Australian Government

Department of Health

MSAC Application 1658 (July 2021 update)

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

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/A
Corporation name: AstraZeneca Pty Limited
ABN: 54009682311
Business trading name: AstraZeneca Pty Limited

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Testing of tumour tissue to determine a positive homologous recombination deficiency (HRD) status in a woman with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Ovarian cancer is the eighth most commonly diagnosed type of cancer for women in Australia, with an estimated 1532 new cases in 2020. The 5-year relative survival for women with ovarian cancer in Australia is low at 46%%. (Cancer Australia 2020). The most common and most aggressive histological subtype is high-grade serous ovarian cancer (HGSOC) with poor prognosis. Most women are diagnosed when their disease is advanced and widespread.

There are a multitude of known risk factors for ovarian cancer, including genetic background. Homologous recombination deficiency is one such risk factor, known to occur in as many a 50% of ovarian cancer cases. Variants in the BRCA 1 or BRAC 2 genes are particularly known to be associated with an increased risk and predisposition to hereditary ovarian cancer. Approximately 25%-29% of overall ovarian cases are BRCA. Non BRCA HRD variants are also associated with risk of ovarian cancer, and are thought to contribute 6% to 27% of genetic risk (Norquist et al 2016, Walsh et al 2011). Prognosis varies with BRCA status, as BRCA wild-type (BRCAwt) patients have significantly worse progression-free and overall survival than BRCA patients (Xu et al 2017).

Cytoreductive surgery and platinum-based chemotherapy are the standard care treatments for women newly diagnosed advanced ovarian cancer.

Although the goal of first-line treatment is to achieve long term remission, approximately 70% of women with advanced disease who initially respond to first-line chemotherapy will eventually relapse and require re-treatment. Once ovarian cancer relapses, the disease becomes largely incurable. The emergence of PARPi inhibitors, such as olaparib has changed the treatment landscape of advance ovarian cancer with respect to maintenance therapy. Currently olaparib is reimbursed as maintenance treatment in women newly diagnosed with advanced (FIGO Stage III-IV) BRCA mutated ovarian cancer.

However, BRCAwt patients represent a substantial population still in need of more efficacious maintenance strategies at this stage.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

HRD is caused by impaired DNA repair mechanisms, such as BRCA pathogenic gene variant which are considered to be a primary driver of ovarian cancer. All women with a BRCA mutation are HRD positive, but BRCA pathogenic gene variant is not the only cause of HRD. Deficiencies in HRD are predictive for response to PARP inhibitors such as olaparib, and testing tumour tissue for HRD at diagnosis can identify all patients with HGSOC likely to achieve a treatment benefit with PARP inhibitors. Therefore, it is proposed that HRD testing of tumour tissue will replace currently available BRCA testing of tumour tissue.

This application requests a new MBS item for HRD testing which will detect HRD; which includes a measure of genomic instability (GIS) and BRCA status in patients with advanced ovarian cancer to determine eligibility for treatment with olaparib in combination with bevacizumab. Olaparib is currently listed on the PBS for treatment of ovarian, fallopian tube or primary peritoneal cancer with BRCA mutations and there are currently MBS items to detect BRCA gene variant status to determine eligibility for olaparib treatment (MBS items 73295, 73301).

However, recent evidence shows that women who have HRD positive, BRCAwt ovarian cancer would also benefit from treatment with olaparib in combination with bevacizumab.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

Currently MBS item 73301 exist for testing of tumour tissue and item 73295 for testing blood to detect somatic or germline BRCA1 or BRCA2 pathogenic gene variants, in women with newly diagnosed advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

No other source of funding for tumour testing to determine HRD status other than the MBS is sought, however in this co-dependent submission public funding for PBS access to olaparib in women with a positive HRD status is also being sought.

(g) If yes, please advise:

Not applicable

7. What is the type of service:

☒ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☒ Co-dependent technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

Only women with a HGSOC BRCA1 or BRCA2 pathogenic gene variants (somatic and germline) are currently eligible for PBS olaparib (PBS Items 12157W, 12170M, 12161C, 12169L, 11528R, 11522K, 11539H, 11503K).

