga.gov.au/prescription-medicines-new-or-extended-uses-registered-medicines):

> Lynparza in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
> - a deleterious or suspected deleterious *BRCA1/2* pathogenic variant (germline or somatic), and/or
> - genomic instability.
>
> HRD status should be determined by an experienced laboratory using a validated test method.

Compared to the proposed TGA indication for this combination of olaparib and bevacizumab, the requested PBS-eligible population excludes patients with a deleterious or suspected deleterious *BRCA1/2* pathogenic variant (germline or somatic), because these patients are already eligible for PBS-subsidised olaparib maintenance as monotherapy. Thus, the requested PBS-eligible population for the combination is patients with "genomic instability" (defined in the trial as an HRD score ≥42) and <u>not</u> having a deleterious or suspected deleterious *BRCA1/2* pathogenic variant (germline or somatic).

Although an improvement in progression free survival (PFS) was observed when adding olaparib to maintenance therapy with bevacizumab in patients who are HRD positive, regardless of *BRCA1/2* pathogenic variant status, the applicant contended that the focus be on the subgroup of patients who are HRD (GIS) positive and negative for a *BRCA1/2* pathogenic variant. The applicant stated that olaparib monotherapy is PBS listed for patients with advanced ovarian cancer with *BRCA1/2* pathogenic variant positive tumours, supported by the SOLO-1 trial [Moore 2018] results which demonstrated improvements in PFS at 4 years. The updated 5-year PFS data demonstrated the continued benefit of olaparib monotherapy at 5 years despite treatment being stopped at 2 years. Based on these results, the applicant contended that the majority of *BRCA1/2* pathogenic variant positive patients will be treated with olaparib monotherapy rather than olaparib + bevacizumab. The applicant also suggested that clinicians were unlikely to prescribe the combination therapy and subject patients to the risk of developing adverse events from the addition of bevacizumab. An outstanding question that needs to be addressed in the integrated codependent submission or ADAR is: on what grounds can there be confidence that prescribers would not contemplate prescribing the combination of olaparib and bevacizumab to those patients with a deleterious or suspected deleterious *BRCA1/2* pathogenic variant?

At its April 2021 meeting, PASC discussed the possibility of adding ovarian cancer patients with BRCA1/2 pathogenic variants (who are by definition HRD positive) to the proposed population of HRD positive but BRCA1/2 negative patients, so both subgroups would be eligible for the combined maintenance treatment with olaparib + bevacizumab after a response to the first-line platinum-

based chemotherapy; clinical benefits for both subgroups were demonstrated in the pivotal PAOLA-1 trial.

Although the applicant is seeking combination therapy with olaparib and bevacizumab in the subgroup of only those who are negative for BRCA1/2 pathogenic or likely pathogenic variants but still positive for HRD via GIS, PASC similarly considered at its August 2021 meeting the population eligible for combination therapy with olaparib and bevacizumab could include those who were positive for BRCA1/2 pathogenic or likely pathogenic variants (who are by definition HRD positive). Use of combination olaparib and bevacizumab in this population is consistent with the TGA indication for olaparib, with the intervention regimen in PAOLA-1 and with evolving international practice. PASC also noted that there is evidence from the PAOLA-1 trial of the improved efficacy with combination olaparib and bevacizumab compared with bevacizumab monotherapy for this population. PASC noted that this has consequences for the comparator for the treatment, which would need to be considered by the PBAC.

Alternatively, PASC also discussed the option of differentiating the population for the proposed test from the population already eligible for the existing listings for somatic or germline BRCA1/2 testing by making the inclusion of bevacizumab as part of the initial first-line platinum-based chemotherapy regimen a prerequisite for the population eligible for the proposed test (see Figure 6 in Attachment 1). This is consistent with the TGA-approved use of bevacizumab in these types of cancer, which requires that bevacizumab be commenced in combination with platinum-based chemotherapy and the two randomised trials which formed the evidentiary basis for the previous PBS restriction (ICON-7 and G-0218, November 2013 PBAC Public Summary Document). *PASC also considered that this would be consistent with the PAOLA-1 protoco*l. This trial required that all participants receive bevacizumab as part of the initial platinum-based chemotherapy regimen for a minimum of six cycles of three weeks. Depending on their response to this initial therapy, they were then randomised to whether or not to add olaparib to ongoing bevacizumab in the maintenance phase of management. *PASC further considered that this might also better achieve the intent of the applicant in subsequently differentiating which patients should receive olaparib maintenance as monotherapy, and which should receive olaparib maintenance in combination with bevacizumab. However, PASC considered that wider consultation is needed on the appropriateness and feasibility of this option in clinical practice*. This is because the other main consequence of this option, if adopted, would be that HRD testing would have to occur after starting this initial regimen with the results of the test used to help decide whether olaparib should be added to bevacizumab in the maintenance setting. *PASC advised that MSAC should consider this consultation feedback when further considering this option.*

There is also a possibility that, once tested, those who are found to be *BRCA1/2* pathogenic variant positive may cease bevacizumab therapy as they would be eligible for olaparib monotherapy as maintenance treatment (see Figure 6 in Attachment 1).

Consultation feedback from Queensland Genomics and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) in response to targeted consultation after the April 2021 PASC meeting, considered that GIS tumour testing should occur at the same time as *BRCA1/2* testing. Queensland Genomics advised that this was to limit the need to use and access tissue, however, it is only needed after chemotherapy.

During this further consultation, the applicant indicated that HRD testing may change the utilisation of bevacizumab. The applicant considered that bevacizumab may not be considered a part of the 'standard of care' for patients with R0 (no visible residual disease post-surgery), Stage III HGSOC. The reasons for this included the previous PBS listing for bevacizumab being for patients with suboptimally debulked Stage IIIB or IIIC disease and the key trials for bevacizumab (ICON-7 and GOG-0218) not demonstrating a strong clinical benefit for bevacizumab in Stage III disease. However, the PAOLA-1 trial demonstrated a benefit for the subgroup of patients with Stage III disease. Therefore, although use of bevacizumab was never dependent on *BRCA1/2* status, the new test will identify those who are HRD (GIS) positive and *BRCA1/2* pathogenic variant negative, and those patients may now initiate bevacizumab (who otherwise may have not) with the intent to add olaparib in the maintenance phase. The new unrestricted PBS listing of bevacizumab would support such use. For this reason, the applicant did not support delaying HRD testing until bevacizumab is started.

At its August 2021 meeting, PASC considered there were three populations that could be considered for HRD testing. Each population would have implications for:

(i) the number of eligible patients;

(ii) the nature of the test (whether HRD testing for BRCA1/*2 pathogenic or likely pathogenic variant and GIS occurred in parallel or sequentially); and*

(iii) the relevant test and treatment comparators.

- *Population 1: Patients with newly diagnosed, advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. This population would have HRD testing for* BRCA1/2 *variant and GIS in parallel. This also constitutes the population that is currently eligible for* BRCA1/2 *testing on the MBS (with those positive for* BRCA1/2 *variants being eligible for olaparib monotherapy on the PBS).*
- *Population 2: Patients with newly diagnosed, advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who have been established to not be carriers of* BRCA1/2 *pathogenic or likely pathogenic variants. Testing for GIS would occur sequentially following a negative* BRCA1/2 *test result*.
- *Population 3 (see Attachment 1): Patients with newly diagnosed, advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who have received bevacizumab as part of initial first-line platinum-based chemotherapy regimen. This population is consistent with those enrolled in PAOLA-1.* BRCA1/2 *variant and GIS could be conducted in parallel or sequentially (following a negative* BRCA1/2 *test result).*

PASC advised that its deliberations concerning the three populations would be outlined in the PICO Confirmation and remain publicly available for transparency and to allow MSAC and PBAC awareness of the alternative decision options. PASC advised that the base case population should be as proposed by the applicant(i.e. Population 1), such that the proposed test would replace the current BRCA1/2 *test for all eligible patients regardless of subsequent therapy and thus also increasing the cost of testing for those receiving olaparib monotherapy maintenance as well as those who do not receive maintenance at all. PASC considered that this requested population would result in the most expensive option per patient treated with olaparib plus bevacizumab maintenance, as well as increasing the current cost per patient treated with olaparib monotherapy maintenance. These costs are essential to estimating the incremental cost-effectiveness of the overall application.*

PASC advised that the PICO Confirmation should outline all available options with respect to the test populations, treatment, the order and timing of the BRCA1/2 *and GIS components of the HRD test, and the corresponding test and treatment comparators. PASC advised that the applicant would need to justify its choices with respect to each of these components in its integrated codependent submission or ADAR. However, in relation to parallel or sequential order of the test, PASC advised that both options should be modelled rather than assuming that parallel* BRCA1/2 *and GIS testing will necessarily replace the* BRCA1/2 *test. This is because the sequential testing would have lower cost implications and identify the same population eligible for treatment with olaparib and bevacizumab. PASC noted that the applicant predicts delayed testing with the sequential approach, particularly for Population 3, and may not provide access to olaparib for all patients who may benefit. In this regard, PASC noted the expected turnaround time for the test is less than the time taken to determine a response to initial first-line platinum-based chemotherapy regimen.*

PASC considered there were advantages to testing for BRCA1/2 *variant and GIS in a sequential manner: (i) fewer patients would need GIS testing, which would be associated with reduced costs; (ii) GIS testing would require a separate MBS item and this may be useful as the implications of tumour HRD positivity is evolving and (iii) there may be a range of alternative HRD tests developed independently by Australian laboratories other than* ***REDACTED****.*

Based on the Australian Institute of Health and Welfare (AIHW) projections, it is estimated that there will be approximately 1,764 new cases of ovarian cancer in 2023, however only 1,482 are epithelial tumours (as depicted in line 2 of Table 1 below, adjusted by 84% to reflect epithelial tumours only as per AIHW 2010). AIHW does not report the incidence of ovarian cancer by stage of disease; Stage III and IV are most relevant to this application. To estimate the proportion of patients diagnosed at advanced stage, data from the Australian Ovarian Cancer Study [AOCS; Alsop 2012] was used. The application stated that, based on Alsop [2012], approximately 70% (67.8%) of these patients are diagnosed with FIGO Stage III or IV disease (as depicted in line 3 of Table 1 below).

It is assumed that 95% of eligible patients are able to provide a quality tumour sample for testing (line 4: Table 1) and therefore take up HRD testing.

In total, the application expected that approximately 986 patients will utilise tumour HRD testing to determine their *BRCA1/2* and genomic instability status in the year 2023, as detailed in Table 1.

Table 1: Estimated utilisation of tumour HRD testing

	Description	Estimated number of patients in 2023
1	Incidence of ovarian cancer in Australia	1,764
2	Ovarian, primary peritoneal & fallopian tube cancer-epithelial Tumour only (84%)	1,482
3	Diagnosed with advanced ovarian cancer (70%)	1,038
4	Eligible patients for tumour testing (95%)	986
5	Patients taking up HRD testing	986

Source: Table 2, p33 of the application

At its April 2021 and August 2021 meetings, PASC advised that the applicant's estimate of the proposed test utilisation may be an underestimate. The available data on the current utilisation of MBS item 73301 (the current BRCA1/2 *tests which the applicant proposed would be completely*

replaced by the proposed test) of 465 services covers only a short period from August 2020 to July 2021, and at the present time, does not appear to be a reliable predictor of future utilisation.

Cancer Australia [2017] recommends that women newly diagnosed with invasive epithelial ovarian cancer, regardless of their age or family history, should be offered assessment of their genetic risk. Currently, a woman with invasive epithelial ovarian cancer is recommended to be offered genetic testing for a germline *BRCA1/2* pathogenic variant if she meets the following criteria:

- has high grade invasive non-mucinous ovarian cancer, diagnosed at any age;
- has invasive non-mucinous ovarian cancer at any age, with a personal history of breast cancer, or a family history of breast or ovarian cancer;
- is from a population where a common founder mutation exists, such as the Ashkenazi Jewish population;
- is assessed as >10% chance of having a *BRCA1/2* mutation, using a prediction tool (such as BOADICEA, BRCAPRO or Manchester score); eviQ [2020] suggests the CanRisk or Manchester score; or
- has relapsed platinum-sensitive ovarian cancer, is a candidate for treatment with PARP inhibitors and meets MBS criteria.

At its April 2021 meeting, PASC noted the advice of the applicant's expert from **REDACTED** that testing HRD status would not identify whether any patient could have a germline pathogenic variant in any gene which is prognostic for ovarian cancer beyond *BRCA1/2* status. As such, PASC advised that there appeared to be no need to anticipate any additional subsequent germline or cascade testing, and so an additional population of family members did not need to be included. PASC advised that if testing GIS were to be performed concurrently with testing *BRCA1/2* status, subsequent germline and cascade testing for *BRCA1/2* would continue as per current practice.

Additional consultation feedback from Queensland Genomics and Australian Genomics, not considered by PASC in April 2021 due to its late receipt, highlighted that HRD can also occur due to germline non-*BRCA1/2* HRD genes that increase the risk of ovarian cancer. Queensland Genomics considered that pathogenic variants of non-*BRCA1/2* HRD genes would be considered clinically actionable from a familial genetics perspective. Australian Genomics also suggested that the population with germline HRD testing may already be tested as most *BRCA1/2* testing would occur as a part of a gene panel.