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: LYNPARZA®
Generic name: Olaparib
As monotherapy or in combination with;
Trade name: AVASTIN®
Generic name: Bevacizumab

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☒ No

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☒ No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☒ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single or multi-use consumables for in-house developed IVD assays would be kits which may be used for DNA extraction or quality assurance, or any kit for PCR amplification methods.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Pharmaceutical product: LYNPARZA® (olaparib)
Manufacturer's name: AstraZeneca Pty Ltd
Sponsor's name: AstraZeneca Pty Ltd

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: **REDACTED**
Sponsor's name: **REDACTED**

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☐ Yes (if yes, please provide details below)
☒ No

Whilst HRD testing is not currently performed in Australia, a local pathology laboratory (**REDACTED**) is developing a HRD test which includes two assays performed simultaneously to identify HRD status: BRCA mutation analysis and GIS. **REDACTED** is currently undertaking additional experiments to assess the performance of the test. It is intended that validation and concordance results against the evidentiary standard will be conducted with the results provided in the **REDACTED** co-dependent submission. Please refer to Attachment 1 with updated information on the **REDACTED** locally developed test.

In addition, AstraZeneca understands that **REDACTED.** *(The redacted text refers to the potential Australian provision of a HRD assay which is similar to the HRD assay utilised in the PAOLA1 study (Myriad® myChoice HRD Plus assay). This test is available overseas but is not currently performed in Australia and not included in the ARTG).*

The co-dependent pharmaceutical product Lynparza® (olaparib) is currently registered on the ARTG with the following ARTG details:

ARTG ID: 288614 Lynparza 150mg tablets
ARTG ID: 288613 Lynparza 100mg tablets

TGA approved indications for olaparib are as follows:
Ovarian Cancer
Lynparza® is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced BRCA-mutated (germline or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. BRCA mutation status should be determined by an experienced laboratory using a validated test method.
- maintenance treatment of adult patients with platinum-sensitive relapsed high grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.

Breast Cancer
Lynparza® is indicated as monotherapy for the:

- treatment of adult patients with germline BRCA-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.

The co-dependent PBAC/MSAC submission will request PBS funding for olaparib as in combination with bevacizumab in patients identified with a positive HRD and BRCAwt status. Applicable to this application the ARTG for bevacizumab is as follows:

ARTG: 99757 Avastin 400 mg/16 ml injection vial
ARTG: 99755 Avastin 100 mg/4 ml injection vial

The TGA approved indication for bevacizumab applicable to this application are as follows:

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
Avastin (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.
Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
Avastin (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

Avastin (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☒ Yes (please provide details below)
☐ No

The TGA approved indication applicable to this application is as follows:

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 BRCA mutation (germline or somatic), and/or

- genomic instability HRD status should be determined by an experienced laboratory using a validated test method.

The TGA has specified that HRD status to be determined by a validated test without referencing a threshold to determine positivity. HRD thresholds are specific to a test and therefore has not been proposed in the MBS descriptor, PBS listing or restrictions. This is to enable other validated locally performed HRD assays (BRCA and GIS) to be utilised and funded on the MBS.

REDACTED

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Not applicable

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Comparative diagnostic study based on randomised phase 3, double-blind, placebo-controlled trial	PAOLA-1: An ENGOT/GCIG phase III trial of olaparib versus placebo combined with bevacizumab as maintenance treatment in patients with advanced ovarian cancer following first-line platinum-based chemotherapy plus bevacizumab.	Comparative efficacy and safety of a PARP inhibitor with bevacizumab as first-line maintenance therapy in patients regardless of BRCAm status. BRCAm tested using Myriad myChoice®HRD Plus assay which includes BRCA testing. Presence of tumour BRCAm or a myChoice®HRD Plus test score of ≥42 classified a patient as HRD positive. Tumour BRCA status required prior to randomisation. From the total population of 806, 387 (48%) were HRD+ (ie tumour BRCA or HRD test score > 42) of which 152 HRD+non-tumour BRCA and 235 (19%) tumour BRCA.	Initial publication https://www.nejm.org/doi/full/10.1056/fklfdlsxdlnejmoa1911361	December 2019
2.	Comparative diagnostic study based on randomised phase 3, double-blind, placebo-controlled trial	Homologous recombination deficiency (HRD) score and niraparib efficacy in high grade ovarian cancer	The therapeutic potential of PARP inhibitors is predicted to extend beyond BRCA mutant (BRCA(mut)) phenotypes to homologous recombination deficient (HRD) cancers. Niraparib treated patient-derived tumour graft models selected from these primary ovarian tumours were utilized to evaluate the correlation between HRD score, BRCA deficiency, platinum sensitivity and niraparib anti-tumour response. The HRD analysis is a DNA-based assay that is capable of detecting homologous recombination deficiency independent of its aetiology. Genome-wide SNP data was generated from a custom Agilent SureSelect XT2 capture followed by sequencing on an Illumina HiSeq2500. SNP data was analysed using all three algorithms; Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI) and Large-scale State Transitions (LST). The final HRD score is the sum of the LOH+TAI+LST scores with numerical outputs ranging from 0- 100. 106 High grade tumours were evaluated for HRD, BRCA and RNAseq analysis	Follow-up publication https://www.embase.com/search/results?subaction=viewrecord&id=L71734290&from=export	November 2014

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Comparative diagnostic study based on randomised phase 3, double-blind, placebo-controlled trial	Prospective molecular identification of ovarian cancer patients benefiting from PARP inhibitor (PARPi, rucaparib) maintenance therapy-reaching beyond germline BRCA mutations	Two clinical trials used to develop a HRD algorithm. First, ARIEL2(NCT01891344) is a phase 2 trial of rucaparib which aims to identify a molecular HRD signature that predicts response to treatment. The signature will be applied prospectively to the final analysis of the Phase 3 pivotal trial ARIEL3 (NCT01968213) in a similar population. ARIEL2 (n=180) is an ongoing, single-arm, open-label biomarker study designed to refine the molecular signature associated with a response to rucaparib. ll pts undergo a pre-dose biopsy and provide archival tumour tissue. Tumour tissue HR status is assessed using Foundation Medicine's next generation sequencing (NGS) platform and University of Washington's BROCA-HR panel, with the current HRD algorithm developed using in vitro/in vivo and TCGA (and similar) bioinformatic data. The optimised algorithm will be tested prospectively in ARIEL 3 (n=540).	Follow-up publication https://www.embase.com/search/results?subaction=viewrecord&id=L71718484&from=export https://cancerres.aacrjournals.org/content/74/19_Supplement/CT339	October 2014
4.	Comparative diagnostic study based on randomised phase 3, double-blind, placebo-controlled trial	Niraparib therapy in patients with newly diagnosed advanced ovarian cancer (PRIMA/ENGOT-OV26/GOG-3012 study)	This study evaluated the efficacy of niraparib in pts (N= 733) with newly diagnosed advanced OC after completion of first-line (1L) CT regardless of BRCA status. Stratification factors were best response to the 1L CT regimen (CR/PR), receipt of neoadjuvant CT (NACT; yes/no), and homologous recombination deficiency (HRD) status (positive/negative/unknown) per the Myriad myChoice HRD test. Niraparib-treated pts in the HRDpos subgroup and overall population had a significant reduction in the risk of disease recurrence or death with a substantial improvement in PFS. Patient randomised prior to study, of the 733 patients (niraparib 489, placebo 246), 373 (51%) were HRD positive.	Initial publication https://www.sciencedirect.com/science/article/pii/S0923753419604126?via%3Dihub	October 2019