*At its August 2021 meeting, PASC noted consultation feedback from several organisations that pathogenic variants of non-*BRCA1/2 *HRD genes would be considered clinically actionable from a familial genetics perspective. Depending on the types of HRD tests that are developed by Australian laboratories, the possibility for cascade genomic testing based on non-*BRCA1/2 *HRD genes cannot be ruled out (although cascade testing for genes other than* BRCA1/2 *is acknowledged to not be relevant to the HRD test being developed by* **REDACTED***, because, like the clinical utility standard test, this is described as only producing an aggregated GIS test result). PASC also noted a potential requirement for amendment of MBS items (73302 + 73297) for cascade testing or for a new MBS item.*

Rationale

The population for testing is patients with FIGO Stage III-IV high grade epithelial ovarian, fallopian tube or primary peritoneal cancer as described above.

PAOLA-1/ENGOT-ov25 [Ray-Coquard 2019] was a phase III trial to investigate the efficacy and safety of a PARP inhibitor with bevacizumab as first-line maintenance therapy in patients with newly diagnosed advanced (FIGO Stage III or IV), high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (i.e. with and without a *BRCA1/2* pathogenic variant). Patients with other non-mucinous epithelial ovarian cancers were eligible, provided they had a deleterious germline *BRCA1* or *BRCA2* pathogenic variant.

The trial enrolled 806 patients with partial or complete response to standard platinum-based chemotherapy and bevacizumab. After completing first-line chemotherapy, patients were randomly allocated 2:1 to olaparib or placebo, both in combination with bevacizumab. Patients received olaparib (300 mg twice daily) for up to 24 months and bevacizumab (15 mg/kg every 3 weeks) for 15 months in total. The primary outcome was investigator-assessed progression-free survival (PFS; time from randomisation until investigator-assessed disease progression or death).

The median follow-up was 24 months in the olaparib arm and 22.7 months in the placebo arm. As shown in Figure 1 and Table 2, median PFS was 22.1 months in the olaparib plus bevacizumab group and 16.6 months in the bevacizumab plus placebo group (hazard ratio 0.59; 95% confidence interval [CI]: 0.49, 0.72; p<0.0001).

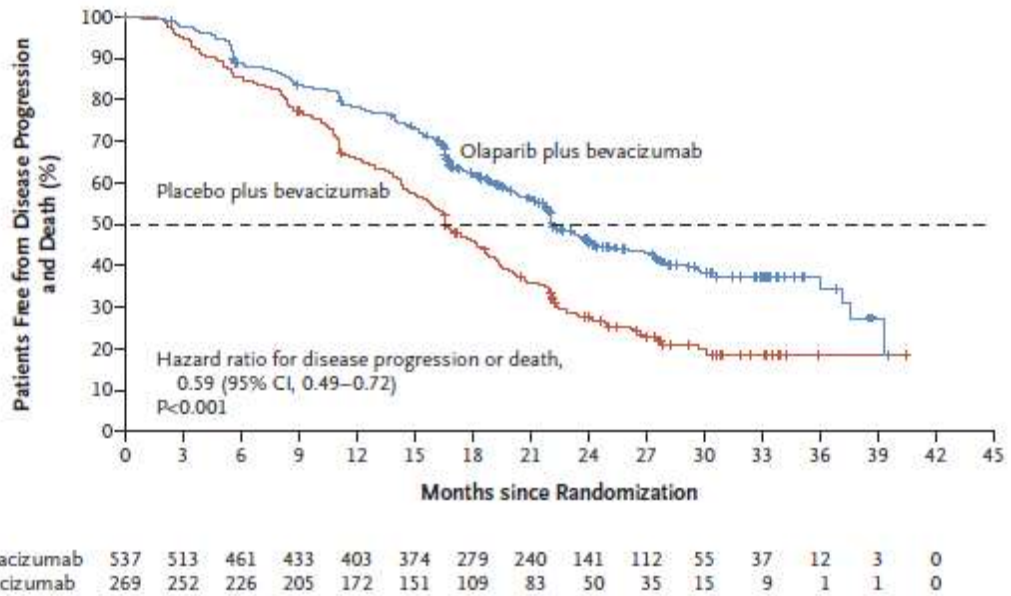

Figure 1: Kaplan–Meier estimates of investigator-assessed progression-free survival in the PAOLA-1 trial

Source: Figure 1, p2421 PAOLA-1 [Ray-Coquard 2019]

Tumour HRD status was retrospectively determined [p10 Ray-Coquard 2019 Supplemental Appendix] with the use of the Myriad myChoice® HRD Plus assay (Myriad Genetic Laboratories) in the PAOLA-1 trial. HRD positive was defined as a tumour *BRCA1/2* mutation or an HRD (GIS) score of 42 or higher. HRD negative was defined as an HRD (GIS) score of less than 42. "Unknown" was

defined as an inconclusive, missing, or failed test [footnote to Table 1, p2419 Ray-Coquard 2019].The trial did not report the rationale for use of a score of 42 as the threshold, however it appears to have been based on Telli [2016], as indicated by the application, see 'Intervention'.

Compared to less favourable intention-to-treat results, prespecified subgroup analyses (Figure 2 and Table 2), indicated the PFS benefit (hazard ratios [95% CIs]) for those treated with olaparib + bevacizumab versus bevacizumab alone appeared more pronounced in patients (i) with a *BRCA1/2* pathogenic variant (0.31 [0.20, 0.47]); (ii) who were HRD positive (including those with *BRCA1/2* pathogenic variants) (0.33 [0.25, 0.45]); and (iii) those who were HRD positive (with no *BRCA1/2* pathogenic variants) (0.43 [0.28, 0.66]). Median PFS with olaparib + bevacizumab reached 37.2 months in patients who were HRD positive (including a *BRCA1/2* pathogenic variant) compared to 17.7 months in patients treated with bevacizumab alone, see Table 2 [Ray-Coquard 2019]. For patients who were HRD positive without a *BRCA1/2* pathogenic variant, median PFS was 28.1 for olaparib and bevacizumab versus 16.6 months for bevacizumab alone, see Table 2 [Ray-Coquard 2019].

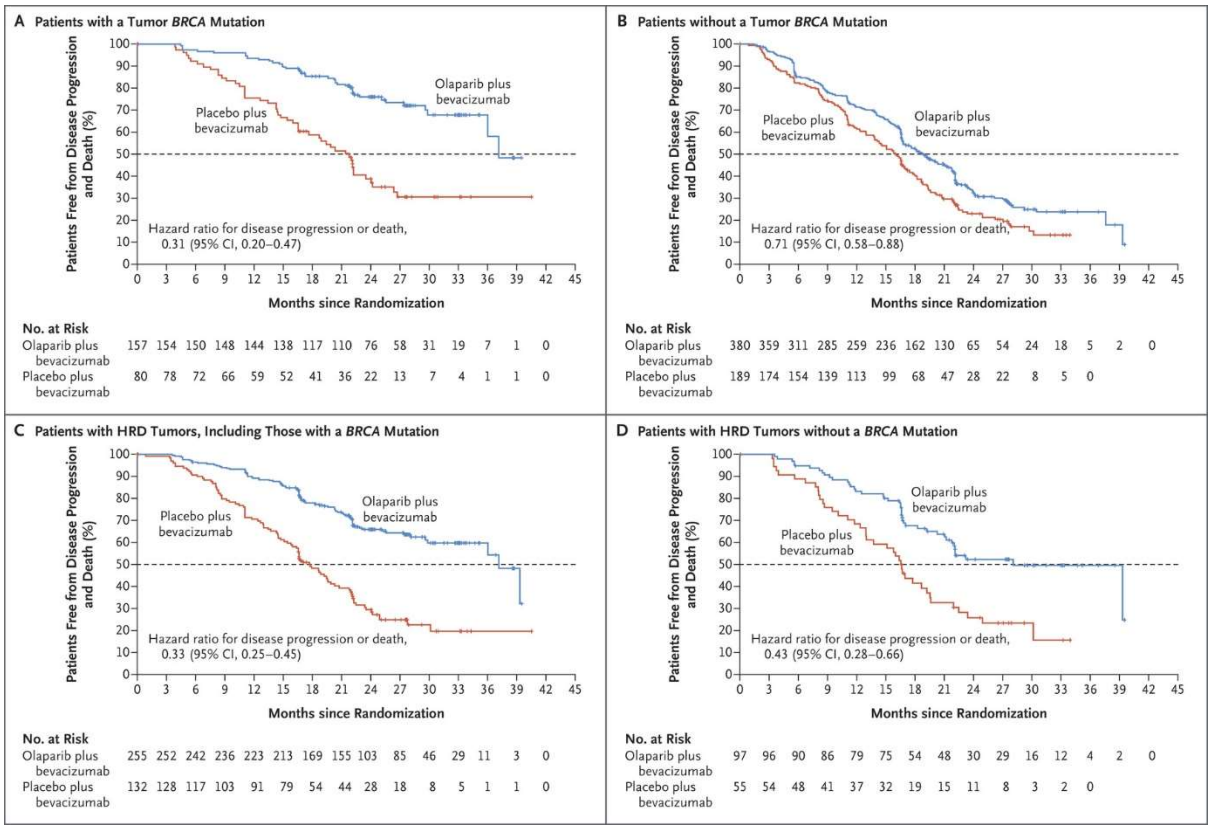

Figure 2: Kaplan–Meier estimates of investigator-assessed progression-free survival, according to tumour BRCA1/2 pathogenic variant status and homologous-recombination deficiency (HRD) status in the PAOLA-1 trial

Source: Figure 3, pp2424-2425 PAOLA-1 [Ray-Coquard 2019]

Table 2: Results for progression free survival (PFS; composite of disease progression and death) in the PAOLA-1 trial

	Ola + Bev (months) [patients]	Bev + PBO (months) [patients]	HR (95% CI)
All - Investigator assessed	22.1 [537]	16.6 [269]	**0.59 (0.49, 0.72)**
All - Blinded independent review	26.1 [537]	18.3 [269]	**0.63 (0.51, 0.77)**
BRCA1/2 pathogenic variant	37.2 [157]	21.7 [80]	**0.31 (0.20, 0.47)**
No *BRCA1/2* pathogenic variant or unknown	18.9 [380]	16.0 [189]	**0.71 (0.58, 0.88)**
HRD +ve including *BRCA1/2* pathogenic variant	37.2 [255]	17.7 [132]	**0.33 (0.25, 0.45)**
HRD +ve, no *BRCA1/2* pathogenic variant	28.1 [97]	16.6 [55]	**0.43 (0.28, 0.66)**
HRD -ve or unknown	16.9 [282]	16.0 [137]	0.92 (0.72, 1.17)
HRD -ve	16.6 [192]	16.2 [85]	1.00 (0.75, 1.35)
HRD unknown	NR [90]	NR [52]	0.71 (0.46, 1.10]
All – time to next treatment	24.8	18.5	**0.59 (0.49, 0.71)**

Source: p2421; Figure 2, p2422; Figure 3, pp2424-2425 PAOLA-1 [Ray-Coquard 2019]
-ve = negative; +ve = positive; Bev = bevacizumab; CI = confidence interval; HR = hazard ratio; Ola = olaparib; PBO = placebo
Bold text indicates statistically significant differences between treatment groups

At its April 2021 meeting, PASC noted little difference in PFS between the ITT population in the PAOLA-1 trial and HRD subgroups (either positive or negative) in the placebo arm of the trial; this observation suggested that HRD status may not have an impact on prognosis. Alternatively, this could indicate that the treatment effect from bevacizumab is similar regardless of HRD status. PASC advised the comparative prognostic value (clinical validity) of the HRD test across all three populations ((1) *BRCA1/2* pathogenic variant and HRD positive; (2) *BRCA1/2* pathogenic variant negative and HRD positive, and (3) *BRCA1/2* pathogenic variant and HRD negative) needs further investigation and assessment.

The application stated that these results support adding olaparib to maintenance therapy with bevacizumab in patients who are HRD positive patients, regardless of *BRCA1/2* pathogenic variant status, as this improves PFS for advanced ovarian cancer. This appears to be supported by the Ray-Coquard [2019] publication, albeit noting that those who were HRD positive (including *BRCA1/2* pathogenic variants) appeared to have a greater PFS than those who were HRD positive without *BRCA1/2* pathogenic variants upon visual inspection of the PFS curves, and also noting that no statistical tests were provided assessing the claimed interaction between the subgroup populations and the treatment effect of bevacizumab/olaparib in combination compared with bevacizumab alone.

Intervention

Test

The medical service for this MSAC application is testing of tumour tissue to determine a positive HRD status, which includes assessment of *BRCA1/2* pathogenic variant status and GIS in patients newly diagnosed with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. *At its August 2021 meeting, PASC confirmed that the proposed test is for tumour testing of for the detection of homologous recombination deficiency (HRD) status based on* BRCA1/2

variant status and/or GIS. The test will be referred to as the HRD test or *BRCA1/2* and GIS test herein.

At its April 2021 meeting, PASC noted that although there are Australian laboratories that offer *BRCA1/2* pathogenic variant tests on a commercial basis, no HRD (*BRCA1/2* and GIS) test is currently approved by the TGA. *This remained unchanged at PASC's August 2021 meeting.*

Although the application described *BRCA1/2*and GIS testing as two assays performed sequentially to determine *BRCA1/2* status and then GIS using next generation sequencing (NGS) technology, the applicant has since advised that *BRCA1/2* and GIS testing will be conducted in parallel. The applicant advised that twice the amount of tissue would be required to perform the test sequentially.