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
5.	Comparative diagnostic study based on randomised phase 2, double-blind, placebo-controlled trial	Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes.	Exploratory analyses, including the long-term outcome of candidate biomarkers of sensitivity to olaparib in *BRCA* wild-type (*BRCA*wt) tumours based on Study 19 (D0810C00019; NCT00753545). Tumour samples from an olaparib maintenance monotherapy trial were analysed. Analyses included classification of mutations in genes involved in homologous recombination repair (HRR), *BRCA1* promoter methylation status, measurement of BRCA1 protein and Myriad HRD score. Study 19 included 265 patients randomised prior to Study. Subgroup analyses included 136 patients with a BRCA1/2m and 118 patients with wild-type BRCAm	Follow-up publication https://www.nature.com/articles/s41416-018-0274-8	October 2018
6.	Exploratory analysis based on comparative randomised phase 3, double-blind, placebo controlled trial.	DNA repair deficiencies in ovarian cancer: Genomic analysis of high grade serous ovarian tumours from the NOVA study.	Genome wide analysis was conducted on tumours obtained from patients enrolled in the NOVA study, a phase 3 clinical trial evaluating the PARP inhibitor niraparib as a maintenance treatment in patients with platinum sensitive ovarian cancer. Homologous recombination deficiency (HRD), sequence analysis of 43 genes involved in DNA damage response and other measures of genomic instability were evaluated. BRCAm and HRD score obtained from 174 samples (68, gBRCAm and 106 non-gBRCAm) In the non-gBRCA	Follow-up publication https://www.embase.com/a/#/search/results?subaction=viewrecord&id=L72066921&from=export	September 2015
7.	Diagnostic study	Homologous recombination deficiency status-based classification of high-grade serous ovarian carcinoma	This study obtained data from The Cancer Genome Atlas (TCGA) on HGSOC and identified scores for the loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions, and calculated the HRD score. The authors investigated the relationships among the score, genetic/epigenetic alterations in HRR-related genes, and the clinical data. N=1257 combined breast and ovarian cases	Initial publication https://www.nature.com/articles/s41598-020-59671-3	October 2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
8.	Diagnostic study	Association of BRCA1/2defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes	This study examines the frequency of BRCA1/2 defects among different breast cancer subtypes, and the ability of the HRD scores to identify breast tumours with defects in the homologous recombination DNA repair pathway. HRD algorithm included in the study as follows: HRD-model= 0.11xHRD-LOH + 0.25xHRD-TAI + 0.12xLST N=215 breast tumour samples included in analysis	Initial publication https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-014-0475-x	December 2014
9.	Diagnostic study	Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer.	This study assessed a combined homologous recombination deficiency (HRD) score, an unweighted sum of LOH, TAI, and LST scores, in three neoadjuvant TNBC trials of platinum-containing therapy. We then tested the association of HR deficiency, defined as HRD score ≥42 or BRCA1/2 mutation, with response to platinum-based therapy. Cohort based on 497 Breast and 561 ovarian chemotherapy-naïve tumours with know BRCA1/2 status	Initial publication based on published clinical trials (NCT00148694, NCT00580333, NCT00813956) https://doi.org/10.1158/1078-0432.ccr-15-2477	March 2016
10.	Review	Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers.	The authors propose the integration of a genomic scar-based biomarker with a marker of resistance in a high genomic scarring burden context may improve the performance of any companion diagnostic for PARP inhibitors.	Initial publication https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr3670	June 2014
11	Review	ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer	To define best practice for HRD testing in HGSC the ESMO Translational Research and Precision Medicine Working Group launched a collaborative project that incorporated a systematic review approach. The main aims were to (i) define the term 'HRD test'; (ii) provide an overview of the biological rationale and the level of evidence supporting currently available HRD tests; (iii) provide recommendations on the clinical utility of HRD tests in clinical management of HGSC.	Initial publication https://www.annalsofoncology.org/article/S0923-7534(20)42164-7/fulltext	September 2020

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

REDACTED

20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

As above

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

REDACTED

22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

HRD testing is not currently available in Australia. A similar test is tumour BRCA testing which is established and MBS funded in Australia.

REDACTED

Myriad MyChoice® and Foundation Medicine®. Both have a commercial HRD approved test which is only available overseas.

REDACTED *(The redacted text refers to the potential Australian provision of a HRD assay which is similar to the HRD assay utilised in the PAOLA1 study (Myriad® myChoice HRD Plus assay). This test is not currently performed in Australia).*

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Ovarian cancer is the eighth most commonly diagnosed type of cancer for women in Australia, with an estimated 1532 new cases in 2020. The 5-year relative survival for women with ovarian cancer in Australia is low at 45% (Cancer Australia 2020) . Ovarian cancer is estimated as the 6th highest cause of cancer related deaths for women in Australia in 2020, with 1068 deaths.

The most common and most aggressive histological subtype of ovarian cancer is high-grade serous ovarian cancer (HGSOC). Cancer of the fallopian tubes or primary peritoneal cancer also frequently shows similar serous features and is usually treated as for ovarian cancer.

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 women are diagnosed when their disease is advanced and widespread. Most women 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 ovarian cancer is platinum-based chemotherapy (Cancer Australia 2014). Ovarian cancer is a highly chemo-sensitive tumour, but more than 70% of women with advanced disease initially responding to first-line chemotherapy will relapse and require re-treatment within the first three years of diagnosis (Lederman et al 2013). Subsequent treatment options for patients with relapsed HGSOC involve repeat courses of platinum-based chemotherapy, with ever-decreasing treatment-free (remission) intervals.

Over the past decade, the most important improvement of established systemic first-line treatment with platinum-taxane chemotherapy has been the introduction of novel targeted therapies in the front-line setting. Ovarian cancer is a highly vascular tumour markedly elevated serum VEGF levels have associated with advanced stage ovarian cancer, high-grade histology, increased incidence of metastases, occurrence of large volume ascites and decreased survival (Tomao et al 2013). The VEGF inhibitor, 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.

In addition to being a VEGF responsive tumour, the high prevalence of homologous recombination repair (HRR) deficiency in high-grade epithelial ovarian cancer provides a strong rationale for targeted treatment with poly-adenosine 5’ diphosphoribose polymerase (PARP) inhibitors in this patient population (Konstantinopoulos et al 2015). Olaparib, a potent PARP inhibitor, exploits deficiencies in deoxyribonucleic acid (DNA) repair pathways to preferentially kill cancer cells with these deficits compared to normal cells.

Pre-clinical data have suggested 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 HRR (Bindra et al 2004, Bindra et al 2005, Bindra et al 2007, Glazer et al 2013, Kaplan et al 2019).

There are a multitude of known risk factors for ovarian cancer, including genetic background. Homologous recombination deficiency is one such risk factor, known to occur in as many a 50% of ovarian cancer cases. Variants in the BRCA 1 or BRAC 2 genes are particularly known to be associated with an increased risk and predisposition to hereditary ovarian cancer. Approximately 25% of overall ovarian cases are BRCA. Non BRCA HRD variants are also associated with risk of ovarian cancer, and are thought to contribute 6% to 27% of genetic risk (Norquist et al 2016, Walsh et al 2011). Prognosis varies with BRCA status, as BRCA wild-type (BRCAwt) patients have significantly worse progression-free and overall survival than BRCAm patients (Xu et al 2017).

In a meta-analysis of data from 18,396 patients with ovarian cancer, OS and progression free survival (PFS) were significantly better in BRCAm patients compared to BRCAwt, with HRs of 0.67 (95% CI 0.57, 0.78; p<0.001) and 0.62 (95% CI 0.53, 0.73; p=0.261), respectively (Xu 2017). This was consistent irrespective of study quality, tumour stage, study design, sample size, number of research centres, duration of follow-up, adjusted baseline characteristics and tumour histology. However, this study did not investigate or adjust for any treatment effect.

Given BRCAwt patients represent a substantial proportion of the AOC population (up to 75%), the above data highlight the unmet need for more efficacious treatments for patients regardless of BRCA status and specifically BRCAwt patients to increase their OS and PFS compared to current rates in line with *BRCA*m.