At its April 2021 meeting, PASC discussed whether the test, as proposed, should be conducted in a staged manner (initially for *BRCA1/2* pathogenic variants and if negative, then for GIS positivity) and, if so, whether a separate MBS item for the latter may be appropriate. This would avoid increasing the cost of testing for the current purpose of determining eligibility for olaparib monotherapy. The applicant's expert acknowledged that staged process is possible but expressed a preference for a single combined HRD assay with identification of *BRCA1/2* pathogenic variants incorporated, because this is associated with a shorter turnaround and other benefits such as requiring less tumour sample. In this regard, PASC considered that the staged testing option could initially result in turnaround delays as samples may need to be sent to a different laboratory for GIS testing as only one pathology provider is currently developing an HRD (*BRCA1/2* and GIS) test. The application also noted that it is expected that if MBS listing of HRD testing proceeds, more laboratories will have capability and accreditation to test for HRD.

PASC considered that if use of bevacizumab as part of the initial platinum-based treatment regimen was made a prerequisite to the proposed composite BRCA1/2 and GIS test, then there would be no need for a two-staged test because there would be no need to detect BRCA1/2 pathogenic variants alone for these patients. This is because these patients would not be suitable for olaparib maintenance as monotherapy (the existing olaparib listing) if managed according to the supporting SOLO-1 trial protocol (which did not include bevacizumab as a treatment option).

The updated application (July 2021) stated that "[t]he application proposes that HRD testing occurs upfront at the time of diagnosis, to ensure that optimal treatment options are provided to the clinicians and patients, maximising improved patient outcomes."

The updated application also stated, in response to use of bevacizumab as a prerequisite for testing, that "… this will reduce the number of patients being tested for HRD however this approach will delay initiation of PARPi maintenance treatment resulting in patients missing the opportunity to maximise patient outcomes demonstrated in the PAOLA-1 study. Given the HRD test will include testing for *BRCA* status, this testing sequence would represent a backward shift in current testing practice and a delay in receipt of this prognostic detail. HRD testing includes two components, *BRCA* mutation status and genomic instability which occur in parallel enabling conservation of tumour tissue, promote testing efficiency and enable timely turnaround time of results. Notwithstanding, first-line treatment with chemotherapy is also known to adversely affect tumour tissue integrity and DNA quality potentially resulting in compromised HRD analysis." *The turnaround time for the test is*

expected to be shorter than the minimum of three 21-day chemotherapy cycle before an assessment of response is made.

At its August 2021 meeting, PASC noted that the applicant did not propose sequential testing as an option and favoured parallel testing of the two components of the HRD test. PASC also noted its arguments favouring parallel testing include the potential shortage of sample tissue, longer turnaround time and thus delay in initiation of olaparib maintenance treatment. PASC further noted that the consultation feedback favoured parallel testing. However, PASC considered that the delay in initiating olaparib maintenance treatment was unlikely because the GIS component can be requested at the start of initial platinum-based chemotherapy regimen when the decision to include bevacizumab in the initial chemotherapy is made. Additionally, the turnaround time for the test is expected to be shorter than the minimum of three 21-day chemotherapy cycles before an assessment of response is made.

The manner in which the tissue sample is obtained and preserved was discussed with the applicant between the two PASC meetings. The Ray-Coquard 2019 Supplemental Appendix states that "Archival tumor samples were sent to one of five central French academic laboratories selected by the Institut National du Cancer (INCA) for assessment of tissue *BRCA* mutation status before patients entered the trial. The results of tumor *BRCA* testing were sent to the study site principal investigator for stratification of patients. Tumor *BRCA* testing used two different next-generation sequencing methods based either on capture or on re-sequencing technology. Retrospective central tumor *BRCA* testing, using the myChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc), was conducted on tumor samples to determine Myriad tumor HRD status."

It is requested that the applicant provide any further details of the nature of samples used in the PAOLA-1 trial. Of particular interest is whether the tumour samples were derived from (1) biopsies or (2) resected tissue from cytoreductive surgery and whether they were archival (1) frozen or (2) fixed.

At its April 2021 meeting, PASC questioned whether there would be a delay in the test being available in multiple laboratories after the item was approved, noting that this would be particularly relevant if the proposed HRD (*BRCA1/2* and GIS) test completely replaced current *BRCA1/2* testing. The applicant's expert indicated that this was unlikely as laboratories were able to quickly adapt to such changes. The application also anticipated that commercial kits would enter the market over the next 1-2 years.

The HRD (*BRCA1/2* and GIS) test is only to be provided once per tumour diagnosis (according to the proposed item descriptor).

PASC advised that the proposed test should be offered once per lifetime, either at the time of tumour diagnosis, or after the initial treatment regimen is shown to include bevacizumab, depending on which option is adopted.

No other medical services or healthcare resources need to be delivered at the same time as HRD (*BRCA1/2* and GIS) testing.

The application described the three main strategies for HRD status:

1. germline variant screening of genes related to homologous recombination (HR) repair (includes *BRCA1/2*);
2. somatic variant screening of genes related to HR repair (includes *BRCA1/2*); and
3. evaluation of a "genomic scar", which represents the genomic instability secondary to HRD. An HRD score to assess this instability can be calculated based on the loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transitions (LST).

The applicant advised that HRD positive status would be defined as:

- tumour *BRCA1/2* pathogenic variant positive. The application noted that "… all [patients] with a *BRCA* pathogenic gene variant are HRD positive or deficient however, a *BRCA* pathogenic gene variant is not the only cause of HRD". The *BRCA1* and *BRCA2* genes are integral members of the homologous recombination (HR) pathway, and are required for functional HR [Abkevich 2012].

  or

- genomic instability status (GIS) positivity. The applicant did not define nor propose a minimum (or threshold) score to define GIS positivity. The applicant noted that the TGA indication for olaparib + bevacizumab combination therapy has specified that HRD status be determined by a validated test without referencing a threshold. The applicant advised HRD thresholds are specific to a test and not proposed in the MBS descriptor or PBS restriction, to enable other validated and locally performed HRD assays (*BRCA1/2* + GIS) to be utilised and funded on the MBS. The applicant anticipated that a number of Australian laboratories will develop an HRD test. It is also expected that commercial kits such as **REDACTED** may enter the market in the next 1-2 years. These HRD tests will have a specific threshold to define HRD status.

The myChoice® HRD Technical Information document states that the test has two major components:

(1) GIS (positive = HRD based on genomic instability score alone; negative = HR proficiency based on genomic instability score alone); and
(2) tumour mutation *BRCA1/2* status (positive or negative for a clinically significant mutation, defined as the presence or absence, respectively, of a deleterious or suspected deleterious sequencing mutation or large rearrangement).

A more detailed description of the Myriad myChoice® test was provided in Southwest Oncology Group [SWOG; 2018], see Attachment 2. The applicant advised that the Myriad myChoice® test as described in SWOG [2018] was also used in Telli [2016] and subsequently, the PAOLA-1 trial. The applicant also confirmed that the methods and threshold for the myChoice® assay is proprietary to Myriad Genetics Inc.

Overall, the approach to determining the HRD score in the Telli [2016] study (discussed further below) and thus the PAOLA-1 trial is insufficiently clear. A fuller description of the methods used to derive HRD scores as this is necessary to more completely define the evidentiary standard test. Firstly, this is important in order to determine whether any of the three components involve the assessment of potential germline variants, in which case the question of whether to also fund the flow-on germline and cascade testing for these variants is expected to fall within the scope of the application to be considered by MSAC. As noted above, there appeared to be no need to anticipate

any additional subsequent germline or cascade testing based on the synthesised result of the HRD test. Secondly, as noted below, this is important in order to provide an evidentiary basis for MSAC to be confident that patients deemed eligible for olaparib and bevacizumab based on Australian test options reflect those who were deemed to have an HRD (GIS) score ≥42 in PAOLA-1.

The application also noted that, at the time of the application (November 2020), **REDACTED** was the only laboratory developing an HRD test and **REDACTED** would offer a national service. The application advised that the test used in the PAOLA-1 trial, myChoice® HRD Plus assay (Myriad myChoice®), and a further commercial HRD approved test by Foundation Medicine®, are performed overseas and are thus ineligible for MBS funding.

At its April 2021 meeting, PASC noted that there are several methods for HRD testing. PASC noted the advice from the applicant's expert that the HRD test being developed by **REDACTED** is assessing a scar signature based on LOH, and not assessing TAI or LST, or the variant status of specific genes (other than *BRCA1/2*).

PASC noted advice from the applicant's expert during its April 2021 meeting who explained that there are several pathways to repair DNA. When deficient, other mechanisms are used but those are error prone and leave genomic scars on the genome. Different assays measure different types of genomic changes and require spanning a large area of genome to measure these scars (which is related to the cost of test).

PASC noted that no specific information was provided in the application on the proposed **REDACTED** test to assess its comparative analytical performance against the approach used for the evidentiary standard test involving the Myriad myChoice® HRD test.

The following information was subsequently provided by **REDACTED**

> The **REDACTED** developed test utilises the Centre's own methodology where HRD status is based on fraction of genome with loss of heterozygosity from sequence-based single nucleotide polymorphism (SNP) detection [Wang 2012].
>
> **REDACTED [COMMERICALLY SENSITIVE & CONFIDENTIAL INFORMATION]**
>
> This test will be proprietary to **REDACTED**. **REDACTED** will be seeking professional advice to patent the test.

The integrated codependent submission or ADAR will need to address whether only those who are 'High Confidence' HRD or whether those who are either 'High Confidence' or 'Probable' HRD would be eligible for combination olaparib + bevacizumab maintenance therapy.

At its April 2021 meeting, PASC advised that since the proposed test is assessing a scar signature, and not assessing specific genes (other than *BRCA1/2*), no additional cascade testing would eventuate from the new MBS item.

At its August 2021 meeting, PASC noted that several HRD tests are available that use other methods to determine HRD positivity. PASC considered that it was unclear whether the different HRD tests identify different patients as having an HRD positive tumour, or more relevantly to this application,

whether they identify different patients as having an HRD positive and BRCA1/2 *negative tumour. PASC advised that an HRD test that has a high level of concordance with the relevant results of the clinical utility standard would be an appropriate test.*

It will be critical for the integrated codependent submission or ADAR to provide a comparison of the patients determined to be HRD positive in the PAOLA-1 trial by the evidentiary standard versus determination of HRD positivity as determined by the test options proposed to be used in Australia. Concordance, and particularly discordance (false negative/positives) in the results across these tests will need to be reported.

At its April 2021 meeting, PASC advised, based on the advice of the applicant's expert, that establishing comparative analytical performance between the test options, namely, current *BRCA1/2* pathogenic variant testing versus the proposed **REDACTED** test and the Myriad myChoice® HRD test (not available in Australia) versus the proposed **REDACTED** test, would not be a trivial matter. In particular, the threshold to determine HRD positive status is test specific and the Myriad myChoice® threshold score of 42 will not apply to the **REDACTED** test. Also, unlike the Myriad myChoice® test, the **REDACTED** test for HRD is largely based on LOH rather than on the combination of LOH, TAI and LST. Such "bridging studies" would also be needed for other future test options to demonstrate that all such tests have acceptable analytical performance compared with the evidentiary standard and initially subsidised test options.

The updated application (July 2021) suggested that the **REDACTED** test may be available in Australia as a test option that could be reimbursed on the MBS*. (The redacted test refers to HRD test 2 - a HRD assay available overseas which is similar to the Myriad® myChoice HRD Plus assay used in the pivotal PAOLA1 study).* **REDACTED.** The assay will be TGA notified as a Class 3 in-house IVD following the completion of a local validation including a sample concordance study with the **REDACTED**.

At its August 2021 meeting, PASC noted that two testing options were presented in the updated application: the **REDACTED** *test (HRD test 1 under development by an Australian pathology laboratory) and the* ***REDACTED*** *test (HRD test 2: a HRD assay available overseas which is similar to the HRD assay used in the PAOLA1 study to be performed in Australia) (**REDACTED).** PASC noted that neither option was currently available in Australia and expressed doubts that the* **REDACTED** *test (HRD test 1) could meet the expected demand in the Australian market.* **REDACTED.**

The applicant is requested to provide an update on the Australian regulatory status of the **REDACTED** *assay (HRD test 2), and whether this test is to be proposed as an alternative intervention for the application. At the time of consideration by PASC in August 2021, the TGA requirements for performing* **REDACTED** *test (HRD test 2) in an Australian laboratory had not occurred.*

As discussed above, the definition of HRD positivity as proposed by the applicant differs to the definition in the PAOLA-1 trial (the evidentiary standard) where:

- HRD status was determined with the use of the myChoice® HRD Plus assay (Myriad Genetic Laboratories).
- HRD positive was defined as a tumour *BRCA1/2* mutation or an HRD (GIS) score of 42 or higher. HRD negative was defined as an HRD (GIS) score of less than 42. "Unknown" was defined as an inconclusive, missing, or failed test [footnote to Table 1, p2419 Ray-Coquard 2019]. The applicant has indicated that this threshold is specific to the myChoice® HRD Plus assay. The trial did not

state the rationale for use of a score of 42 as the threshold, however it appears to have been based on Telli [2016], as indicated by the application.