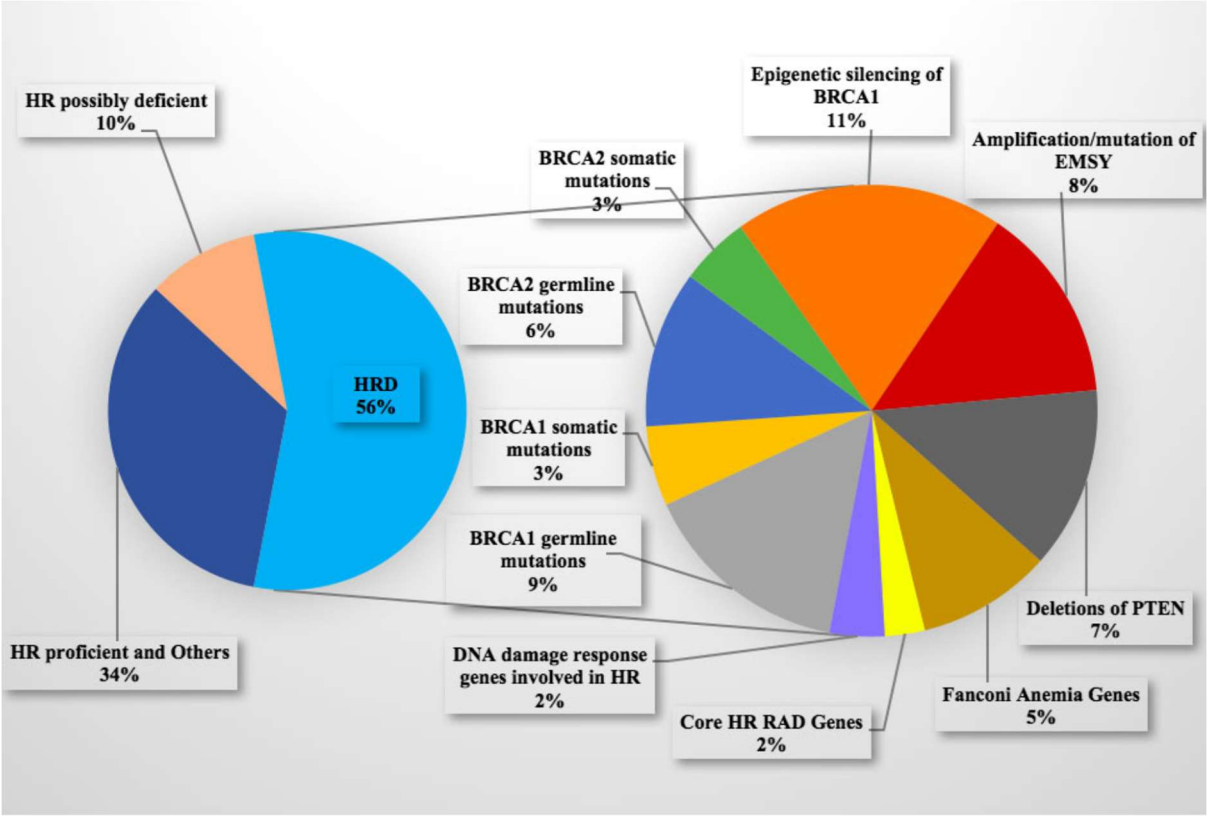
Therefore, the target population for treatment in the upcoming co-dependent submission are HGSOC patients with a HRD positive, BRCAwt status.

HRD carcinomas exhibit an increased responsiveness to chemotherapy, especially platinum based agents in different treatment lines. (Bonadio et al 2018). Platinum agents act via directly damaging DNA, and when HRD is present, the reduction of DNA repair increase the accumulation of DNA damage, leading to apoptosis. Pennington et al (2014) showed that somatic BRCA1/2 pathogenic gene variants and variants in other HR genes predict platinum responsiveness and positively impact overall survival, similar to germline BRCA 1 or 2 pathogenic gene variants. PARP inhibitors in patients with HRD compromises two pathway of DNA repair, resulting in synthetic lethality (Bonadio et al 2018). Recent studies have confirmed that the efficacy of PARP inhibitors is improved not only in ovarian cancers displaying germline or somatic BRCA pathogenic gene variant but also cancers in which HRD is caused by other underlying aetiologies (ARIEL3, NOVA, PAOLA1, PRIMA).

Approximately 56% of ovarian carcinomas are estimated to exhibit defect DNA repair by HRD. Germline BRCA1 and BRCA2 pathogenic gene variants are the most well-known HRD aetiology, others include somatic BRCA 1 or BRCA 2 gene variants and germline and somatic gene variants in other genes related to HRD repair (Bonadio et al 2018, Panagiotis et al 2015). Overall, BRCA pathogenic gene variants contribute to 29% of the HRD positive pathway. That is all women with a BRCA pathogenic gene variants are HRD positive or deficient however, a BRCA pathogenic gene variants is not the only cause of HRD.

Figure 1 shows the aberration in HR genes or potentially relevant HR genes responsible for HRD. According to the Cancer Genome Altas (TCGA) ovarian cancers can be classified as HR-proficient and other (34%), possibly HR-deficient (10%) (including those with alterations in 42 other potentially relevant HR genes and HR-deficient (56%) including those with alterations of BRCA1/2; the amplification or variant of EMSY; the deletion of PTEN, Fanconi anaemia genes, core HR RAD genes or HR-related DNA damage response genes (Jiang et al 2018).

Figure 1 Frequency of genetic and epigenetic genes involved in homologous recombination and non-homologous recombination pathway based on The Cancer Genome Atlas (TCGA) – Jiang et al 2018



HRD can be tested using the three main strategies:

1. Germline variant screening of genes related to HR repair;
2. Somatic variant screening of genes related to HR repair; and
3. Evaluation of a genomic scar, which represents the genomic instability secondary to HRD. An HRD score can be calculated based on the loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale transitions.

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

The target population for the proposed medical service are women newly diagnosed, histologically confirmed, with high risk advanced (FIGO III-IV) a high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. The proposed population for testing is consistent with the patient population in the pivotal olaparib clinical trial (described in Q42).

Diagnosis of ovarian cancer

A number of tests may be performed to investigate the symptoms of ovarian cancer and confirm diagnosis. The commonly performed tests include (Cancer Australia 2020):

- physical examination of the abdomen and pelvis, including rectal examination.

- imaging of the pelvis and abdomen using transvaginal ultrasound, abdominal ultrasound, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans or positron emission tomography (PET) scans
- chest X-rays
- blood tests to check for tumour markers such as CA125, and to measure complete blood count and levels of chemicals in the blood
- use of scopes to see inside the gastrointestinal tract
- biopsy – where a small sample of tissue is removed to be examined under a microscope. This is usually done as part of the initial surgery, because the only way to confirm a diagnosis of ovarian cancer is through an operation. The surgeon will also take samples of any fluid in the abdomen

Staging of ovarian cancer

Ovarian cancer is surgically staged, based on the extent of the cancer. Knowing the stage of the disease helps your medical team plan the best treatment for you.

Surgical staging involves taking biopsy samples from tissues and organs that ovarian cancer often spreads to.

Ovarian cancer is divided into 4 main stages:

- Stage I: the cancer is in 1 or both ovaries and has not spread to other organs or tissues.
- Stage II: the cancer is in 1 or both ovaries and has spread to other organs in the pelvis, such as the uterus, fallopian tubes, bladder or colon.
- Stage III: the cancer is in 1 or both ovaries and has spread outside the pelvis to other parts of the abdomen or nearby lymph nodes.
- Stage IV: the cancer has spread to other parts of the body beyond the pelvis and abdomen, such as the lungs or liver.

Each stage has a number of substages.

Genetic testing

Cancer Australia 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. It is recommended that women with a previous diagnosis of invasive epithelial ovarian cancer be offered assessment of genetic risk if she meets the criteria from the EVIQ guidelines (July 2019). Currently, a woman with invasive epithelial ovarian cancer are offered genetic testing for a heritable pathogenic BRCA1 or BRCA2 gene 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 CanRisk or Manchester score).
- has relapsed platinum- sensitive ovarian cancer, is a candidate for treatment with PARP inhibitors and meets MBS criteria.

Until recently, testing for BRCA pathogenic gene variants is included as part of the routine diagnostic work-up for patients with advanced ovarian cancer. The medical oncologist or gynaecological oncologist would request the test or refer the patient on for BRCA testing. BRCA testing currently funded under the MBS are listed in Table 1.

Table 1 MBS items for testing BRCA 1 or BRCA2 mutations for ovarian cancer patients currently on MBS