Telli [2016] reported that three independent DNA-based measures of genomic instability reflecting underlying tumour homologous recombination DNA repair deficiency have been developed on the basis of loss of LOH [Abkevich 2012], TAI [Birkbak 2012] and LST [Popova 2012]. Timms [2014] further explained that HRD scores (HRD-LOH, HRD-TAI and HRD-LST) are highly correlated with defects in *BRCA1/2*.

Telli [2016] used a training set assembled from four publicly available or previously published cohorts (497 breast and 561 ovarian cases) that included 78 breast and 190 ovarian cancers lacking a functional copy of either *BRCA1* or *BRCA2* (i.e. *BRCA1/2* deficient) based on mutation and methylation data. Tumours selected as *BRCA1/2* deficient had either (i) one deleterious mutation in *BRCA1* or *BRCA2*, with LOH in the wild-type copy, (ii) two deleterious mutations in the same gene, or, (iii) promoter methylation of *BRCA1* with LOH in the wild-type copy. This cohort was used to define a threshold for the HRD score (defined as an unweighted numeric sum of LOH, TAI, LST scores) intended to have a "95% sensitivity to detect those tumours with *BRCA1/2* mutations or *BRCA1* promotor methylation". Further explanation of the methods used to derive the three components of the HRD score by Telli [2016] were provided in a supplemental appendix and are reported in Attachment 3.

Figure 3 presents the HRD score distribution in the combined breast and ovarian training set used in Telli [2016]. The threshold score (≥42) selected was the 5th percentile of HRD (GIS) scores in tumours lacking a functional copy of *BRCA1* or *BRCA2* (*BRCA1/2* deficient).

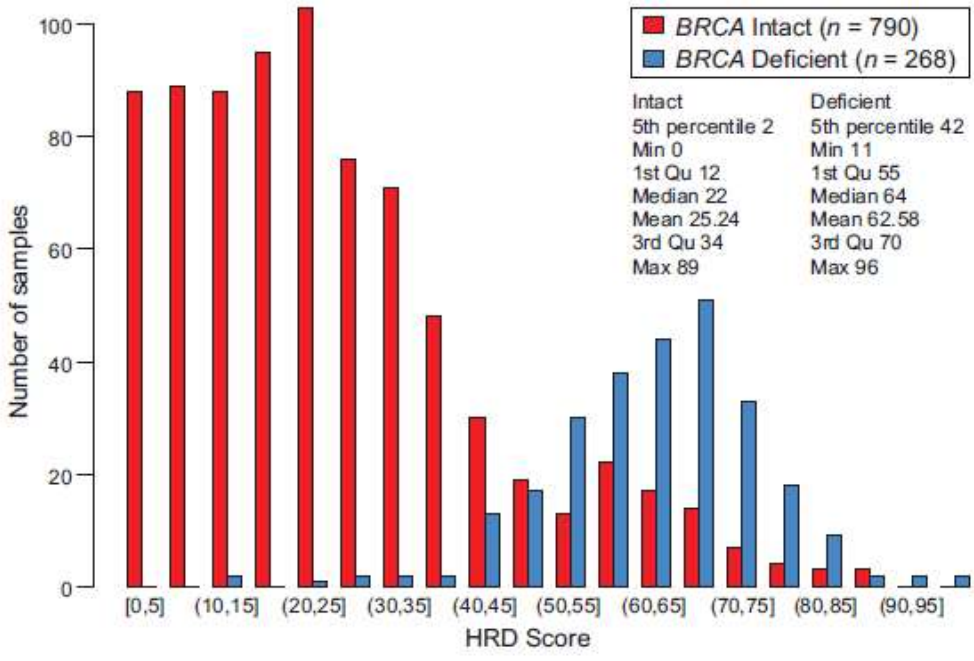

Figure 3: HRD score distribution in the combined breast and ovarian training set. *BRCA*-deficient tumours include those with a *BRCA1/2* mutation and/or *BRCA1* methylation

Source: Figure 1, p3767 Telli [2016]

Consistent with the definition of the HRD score threshold, and as is evident from Figure 3, most but not all patients with a *BRCA1/2* pathogenic variant also had an HRD (GIS) score of ≥42. Similarly, not all patients without a *BRCA1/2* pathogenic variant in the PAOLA-1 trial had an HRD (GIS) score <42, see Table 3.

Table 3: Number of patients who were HRD positive (score ≥42) compared with HRD negative (score <42) with respect to *BRCA1/2* pathogenic variant in the treatment arms of PAOLA-1

	Patient subgroup	Ola + Bev; N	Bev + PBO; N
1	HRD positive including *BRCA1/2* pathogenic variant	255	132
2	HRD positive, no *BRCA1/2* pathogenic variant	97	55
3	*BRCA1/2* pathogenic variant	161	80
4	HRD positive, no *BRCA1/2* pathogenic variant (2) + *BRCA1/2* pathogenic variant (3)	258	135
5	Patients who are HRD negative with a *BRCA1/2* pathogenic variant (4) minus (1)	3	3

Source: PAOLA-1 [Ray-Coquard 2019 _supplementary appendix Table S2] #1 & #2 based on Myriad myChoice HRD; #3 based on tumour *BRCA1/2* mutation test as per randomisation
Bev = bevacizumab; N = number of patients; Ola = olaparib; PBO = placebo

Compared with the Telli [2016] training set definition of 95% patients with an HRD (GIS) score ≥42 having "tumours with *BRCA1/2* mutations or *BRCA1* promotor methylation", the PAOLA-1 trial recruited 161/258 = 62% of such patients. This difference might be explained by a recent publication by Takaya [2020], who analysed HGSOC specifically (compared with breast and ovarian cancers in Telli [2016]) and reported that *BRCA1/2* mutations were enriched in the group with HRD scores ≥63. In the analysis of ovarian cancer alone, Takaya [2020] described that *BRCA* mutations represented 38% (49/128) of the cases with HRD scores ≥63, 10% (12/118) with HRD scores between 42 and 62, and 10% (5/50) with HRD scores 41 and below. The authors also reported there was no enrichment of *BRCA* mutation cases with HRD scores from 42 to 62 compared with those with scores ≤41. The survival curve for those who had HRD scores ≥63 (n=242) was statistically significantly improved compared with patients with HRD scores of 42–62 (n=211) and ≤41 (n=84), which overlapped. The publication did not report use of the myChoice® assay, and no comparison of the methods used to derive HRD scores were reported. The applicant may wish to address this in its integrated codependent submission or ADAR.

At its April 2021 meeting, PASC noted that the Myriad myChoice® threshold score of 42 from Telli (2016) was based on the training set of patients with either breast or ovarian cancer and prespecified to identify 95% of patients with *BRCA1/2* pathogenic variants. PASC noted that this 95% proportion was not replicated in the PAOLA-1 population of patients with ovarian cancer only, which PASC considered raised questions over whether this test was performing as intended for the population consisting exclusively of ovarian cancer patients. PASC further considered that this has consequences for the greater than expected proportion of patients who would be eligible for the proposed listing of olaparib maintenance in combination with bevacizumab.

At its August 2021 meeting, PASC noted that BRCA1/2 *testing and GIS testing were different types of tests.* BRCA1/2 *tests for pathogenic variants in the* BRCA1/2 *genes whereas the proposed GIS tests assess genomic instability. PASC advised that although a GIS test may identify genomic scarring, it does not identify the cause which may be due to germline pathogenic genetic variants in HRD genes. PASC advised that the role of genomic instability and immunotherapy was still being investigated and therefore it may be appropriate to have a separate item for the proposed test. PASC also confirmed*

the general MBS policy preference for the item descriptor to be agnostic to the type of HRD test (subject to acceptance of sufficient concordance) and for it not to include a threshold value for any test result in order to avoid confusing eligibility for the test with eligibility for treatment. PASC noted that the threshold for GIS positivity would be considered by the PBAC in its consideration of the population eligible for treatment in a PBS restriction, but would likely reflect that used for the clinical utility standard.

At its April 2021 meeting, PASC considered that, should the proposed test replace the current MBS item for testing for *BRCA1/2* pathogenic variant status in tumour samples (MBS item 73301), it would also be important to demonstrate that the proposed test, which tests for GIS and *BRCA1/2* pathogenic variant status, has the same or very similar concordance for detecting *BRCA1/2* pathogenic variants as the current MBS tests. In particular, it should be demonstrated that the new test would identify the same patients that respond to olaparib monotherapy as the current tests for MBS item 73301.

Similarly, it would be important to demonstrate that the Myriad myChoice® HRD test has the same or very similar concordance in identifying *BRCA1/2* pathogenic variants as the current MBS tests.

At its August 2021 meeting, PASC noted that a few issues remain unresolved, accepting that the application could proceed on the basis proposed by the applicant:

- *timing and nature of HRD testing components in the clinical management algorithm sequence still needs to be clarified, and;*
- *there is an outstanding uncertainty associated with cascade testing, however it may not be applicable if future GIS testing only provides aggregated results.*

<u>Drug</u>

The application proposed that use of combination olaparib and bevacizumab on the PBS would be limited to those patients who are HRD (GIS) positive with no *BRCA1/2* pathogenic variants. *At its August 2021 meeting, as noted above, PASC discussed the possibility of the use of combination olaparib and bevacizumab treatment in those were positive for* BRCA1/2 *pathogenic or likely pathogenic variants (who are, by definition, also HRD positive).*

The application did not specify the doses of olaparib and bevacizumab when used in combination. The doses used in the PAOLA-1 trial were:

- olaparib tablets (300 mg twice daily) for up to 24 months; and
- bevacizumab (15 mg/kg every 3 weeks) for 15 months *(approximately 22 cycles)* in total.

The dose of olaparib in the trial was consistent with TGA approved dosing for tablets.

Bevacizumab dosing in the trial was consistent with TGA-approved dosing (although it was inconsistent with the dose of the previous PBS restriction).

At its April 2021 meeting, PASC noted that the bevacizumab dose and duration used in the PAOLA-1 trial may not be consistent with current PBS-subsidised use. PASC also noted that combination use of olaparib and bevacizumab was administered to all participants in the treatment arm regardless of *BRCA1/2* pathogenic variant status, which made it difficult to ascertain how this combination would

relate to the current listing of olaparib as a monotherapy. PASC considered that these issues should be addressed in the integrated codependent submission or ADAR.

Following the June 2021 changes to the PBS listing of bevacizumab, these matters relating to the bevacizumab dose and duration of treatment were less important for the integrated codependent submission or ADAR.

The applicant indicated that the dose of bevacizumab, when used in combination with olaparib, would be 15 mg/kg for 15 months, which is consistent with its TGA-approved dose in this indication (but not with its previous PBS restriction).

The applicant indicated the following were matters for the PBAC to consider:

- Will the bevacizumab TGA indication need to change to specify combination use with olaparib?
- What if patients are contraindicated to bevacizumab? Can they use olaparib monotherapy? The applicant advised that there is currently no evidence to support the use of olaparib monotherapy in HRD positive, *BRCA1/2* pathogenic variant negative population. This was also indicated to be a matter for clinicians to consider.

Comparator

Test

The application proposed that tumour testing for *BRCA1* and *BRCA2* pathogenic variants was the main comparator for the proposed medical service: tumour testing for *BRCA1* and *BRCA2* in parallel with GIS testing. Currently, tumour testing for *BRCA1* and *BRCA2* pathogenic variants is funded under MBS item 73301 for the same population of patients newly diagnosed with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer with a fee of $1,200 to establish eligibility for treatment with olaparib. The applicant subsequently revised the intervention to 'HRD testing' and the main comparator to 'no HRD testing'.

The application stated that the HRD test will be used instead of the *BRCA1/2* alone test as it provides both *BRCA1/2* and GIS status. The applicant further confirmed that there are no clinical or other reasons that would allow a clinician to delineate which patients would receive either test.

On the basis that the patients who would be eligible for the HRD test are the same as those who are eligible for the current tumour *BRCA1/2* alone test, the *BRCA1/2* alone test is the appropriate comparator, acknowledging that the proposed test provides the same information (*BRCA1/2* pathogenic variant status) and additional, incremental information (GIS) compared with the current *BRCA1/2* alone test.

At its April 2021 meeting, PASC considered that, as proposed by the applicant, the current testing for *BRCA1/2* pathogenic variants (MBS item 73301) is an appropriate comparator for the proposed HRD test that would also test for *BRCA1/2* pathogenic variants in a parallel (rather than a sequential) manner. As such, PASC accepted the intention for MBS item 73301 to be completely replaced by the new item corresponding to the proposed HRD test.

PASC also advised that, if the option for sequential testing of *BRCA1/2* pathogenic variants and then GIS testing (not preferred by the applicant's expert), then there would be no replacement of MBS item 73301, and a different item for the sequential GIS test only would be needed.

PASC further advised that, if the alternative option for distinguishing the populations for testing to determine eligibility for olaparib maintenance as monotherapy and eligibility for olaparib maintenance with bevacizumab, then the comparator for the proposed test would be no testing. This is because patients already taking bevacizumab would not be evidence-based candidates for olaparib maintenance as monotherapy, so there would be no rationale for testing their *BRCA1/2* pathogenic status alone. MBS item 73301 would be retained for those patients who did not start bevacizumab as part of their initial chemotherapy regimen in order to help determine their eligibility for olaparib maintenance as monotherapy.

In discussions with the applicant after the April 2021 PASC meeting, it was confirmed that changing the definition of the test population and the test intervention would affect the determination of the comparator. The opportunity for a second PASC consideration at its August 2021 meeting also provided an opportunity to seek further input from professional groups (see below). The Department has specifically requested further advice from The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) to help address some of the outstanding matters for MSAC Application 1658 (Attachment 4).

At its August 2021 meeting, PASC considered that the relevant test comparator was dependent on the tested population:

- *Population 1: the current MBS-listed* BRCA1/2 *variant test (Item 73301);*
- *Population 2: no add-on GIS testing; and*
- *Population 3: the current MBS-listed* BRCA1/2 *variant test (parallel* BRCA1/2 *and GIS) or no add-on GIS testing (sequential* BRCA1/2 *and GIS testing).*

A comparison of the analytical performance (sensitivity, specificity, positive predictive value, negative predictive value) of the *BRCA1/2* component of the combined *BRCA1/2* and GIS test being developed by **REDACTED** compared with current tumour *BRCA1/2* testing to determine *BRCA1/2* pathogenic variant status will need to be conducted in the integrated codependent submission or ADAR. This would need to be presented alongside the related comparison of the analytical performance of both components compared with both components of the evidentiary standard.

Drug

For patients who do not have a *BRCA1/2* pathogenic variant, the current main treatment option for maintenance is bevacizumab. Up to 31 May 2021, bevacizumab was PBS restricted as maintenance treatment for patients with advanced (FIGO Stage IIIB, IIIC or Stage IV) epithelial ovarian, fallopian tube or primary peritoneal cancer with high-risk prognostic factors, which includes suboptimally debulked and have a WHO performance status of 2 or less. Otherwise, the management option is 'watch and wait' if PBS criteria is not met. From 1 June 2021, bevacizumab has an unrestricted PBS listing. Regardless, the original application assumed that the majority of patients receive bevacizumab rather than the 'watch and wait' option. This is in contrast to the nominated comparator in the July 2020 PBAC consideration of olaparib for first-line therapy where 'watch and wait' was considered the appropriate comparator, but the PBAC accepted that bevacizumab was "… an appropriate comparator for the subgroup of patients with suboptimally debulked Stage III ovarian cancer" (Olaparib PSD July 2020, paragraph 5.2); indicating most are 'watch and wait'. This may be explained by the statement on p27 of the application that "[p]atients eligible for bevacizumab treatment rarely harbour a *BRCA1/2* pathogenic gene variant and their clinical features

tend to be distinct from patients who do. Compared to patients eligible for bevacizumab, patients with a *BRCA1/2* pathogenic gene variant are usually younger, less likely to have bulky disease, are platinum sensitive and their prognosis is associated with improved survival [Alsop 2012, Cancer Research UK 2016]".

At its April 2021 meeting, PASC noted that the applicant nominated bevacizumab maintenance monotherapy as a comparator for the proposed maintenance with olaparib plus bevacizumab for the proposed population of patients shown to be *BRCA1/2* pathogenic variant negative/GIS positive.

PASC further noted that, for patients with *BRCA1/2* pathogenic variants, the comparator in the pivotal PAOLA-1 trial was bevacizumab monotherapy, unlike current Australian clinical practice. In the pivotal SOLO-1 trial in patients with *BRCA1/*2 variants, the comparator for olaparib as a monotherapy maintenance (consistent with current Australian practice) was 'watch and wait'.

For patients identified as GIS positive with no *BRCA1/2* pathogenic variant via tumour HRD testing, the application therefore nominated placebo + bevacizumab as the main drug comparator. As for the intervention above, the application did not specify the dose of bevacizumab. The dose of bevacizumab in the PAOLA-1 trial was bevacizumab (15 mg/kg every 3 weeks) for 15 months (approximately 22 cycles) in total, consistent with its TGA-approved dosing. The comments made with respect to bevacizumab dosing under 'Intervention' equally apply to the 'Comparator'.

Although acknowledged as an option, the application has not nominated 'watch and wait' as a comparator. The applicant subsequently acknowledged that 'wait and watch' (i.e. placebo) may be considered a comparator in a minority of patients, especially for those patient who are not eligible for bevacizumab under the current PBS criteria, noting this will be addressed in the codependent MSAC/PBAC submission.

At its April 2021 meeting, PASC advised that more information was needed on the frequency of using the 'watch and wait' strategy in current practice.

As of 1 November 2020, a patient newly diagnosed with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer and a *BRCA1/2* pathogenic variant is eligible for PBS-subsidised olaparib. Although the application indicated that combination olaparib and bevacizumab treatment would be relevant for patients who were GIS positive with a *BRCA1/2* pathogenic variant, the applicant has since indicated these patients would remain being treated with olaparib monotherapy, except "[f]or the small number of patients currently receiving bevacizumab and identified with a *BRCA* [pathogenic variant positive] status, olaparib could be included as combination regimen". It is not clear that this would be the case given the proposed TGA indication also encompasses these patients. The applicant is requested to address this further in its integrated codependent submission or ADAR.

Should patients who are *BRCA1/2* pathogenic variant positive (that is, HRD positive) be eligible for treatment with combination olaparib and bevacizumab, the appropriate comparator would be olaparib alone. An indirect comparison (or possibly a naïve comparison) would be needed to inform the incremental benefit (if any) of olaparib + bevacizumab compared to olaparib alone.

The applicant reiterated that the target population for this codependent MSAC/PBAC submission are those patients who are GIS positive and *BRCA1/2* pathogenic variant negative, a subgroup of the

population in the PAOLA-1 trial. The applicant considers the clinical need of patients with a *BRCA1/2* pathogenic variant are met with olaparib maintenance monotherapy (PBS listed November 2020).

At its August 2021 meeting, PASC considered that the relevant drug comparator was a matter for the PBAC and would depend on the proposed treatment population and whether people with BRCA1/2 *pathogenic variants would be eligible for treatment with olaparib and bevacizumab:*

- *Those who are* BRCA1/2 *negative and GIS positive: bevacizumab maintenance alone, with some 'watch and wait'.*
- *Those who are* BRCA1/2 *positive: olaparib maintenance alone, some bevacizumab maintenance alone and some 'watch and wait'. Olaparib alone becomes a relevant comparator for the remainder of patients who are HRD positive as a consequence of being* BRCA1/2 *positive and are currently eligible for olaparib monotherapy. These patients could also cease bevacizumab treatment upon testing positive for* BRCA1/2 *pathogenic variant status. PASC advised that this comparative assessment would require an indirect treatment comparison of SOLO-1 and PAOLA-1 outcomes. The applicant advised that this will be presented in the application.*

The applicant further stated that Australian clinicians have indicated that they would most likely use olaparib + bevacizumab as maintenance therapy in only a small number of patients positive for a *BRCA1/2* pathogenic variant. Olaparib monotherapy is the preferred option and will be used in the majority of these patients. The applicant advised that a *post-hoc,* match adjusted indirect treatment comparison of SOLO-1 versus PAOLA-1 did not demonstrate any statistically significant benefit of the combination versus olaparib monotherapy; this analysis will be presented in the codependent submission. The applicant further stated that combination therapy also increases the risk of possible side effects.

PASC discussed the published results of the indirect comparison of the outcomes SOLO-1 and PAOLA-1 trials as the basis for assessing the comparative effectiveness of olaparib and bevacizumab maintenance versus olaparib monotherapy maintenance for the BRCA1/2 *positive population. The reported progression-free survival at 24 months was 82% for the combination therapy and 73% for olaparib monotherapy (HR 0.71; 95% CI: 0.45-1.09) (Vergote et al Conference presentation (2020) Gynecologic Oncology; 2020:159; pp19-20. DOI: 10.1016/j.ygyno.2020.06.038 https://sgo.confex.com/data/abstract/sgo/2020/Paper_16926_abstract_13205_0.JPG). There was insufficient detail in the conference paper to independently evaluate its methods, but although the HR did not reach statistical significance, there is a trend towards better patient outcomes associated with olaparib and bevacizumab maintenance.*

Outcomes

The outcomes nominated by the application (and others considered relevant) are as follows.

Safety outcomes

- Adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing.
- Comparative safety and tolerability of olaparib + bevacizumab treatment compared with bevacizumab + placebo (and potentially olaparib + placebo and/or placebo for 'watch and wait') assessed by adverse events and collection of clinical chemistry/haematology parameters.

Clinical effectiveness outcomes

Test outcomes

- Comparison of the concordance and particularly discordance between the evidentiary standard and the test being developed by **REDACTED** and proposed to be used in Australia to determine HRD (and *BRCA1/2*) status.
- Comparison of the analytical performance of the test being developed by **REDACTED** compared with current tumour *BRCA1/2* testing to determine *BRCA1/2* pathogenic variant status.
- Comparison of the analytical performance of the clinical utility standard with respect to *BRCA1/2* status compared with current tumour *BRCA1/2* testing to determine *BRCA1/2* pathogenic variant status.
- Clinical validity of test:
  - Differential prognostic effect of positive GIS in advanced ovarian cancer, particularly including an assessment of whether this prognostic effect varies further according to whether the patient is also *BRCA1/2* positive or not.
- Clinical utility of test:
  - Treatment effect modification of olaparib by positive GIS in patients with advanced ovarian cancer following prior treatment with platinum-based chemotherapy/bevacizumab, preferably also with an assessment of whether this prognostic effect changes according to whether the patient is also *BRCA1/2* positive or not.
- Other test-related considerations:
  - Test failure rates and re-biopsy rates.
  - Test turnaround time.
  - Estimated number of patients being tested.
  - Cost of testing per patient.

At its April 2021 meeting, PASC noted that the test-specific outcomes (analytical performance against the evidentiary standard, clinical validity, clinical utility, failure rates, turnaround time, etc.) are the standard outcomes for a diagnostic test that identifies a biomarker.

PASC also emphasised the need to assess the analytical performance (concordance and particularly discordance) between the evidentiary standard and the proposed Australian test options to determine genomic instability (and *BRCA1/2*) status. PASC also emphasised the need to assess the

analytical performance of these tests with current tumour *BRCA1/2* testing to determine BRCA1/2 pathogenic variant status.

In establishing the comparative analytical performance between the proposed **REDACTED** *test and the Myriad myChoice® HRD test, PASC considered at its August 2021 meeting that the particular value of the threshold for the clinical utility standard (HRD score of ≥42) be used to assess the analytical concordance of the proposed* **REDACTED** *test. PASC noted that the matter of what constitutes sufficient concordance is currently under discussion with National Pathology Accreditation Advisory Council (NPAAC) and TGA with the opinion emerging that the sufficient threshold of concordance may be increased from 90% to 95%. In the absence of an independently established threshold of concordance, PASC advised that the integrated codependent submission or ADAR should address the clinical and economic consequences of test discordance between the proposed* **REDACTED** *test and Myriad myChoice®. As a prerequisite to this concordance study, PASC advised that the clinical evidence for the* **REDACTED** *test should also include appropriate information about the assay training set and validation set to establish its threshold separating GIS positive from GIS negative, and thus HRD positive from HRD negative.*

Drug outcomes

- Progression-free survival (PFS).
- Overall survival (OS).
- Objective response rate (ORR).
- Health-Related Quality of Life (HRQoL).

The applicant advised that it agreed with the majority of outcomes described above which will be addressed in the codependent MSAC/PBAC submission.

PASC noted that safety and clinical effectiveness outcomes (PFS, overall survival, objective response rate and health-related quality of life) are also the standard outcomes to be assessed for cancer drugs.

Clinical Management Algorithms

Current clinical management algorithm for identified population

First-line treatment for patients with newly diagnosed advanced high grade epithelial ovarian cancer (HGEOC) is curative in intent, aiming to achieve and maintain complete remission [Raja 2012, Ledermann 2017]. The mainstay of treatment involves cytoreductive surgery, platinum-based chemotherapy (which may also include a taxane). In some patients this may include bevacizumab initiated during platinum-based chemotherapy and followed by bevacizumab alone as maintenance treatment. The applicant described the place of bevacizumab as following: “bevacizumab in combination with carboplatin and paclitaxel followed by bevacizumab maintenance, is the first targeted non-chemotherapy treatment approved in the first-line ovarian cancer setting and has become an established standard of care, regardless of their *BRCA* mutation status”. This is consistent with the diagrams depicting the current and the proposed clinical pathways (Figure 4 and Figure 5 in the July 2021 updated application).

Surgery for advanced ovarian cancer is intensive and aims to achieve complete resection with no residual visible disease, as this is associated with significantly improved PFS and OS [Ledermann 2013, du Bois 2009, van der Burg 1995, Vergote 2010]. A maximal surgical effort is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy. Surgery is quickly followed by chemotherapy to reduce the risk of disease recurrence. The standard first-line regimen is carboplatin in combination with paclitaxel, both administered intravenously every 3 weeks, for six cycles [Fotopoulou 2017, Ledermann 2013, AIHW 2018, NICE Clinical Guideline 122 2011]. The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. Docetaxel may be given as an alternative in patients who cannot tolerate paclitaxel [Ledermann 2013, NICE Clinical Guideline 122 2011].

From 1 June 2021, bevacizumab has an unrestricted PBS listing. It is TGA-approved for being initiated with platinum-based chemotherapy and use as monotherapy for continued maintenance treatment for patients with advanced (FIGO Stage IIIB, IIIC or Stage IV) epithelial ovarian, fallopian tube or primary peritoneal cancer. TGA-approved treatment is limited to a total of 15 months therapy or until disease progression, whichever occurs earlier.

Based on current ovarian cancer guidelines it is recommended that patients newly diagnosed with ovarian cancer be referred for *BRCA1/2* testing.

BRCA1/2 testing is MBS funded under MBS item 73295 for germline testing or MBS item 73301 for tumour testing to determine eligibility for olaparib as maintenance treatment. Patients with a positive *BRCA1/2* pathogenic variant will be eligible for olaparib after first completing and responding to a course of platinum-based chemotherapy.

Those patients who are *BRCA1/2* negative will be treated with platinum-based chemotherapy followed by continued bevacizumab as maintenance treatment or by 'wait and watch'.

Germline *BRCA1/2* testing is offered to those patients with a positive tumour *BRCA1/2* result to determine if the pathogenic variant originated from a germline mutation and thus will provide information of any familial risk. Cascade testing is also available under MBS item 73297, for biological relatives of a patient who has had a pathogenic or likely pathogenic gene variation identified in the following genes: *BRCA1, BRCA2, STK11, PTEN, CDH1, PALB2* and *TP53;* the service must be requested by a specialist or consultant physician.

Figure 4 presents the current clinical management pathway developed by the applicant in the July 2021 updated application for patients after they have received tumour *BRCA1/2* testing (the main comparator). A small proportion of patients may be tested with a germline *BRCA1/2* test, if there is no available or quality tumour tissue sample.

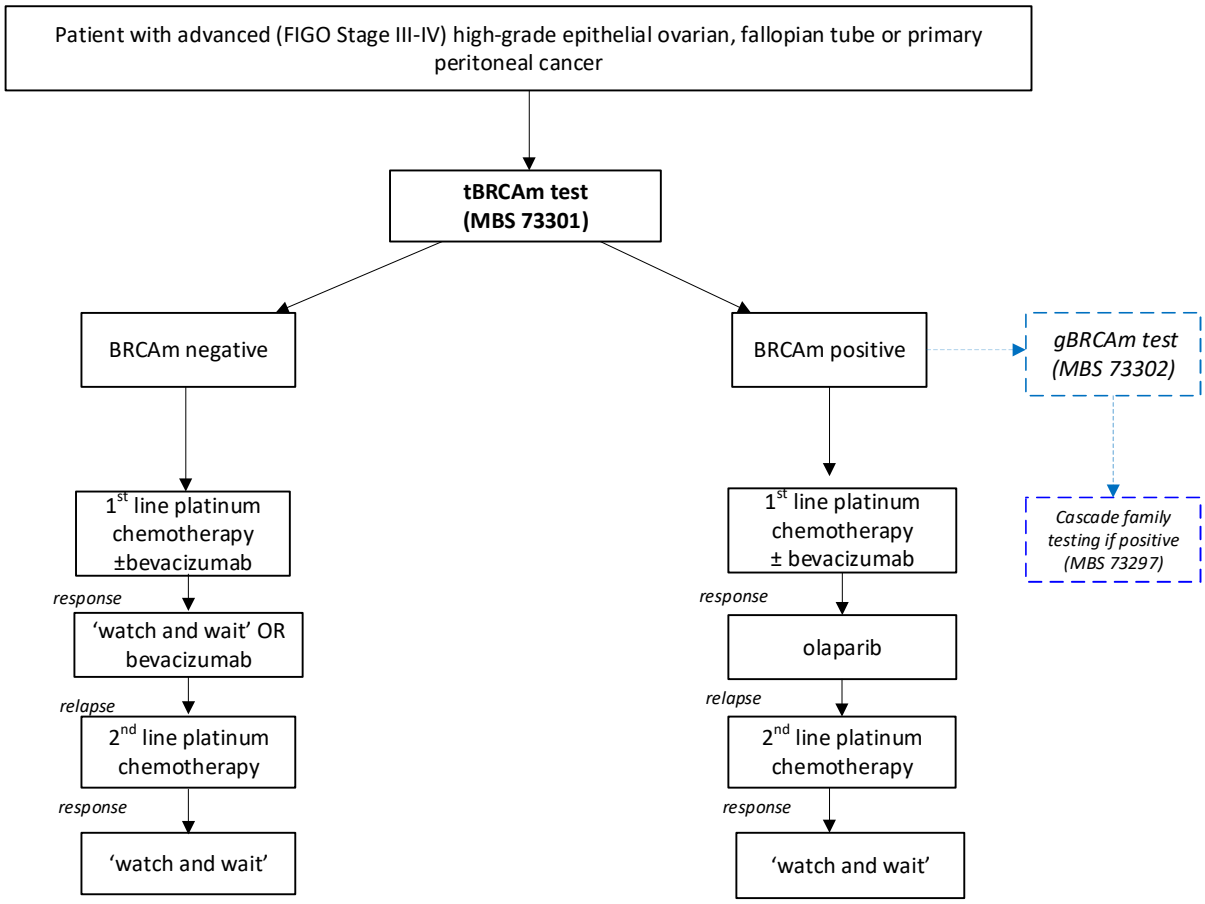

Figure 4: Current clinical treatment management for patients with advanced ovarian cancer

Source: Figure 4, p29 of the July 2021 updated application.
Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline *BRCA1* or *BRCA2* pathogenic variant, tBRCAm = tumour *BRCA1* or *BRCA2* pathogenic variant

BRCA1/2 pathogenic variant positive patients may also receive PBS-subsidised olaparib after two failed platinum treatments, provided they have not received olaparib previously.

At its April 2021 meeting, PASC noted (with respect to the current pathway):

- the lack of clarity and consistency with respect to the 'watch and wait' option in the *BRCA1/2* pathogenic variant positive (BRCAm) population; and
- the absence of bevacizumab as a first-line therapy (alongside platinum-based chemotherapy) in both arms.

The updated current algorithm has addressed the absence of bevacizumab as a first-line therapy.

Proposed clinical management algorithm for identified population

The proposed medical service provides both *BRCA1/2* and GIS status (conducted in parallel) and the test will replace the tumour *BRCA1/2* test (MBS item 73301) as the one test will cover both GIS and *BRCA1/2*.

In Figure 5, HRD testing determines the GIS of patients, and the *BRCA1/2* status of those who are GIS positive. The treatment algorithm for those patients with a positive *BRCA1/2* pathogenic variant status will be the same as current practice (i.e. they will be eligible to access olaparib as first-line

maintenance treatment after first completing and responding to a platinum-based chemotherapy regimen that may also include a taxane, and that may also be followed by bevacizumab. As discussed under 'Population' and 'Comparator', the exclusion of combination therapy in those who are *BRCA1/2* pathogenic variant positive may not be justified.

For those patients with a negative *BRCA1/2* pathogenic variant status and positive GIS, first-line treatment will include platinum-based chemotherapy, which may also include paclitaxel, and be followed by bevacizumab. Patients who are in response after initial chemotherapy have the option to be maintained with treatment with olaparib in combination with bevacizumab. This new combination maintenance regimen is proposed based on evidence from the pivotal clinical trial PAOLA-1.

Patients who are HRD negative (both *BRCA1/2* pathogenic variant and GIS negative) will receive similar treatment to those patients who are *BRCA1/2* negative. These patients will either receive platinum/paclitaxel, followed by bevacizumab as maintenance or be actively monitored ('watch and wait').

Tumour HRD testing is proposed prior to receipt of any treatment. Figure 5 illustrates the proposed clinical management pathway with the proposed HRD test **REDACTED** in the July 2021 updated application.

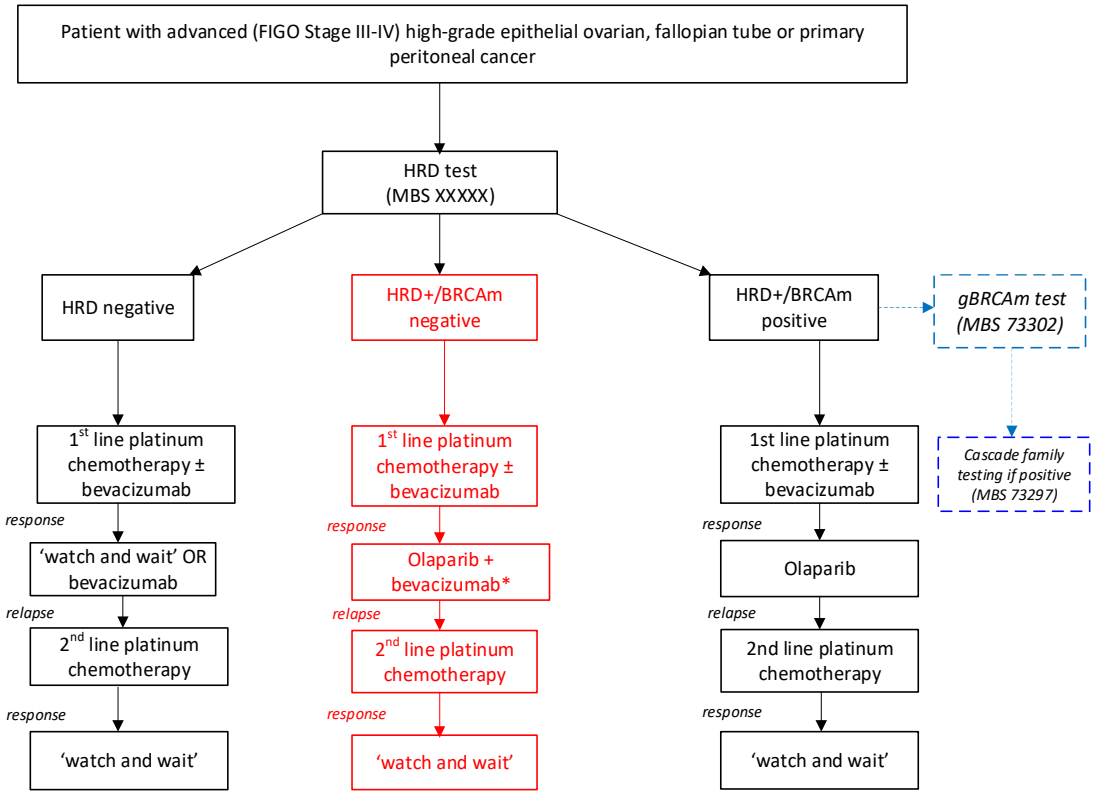

Figure 5: Clinical treatment pathway with proposed medical service - HRD test (includes *BRCA1/2* and GIS status)

Source: Figure 5, p32 of the July 2021 updated application
Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; g*BRCA*m = germline *BRCA1* or *BRCA2* pathogenic variant; GIS = genomic instability status; HRD = homologous recombination deficiency
Note: *BRCA*m negative is the same as *BRCA*wt

The applicant commented that three maintenance options were nominated for the *BRCA1/2* pathogenic variant positive and GIS positive population: 'wait and watch' or bevacizumab or olaparib monotherapy. The applicant claimed that olaparib monotherapy was the treatment option for this population due to the results of SOLO-1 and the potential for patients to remain in complete remission; based on this, it is unlikely that clinicians would consider 'wait and watch' or bevacizumab as a treatment option.

At its April 2021 meeting, PASC noted (with respect to the proposed pathway):

- the treatment algorithm appears to assume staged testing with *BRCA1/2* pathogenic variant (BRCAm) test preceding GIS testing which is inconsistent with the expressed preference for parallel testing for the two components (this has since been addressed);
- for patients who are *BRCA1/2* pathogenic variant positive (BRCAm), bevacizumab is not administered as in the PAOLA-1 trial treatment;
- the absence of bevacizumab as a first-line therapy (alongside platinum-based chemotherapy) in both arms (this has since been addressed); and
- the lack of clarity and consistency with respect to the 'watch and wait' option (this has since been addressed).

At its April 2021 meeting, PASC advised that further information of the current and proposed treatment pathways is needed in order to clarify the appropriateness and eligibility for the current options of 'watch and wait', bevacizumab maintenance monotherapy, olaparib maintenance monotherapy and the proposed maintenance combination of olaparib and bevacizumab.

PASC further advised that input from clinical experts is required to better inform the position of the test in the clinical pathways. PASC requested that the Department seek further targeted consultation input from gynaecologic oncologists regarding the standard of care for the proposed population and when HRD testing should be performed with respect to initial diagnosis and the start of first-line chemotherapy following surgery. PASC advised that this input may result in further revisions to the PICO and thus the clinical management algorithms.

PASC also suggested a possible revision to the current *BRCA1/2* pathogenic variant positive (BRCAm) treatment pathway since the HRD test may result in changes in classification of *BRCA1/2* pathogenic variant status, and thus eligibility for olaparib monotherapy.

The applicant advised that 'wait and watch' (i.e. placebo) may be considered a comparator in a minority of patients, especially those patients who are not eligible for bevacizumab under the current PBS criteria. PBS eligibility for bevacizumab is no longer an issue.

At its April 2021 meeting, PASC discussed the place of bevacizumab in the treatment algorithm. Currently, the 'watch and wait' strategy is used if PBS criteria for bevacizumab are not met, although this is no longer relevant. However, it is assumed by the applicant that the majority of patients receive bevacizumab. Also, bevacizumab was understood to be started in combination with first-line platinum-based chemotherapy, and as such may conceivably precede the HRD test to establish eligibility for olaparib. As noted under "Population" and "Comparator" above, PASC queried whether the proposed MBS item should require first-line patients to have started on bevacizumab before they get tested with the proposed test. PASC considered further consultation was needed on the

feasibility and the acceptability of this option, including whether bevacizumab may be started later in current clinical practice.

PASC noted that, if considered acceptable and feasible, *BRCA1/2* testing alone could then be limited to those first-line patients who have not started on bevacizumab or to second-line patients, because *BRCA1/2* pathogenic variant status only is required to help determine eligibility for olaparib maintenance monotherapy. In this regard, PASC also noted the applicant's response to these algorithms in the draft PICO Confirmation, which confirmed that bevacizumab is part of the prerequisite regimen of first-line platinum-based therapy.

At its August 2021 meeting, PASC advised that the clinical management algorithm for Population 1 (as requested by the applicant) be revised where relevant to reflect the updates in this discussion.

Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies of tumour testing to identify HRD status and treatment with olaparib + bevacizumab as maintenance therapy in patients with HRD positive with no *BRCA1/2* pathogenic variant is:

> Superior in terms of comparative effectiveness and non-inferior in terms of safety versus the main comparator, 'no HRD testing' (i.e. *BRCA1/2* testing only) and placebo + bevacizumab as maintenance treatment.

At its April 2021 meeting, PASC noted the clinical claim.

In the July 2021 updated application, the corresponding statement reads

> Overall, the clinical claim is that the proposed codependent technologies of HRD testing, and treatment with olaparib plus bevacizumab as maintenance therapy following a response to platinum-based chemotherapy, in HGSOC patients who test HRD positive *BRCA*wt is superior to tumour *BRCA1/2* testing and standard of care (i.e., placebo plus bevacizumab) in terms of efficacy and non-inferior in terms of safety with manageable adverse events.

Based on the clinical claim, the economic evaluation should be a cost-effectiveness analysis, preferably a cost-utility analysis.

At its April 2021 meeting, PASC questioned whether, depending on resolution of the population, intervention and comparator issues identified above, the economic evaluation should also include a *BRCA1/2* pathogenic variant positive arm given the proposed test would result in a change to identification of *BRCA1/2* pathogenic variant status and eligibility for olaparib monotherapy.

Proposed item descriptor

The current MBS fee for detection of germline or tumour *BRCA1* or *BRCA2* pathogenic variants to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS) according to MBS items 73295 and 73301, respectively, is $1,200.

REDACTED. The applicant explained that testing of tumour tissue to identify GIS has additional complexity over tumour *BRCA1/2* testing as a number of components are involved including but not

limited to developing a quantitative assessment of genomic tissue scarring to measure genomic instability. **REDACTED**.

The July 2021 updated application states that "Given the PASC concerns with regards to the **REDACTED**. AstraZeneca seeks guidance from MSAC to advise an appropriate pricing structure to support a cost-effective price of the HRD test".

The basis for establishing the composition of an MBS fee is not primarily a matter for MSAC; rather MSAC is tasked with advising whether the service is acceptably cost-effective at a proposed MBS fee. The applicant is requested to confirm whether its application is requesting consideration of the **REDACTED**. The applicant's integrated codependent submission or ADAR will need to include an appropriate proposed fee so that it can complete its economic evaluation and financial analyses.

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

The application stated that results of the testing should be interpreted and reported by suitably qualified and trained pathologists, and that testing should be conducted in specialist laboratories that hold the appropriate accreditation and registration for this diagnostic testing procedure.

At its April 2021 meeting, PASC questioned whether the item descriptor should extend the reference to determining eligibility for accessing olaparib to define its use as being for first-line maintenance and concluded that this was not necessary as this is not stipulated in the existing MBS item 73301.

PASC noted that apart from the above queries, there are no other issues with the proposed item descriptor in relation to the population or intervention, but the fee **REDACTED** than current fee for MBS item 73301. Also, whole genome sequencing has fees of $2,100.

PASC further noted consultation feedback from the Royal College of Pathologists of Australasia (RCPA) stated that several factors contribute to a high cost to perform HRD testing on tumour tissue. These include additional histopathological review of tumour samples, HRD assays are made in smaller quantities resulting in higher cost, and the need for a greater sequencing depth than for a germline test.

At its August 2021 meeting, PASC considered that the current MBS item for detection of tumour BRCA1/2 *pathogenic variants to determine eligibility for olaparib on the PBS (item 73301) could be replaced by a new item (or amended) to detect homologous recombination deficiency, including* BRCA1 *or* BRCA2 *pathogenic variants to determine eligibility to (a) access olaparib for Populations 1 and 3 or (b) access the combination of bevacizumab and olaparib for all HRD positive patients*

comprising Population 2. However, PASC considered that if the sequential testing approach is accepted, item 73301 could be retained and a new item developed for tumour HRD testing following a negative tumour BRCA1/2 *test.*

*PASC also considered that the item descriptor should specify that proposed test also uses a genomic instability score to differentiate it from germline testing of non-*BRCA1/2 *genes in HRD pathway. As indicated above, PASC confirmed a preference for the item descriptor to be agnostic to the type of HRD test (subject to acceptance of sufficient concordance) and for it not to include the threshold value for any test result in order to avoid confusing eligibility for the test with eligibility for treatment.*

Consultation feedback

Three consultation surveys were received for April 2021 PASC consideration: one from a pathology service provider, one from a pathology professional organisation, and one from a consumer group. The consumer group was supportive of the application.

At its April 2021 meeting, PASC noted that the remaining consultation feedback raised concerns that:

- the proposed service (HRD testing) is in development and is not well defined;
- the proposed service should be compared to the evidentiary standard; and
- the clinical utility of HRD tests needs to be established.

The pathology service provider highlighted that specialist genetic follow-up is required for some patients. The pathology professional organisation provided a rationale for the higher cost associated with HRD testing.

Consultation feedback, not considered by PASC in April 2021 due to its late receipt, was received from two pathology providers: Queensland Cancer Clinical Network and Queensland Cancer Genomics Steering Committee (referred to as Queensland Genomics) and Australian Genomics; and one network of genomic cancer medicine centres (Omico, Australian Genomic Cancer Medicine Centre). This late consultation feedback was generally supportive of the proposed intervention, noting the unclear description of the proposed test in the application. However, the feedback highlighted the complexity of the concept of HRD. This included:

- Several approaches to testing HRD with the original application not clearly specifying the type of HRD test. The other measures include:
  - pathogenic variants in somatic HRD genes;
  - pathogenic variants in non-*BRCA1/2* germline HRD genes;
  - evaluation of a genomic scar; or
  - a combination of the above.

Consultation feedback provided varied comments about the timing of HRD testing. Queensland Genomics and RANZCOG (in its response to PASC questions) stated that tumour HRD testing should occur at the same time as *BRCA1/2* testing. Queensland Genomics advised that this is to limit the need to use and access tissue, however, the result is only needed after initial chemotherapy.

Australian Genomics considered the proposed MBS fee should be considered in the context of the current published price of the Myriad HRD test (US$4,040).

The consultation feedback also advocated for subsiding a gene panel that includes HRD genes. Queensland Genomics and Omico advocated for reflex testing of germline HRD genes.

The Department has requested further targeted consultation from RANZCOG (Attachment 4).

At its August 2021 meeting, PASC noted that seven organisations had provided consultation feedback. This included: one pathology service provider, one professional college, one pathology professional college, three state or national genomics networks and one consumer group.

PASC noted that the consultation feedback advised the HRD can occur due to pathogenic variants in non-BRCA1/2 gene and that some patients may be tested for this as a part of a gene panel.

PASC noted the following feedback from NPAAC:

- *Main issue is validation of any HRD test for clinical utility.*
- *No single source of truth for such multivariant index assays (MVA); tests are not equivalent; each requires evidence of clinical utility.*
- *If the test is not approved by the TGA, they are regarded as an in-house IVD subject to requirements in NPAAC standards.*
- *Laboratories that want to offer this test send tissue to overseas companies (presumably at patient expense).*
- *There is no quality assurance program for these tests in Australia or overseas.*

According to NPAAC, MVA "provides a result whose derivation is non-transparent and cannot be independently derived or verified" and "validation, verification and documentation of the algorithm in relation to clinical utility of the assay must be subject to the same level of rigor as other analytical aspects of the assay".

Next steps

The applicant advised that it intends to lodge an integrated codependent submission or ADAR (applicant-developed assessment report) in ***REDACTED****.*

Following the August 2021 PASC meeting, the applicant clarified that ***REDACTED****. PASC advised out-of-session that the assessment report will need to present a comparison of the concordance and particularly discordance between the evidentiary standard and the* ***REDACTED*** *HRD assay (HRD test 2, a HRD assay similar to the HRD assay used in the PAOLA-1 study) to be used in Australia to determine HRD (and BRCA1/2) status.*

In addition, following the August 2021 PASC meeting, the applicant provided additional information about the ***REDACTED*** *that will be used to provide the* ***REDACTED*** *HRD assay (HRD test 2) in Australia:* ***REDACTED****. (The redacted text refers to additional information about how HRD test 2 will be provided in Australia).*

Applicant Comments

Population

As mentioned in the previous Pre-PASC PICO confirmation document (for the second PASC consideration), AstraZeneca has an agreement in place with the ***REDACTED*** *laboratory to develop and validate an HRD assay that will identify the equivalent patient population as in PAOLA-1.*

REDACTED*. However, dependent on the progress of the local validation and concordance data to meet the MSAC requirements, only one HRD test will be included in AstraZeneca's codependent submission.*

Intervention

At the August 2021 PASC meeting the PASC considered there were three populations that could be considered for HRD testing.

*Population 1****:*** *Patients with newly diagnosed, advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. This population would have HRD testing for BRCA1/2 variant and GIS in parallel at diagnosis. This is AstraZeneca's proposed test population.*

The following Populations 2 and 3 were identified by PASC.

Population 2: Similar to Population 1 at diagnosis, but is contingent on sequential HRD testing, that is testing for GIS would occur sequentially following a negative BRCA1/2 test result.

Population 3: Also contingent on sequential HRD testing would occur in patients who have received bevacizumab as part of initial first-line platinum-based chemotherapy regimen. The PICO document points out that this population is consistent with those enrolled in PAOLA-1 (page 11 above). The PAOLA1 study was a maintenance study in an untested population. Entry criteria required a patient to be able to provide a tumour tissue for tumour BRCA1/2 testing. HRD status was determined retrospectively to enable subgroup analysis.

AstraZeneca has previously discussed why GIS and BRCA testing should occur in parallel at diagnosis, with this approach in line with how clinicians view testing of biomarkers such as HRD at diagnosis is critical to making optimal treatment decisions. Most importantly, testing at diagnosis guides treatment decisions rather than taking an approach whereby a treatment guides testing (as proposed in Population 3).

AstraZeneca's approach was supported by feedback received as part of the PASC consultation from Queensland Genomic and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), whom considered that HRD tumour testing should occur at the same time as BRCA testing.

HRD testing upfront at diagnosis provides two results: BRCA and GIS. The clinicians gain timely comprehensive clinical information to generate a treatment plan. This may also result in treatment sparing decisions.

For patients the value of knowing earlier allows them to be prepared and informed to manage their expectation of their disease and treatment. Patients face many decisions concerning their treatment, which are extremely intimidating. Testing upfront at diagnosis provides patients time to consider all critical information and the opportunity to prepare prior to starting treatment.

Sequential test will significantly impact more patients by the following:

- *Delays treatment due to further counselling with clinicians to seek informed test consent, test turnaround time*
- *Risk in adequate tumour tissue available for second test. Flow-on effect to patients include re-test anxiety and false expectation of a treatment option if testing Is not possible. First-line treatment with chemotherapy is also known to adversely affect tumour tissue integrity and DNA quality potentially resulting in compromised HRD analysis.*

Sequential testing is not practical for pathologists. As discussed previously by the Clinical expert at the PASC meeting, there may not be adequate tumour tissue to conduct sequential testing. Sequential testing results in duplication of processes to prepare the tumour tissue for testing and is not efficient. Parallel testing of BRCA and GIS conserves tumour tissue samples, promotes testing efficiency as tissue preparation occurs only once rather than twice if testing is conducted separately. It is also possible that multiple laboratories will need to be involved in this process. That is the parent laboratory holding the tumour tissue will need to send to a molecular laboratory (2nd lab) who performs tumour BRCA testing who will need to send to a 3rd lab (i.e. ***REDACTED****) to perform HRD testing. This process is inefficient, labour intensive and more expensive for patients who undergo both tests.*

However, to demonstrate that testing BRCA and GIS in parallel is the most cost-effective approach to the Commonwealth, AstraZeneca will also evaluate the cost-effectiveness of testing BRCA and GIS sequentially to inform MSAC and PBAC decision making.

Comparator

AstraZeneca acknowledges the remaining issues identified at the PASC meeting as documented above, these issues will be addressed in the upcoming codependent submission to MSAC and PBAC.

Outcomes

AstraZeneca agrees with the proposed outcomes.

Proposed Item Descriptor

The Applicant is aware of its requirement to provide a cost for HRD testing and associated assessment of budget impact, and commits to doing so as part of the preparation of the Applicant Developed Assessment Report for consideration by MSAC. The codependent submission to MSAC and PBAC will consider only one HRD test with the appropriate test cost included as part of the evaluation.

AstraZeneca is in agreement with PASC that the MBS descriptor should be agnostic to the type of HRD test (subject to acceptance of sufficient concordance) and for it not to include the threshold value for any test result in order to avoid confusing eligibility for the test with eligibility for treatment.

Consultation Feedback

AstraZeneca welcomes the consultative feedback received at the April/August PASC considerations and aims to address the concerns raised in the upcoming codependent submission to MSAC and PBAC.

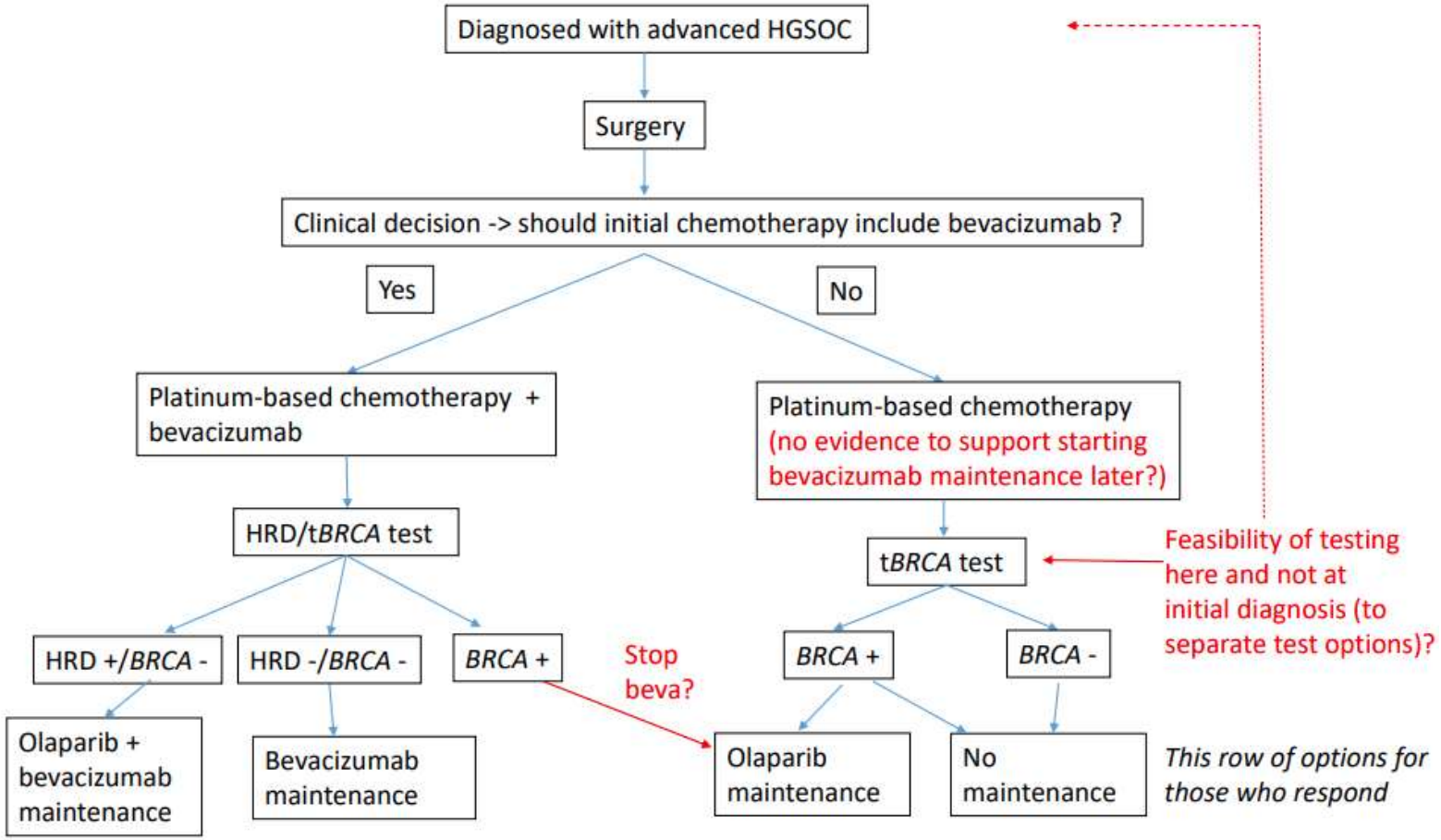

Figure 6: Alternative clinical treatment pathway with proposed medical service – HRD test (includes *BRCA1/2* status and a measure of genomic instability to assess homologous recombination deficiency - HRD)

Abbreviations: HGSOC = high-grade serous ovarian cancer; HRD = homologous recombination deficiency

Attachment 2

A more detailed description of the Myriad myChoice® test was provided in Southwest Oncology Group [SWOG; 2018], where the HRD score was defined as the unweighted sum of LOH, TAI and LST measured on a scale from 0-100. The definitions of the three components were as follows: (1) LOH score is the number of LOH regions of intermediate size (>15 Mb and <whole chromosome), (2) LST score is the number of chromosome breaks points (translocations, inversions or deletions) in adjacent segments of DNA of at least 10Mb and (3) TAI score is the number of regions with allelic imbalance which extend to the subtelomere but do not cross the centromere. The citation also provides the following information "The HRD assay is a next generation sequencing assay that targets ~54,000 SNPs [single nucleotide polymorphisms] which are evenly dispersed across the human genome. A by-product of this assay is the generation of 400 bp [base pair] of sequence flanking each SNP location, resulting in a total of 21 Mb [megabases] of genome sequencing data from each tumor sample analyzed. By cataloging the frequency of microsatellite repeat mutations and random somatic mutations within this 21 Mb of sequence data we are able to identify tumors with MSI [microsatellite instability] or high somatic mutation burden due to underlying defects independent of MMR [mismatch repair] defects. In addition, the assay directly targets 43 genes known to be involved in DNA damage repair pathways and/or tumorigenesis, allowing the identification of both germline and somatic mutations within these genes (*AKT1, ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, CTNNB1, ERCC4, FAM175A, FANCA, FANCD2, FANCE, FANCI, FANCL, KRAS, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PIK3CA, PPP2R2A, PTEN, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54B, RAD54L, RPA1, TP53, TP53BP1, XRCC2, XRCC3*). Finally, hypermethylation of the *BRCA1* promoter has been proposed as a mechanism for *BRCA1* epigenetic inactivation, and will be evaluated in this assay".

Of the genes listed, at least *BRIP1* [Weber-Lassalle 2018] and *RAD51B* [Golmard 2013] can be germline inherited and confer an increased risk of ovarian cancer.

Attachment 3

The supplemental appendix to Telli [2016] stated: "TAI, LST, and LOH were calculated as described by Timms [2014][2], which includes modifications from the initial reporting of TAI and LST calculations. For samples analyzed by MIP assay, allele intensities from CEL files were used to generate allelic imbalance profiles. A hidden Markov model (HMM) was used to define regions and breakpoints with these profiles. Allele specific copy number (ASCN) for each of the regions was determined using an algorithm similar to that described by Popova [2012]. TAI (number of regions of allelic imbalance that extend to one of the subtelomeres but do not cross the centromere) and LST (number of break points between regions longer than 10 Mb [megabases] after filtering out regions shorter than 3 Mb) scores were calculated using the allelic imbalance profiles, while LOH (number of subchromosomal LOH regions longer than 15 Mb) was calculated using ASCN. To calculate the HRD score based on SNP [single-nucleotide polymorphisms] data, noise to signal ratio (NSR) for SNP data was used as a quality metric. Noise was calculated as the standard deviation of allele dosage for informative SNPs (SNPs that are heterozygous in normal DNA). Signal was calculated as the weighted average of the difference in allele dosage between adjacent regions with weights defined as 1/S1+1/S2, where S1 and S2 are sizes of the adjacent regions. By comparing HRD scores between samples run in duplicate, a cutoff of 0.85 for NSR was established. Samples with NSR below 0.85 were considered passing HRD scores."

[2] https://github.com/luntergroup/octopus.*tail. Allelic specific copy number at each SNP location was described as being determined using the algorithm described in Popova [2012]. The 'Material and Methods in Additional File 1' of Timms [2014] reported to provide a description of the HRD scores, this document could not be sourced.*

Attachment 4

Letter to Royal Australian and New Zealand College of Obstetricians and Gynaecologists (excerpt)

Following its April 2021 ratification of a PICO Confirmation document for this application, the PICO Advisory Sub-Committee (PASC) of MSAC has requested the Department seek input from professional groups to clarify the following:

- The preferred definition of the eligible population, with consequences for the definition of the test interventions and the test comparators.
- The current and proposed clinical management algorithms. Specifically focusing on the role of bevacizumab and on no maintenance after response ("watch and wait").
- The definition of several possible HRD testing methods that may become available as alternative options in Australia, but may be measuring different types of genomic aberrations. As such, these tests would seem unlikely to identify equivalent patients as being eligible or not for the proposed combination of medicines.

PASC has requested further guidance about how patients with high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (HGSOC) are currently managed and how they would likely be managed with the proposed test and treatment options.

Could RANZCOG clarify when patients typically have *BRCA* testing in relation to diagnosis, surgery, and first-line platinum-based chemotherapy? For example is *BRCA* testing typically performed at initial diagnosis or is *BRCA* testing typically performed following surgery?

Is bevacizumab generally started in combination with chemotherapy and continued as maintenance therapy? Our understanding was that Australian practice would be informed by the relevant clinical trials (ICON-7, GOG-0218 and recently PAOLA-1) where bevacizumab was started with chemotherapy, and then maintained as appropriate. Is bevacizumab ever started as maintenance if it has not been started with chemotherapy? When do clinicians decide whether a patient is suitable for bevacizumab? What are some reasons that would make a patient unsuitable for bevacizumab? Does the choice to start bevacizumab differ based on *BRCA* status?

The PICO currently has three options for patients who respond to first-line platinum-based chemotherapy: olaparib maintenance therapy (for *BRCA* positive patients), bevacizumab maintenance therapy, and "watch and wait". PASC requested further advice on how frequently the "watch and wait" strategy is used in current practice.

The application has proposed that all patients who respond to first-line platinum-based chemotherapy and are *BRCA* positive will receive olaparib monotherapy as maintenance. Does this reflect current practice for patients who started bevacizumab with chemotherapy, specifically that the bevacizumab would be stopped (and not continued as maintenance) and olaparib maintenance started instead?

PASC discussed the possibility of patients who are *BRCA* positive also being considered for combined maintenance treatment with olaparib + bevacizumab after a response to the chemotherapy as clinical benefits for this population were demonstrated in the PAOLA-1 trial. We would appreciate RANZCOG's advice whether, for *BRCA* positive patients who started bevacizumab with chemotherapy, consideration be given to the option of combined maintenance with olaparib +

bevacizumab. Further, would consideration be given to starting both bevacizumab and olaparib maintenance in this situation, even if such an option would not be based directly on the pre-maintenance regimen in the PAOLA-1 trial? Or, for these two scenarios, would maintenance with olaparib monotherapy be considered sufficient as proposed in the application?

With respect to HRD testing and its relationship with *BRCA* testing, the application has proposed that all patients who respond to first-line platinum-based chemotherapy and are *BRCA* negative and HRD positive will receive combined maintenance treatment with olaparib + bevacizumab. PASC discussed several options:

- Whether *BRCA* and HRD testing should be conducted as a combined single test. The benefits of the approach were more efficient pathology laboratory processes requiring less tumour sample and resulting in shorter turnaround times for test results.
- Whether HRD testing could be conducted sequentially – after a negative *BRCA* test result. PASC noted that this may result in less efficient pathology laboratory processes, including delays as samples may need to be sent to a different laboratory for HRD testing.
- Whether combined *BRCA* and HRD testing should be limited to patients who have started platinum-based chemotherapy in combination with bevacizumab with a view to potentially continue bevacizumab as maintenance therapy and possibly add olaparib as maintenance therapy. This would reduce the number of patients who would need to be tested using the more expensive combined *BRCA* and HRD test. PASC considered that wider consultation is needed on the appropriateness and feasibility of this option in clinical practice. This is because the other main consequence of this option, if adopted, would be that this testing would have to occur after starting this initial regimen with the results of the test used to help decide whether olaparib should be added to bevacizumab in the maintenance setting. It also opens the option of ceasing bevacizumab as maintenance and starting olaparib as maintenance, which would align with the applicant's intent. Please see the diagram attached for an illustration of this alternative, and some of the issues that it raises. We would appreciate RANZCOG's advice on the appropriateness and feasibility on this option.

PASC also requested further consultation of the following outstanding issues:

- The definition of several possible HRD testing methods that may become available as alternative options in Australia, but may be measuring different types of genomic aberrations. As such, these tests would seem unlikely to identify equivalent patients as being eligible or not for the proposed combination of medicines.
- The lack of full transparency regarding how HRD positivity is determined in the test in the PAOLA-1 trial, including whether the nominated threshold HRD (GIS) score of 42 is performing as intended and what the consequences of this variation might be for predicting the size of the population eligible for the proposed combination of medicines and for predicting the variation in the effectiveness of this combination.

We would greatly appreciate RANZCOG's views on the options for *BRCA* and HRD testing, particularly the feasibility of the third option.

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