MBS Item	Description	
73295	Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS). Maximum one test per lifetime	**Fee:** $1,200.00 **Benefit:** 75% = $900.00 85% = $1,115.30
73296	Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in BRCA1 and BRCA2 genes and one or more of the following genes STK11, PTEN, CDH1, PALB2, or TP53 in a patient with breast or ovarian cancer for whom clinical and family history criteria, as assessed by the specialist or consultant physician who requests the service using a quantitative algorithm, place the patient at >10% risk of having a pathogenic mutation identified in one or more of the genes specified above.	**Fee:** $1,200.00 **Benefit:** 75% = $900.00 85% = $1,118.30
73297	Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11, PTEN, CDH1, PALB2*, or *TP53* in a patient who is a biological relative of a patient who has had a pathogenic mutation identified in one or more of the genes specified above, and has not previously received a service under item 73296.	**Fee:** $400.00 **Benefit:** 75% = $300.00 85% = $340.00
73301	A test of tumour tissue from a patient with advanced (FIGO III-IV), high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, requested by a specialist or consultant physician, to determine eligibility relating to BRCA status for access to olaparib under the Pharmaceutical Benefits Scheme (PBS). Applicable once per primary tumour diagnosis	**Fee:** $1,200.00 **Benefit:** 75% = $900.00 85% = $1,115.30
73302	Characterisation of germline gene variants including copy number variants, in BRCA1 or BRCA2 genes, in a patient who has had a pathogenic or likely pathogenic variant identified in either gene by tumour testing and who has not previously received a service to which items 73295, 73296 or 73297 applies, requested by a specialist or consultant physician. Applicable once per primary tumour diagnosis	**Fee:** $400.00 **Benefit:** 75% = $300.00 85% = $340.00

Source: MBS Online http://www9.health.gov.au/mbs/search. MBS = Medicare Benefits Schedule

Tumour tissue specimens for the majority of target patient population will be available for testing following primary tumour debulking surgery or may be obtained as formalin-fixed paraffin-embedded (FFPE) blocks, which were archived following primary tumour debulking surgery. Retrieval and review of one or more archived FFPE block is funded under MBS item 72860 are forwarded on to the specialist molecular diagnostic laboratories who are able to analyse the tissue.

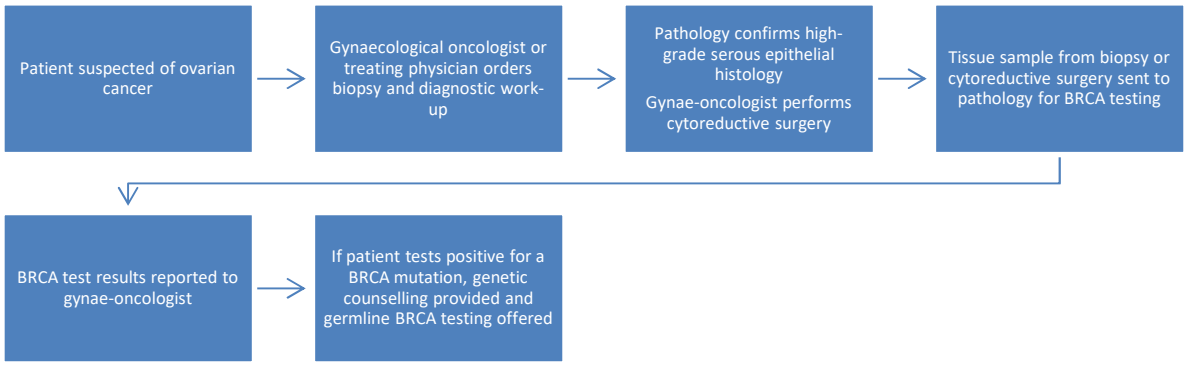
26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

Currently BRCA mutation testing via NGS is included as part of routine diagnostic work-up for patients with advanced ovarian cancer. The medical oncologist or gynaecological oncologist orders or refers the patient for BRCA testing. A positive BRCA result allows a patient to access olaparib as maintenance treatment for advanced ovarian cancer. If required, patients are also provided genetic counselling and a germline BRCA test is offered to determine if the pathogenic gene variant is hereditary.

The referral pathway to BRCA testing is illustrated in

Figure 2.

Figure 2 Current referral pathway for BRCAm testing to determine eligibility for olaparib



PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

The medical service for this MSAC application is testing of tumour tissue to determine a positive HRD status, which includes BRCA and GIS status in women newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

In addition to determining BRCA status, HRD testing determines GIS status, which is a quantitative assessment of the genomic scarring which measures genomic instability status based on either loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST).

The HRD test includes two assays performed simultaneously to determine BRCA status and GIS status using next generation sequencing (NGS) technology.

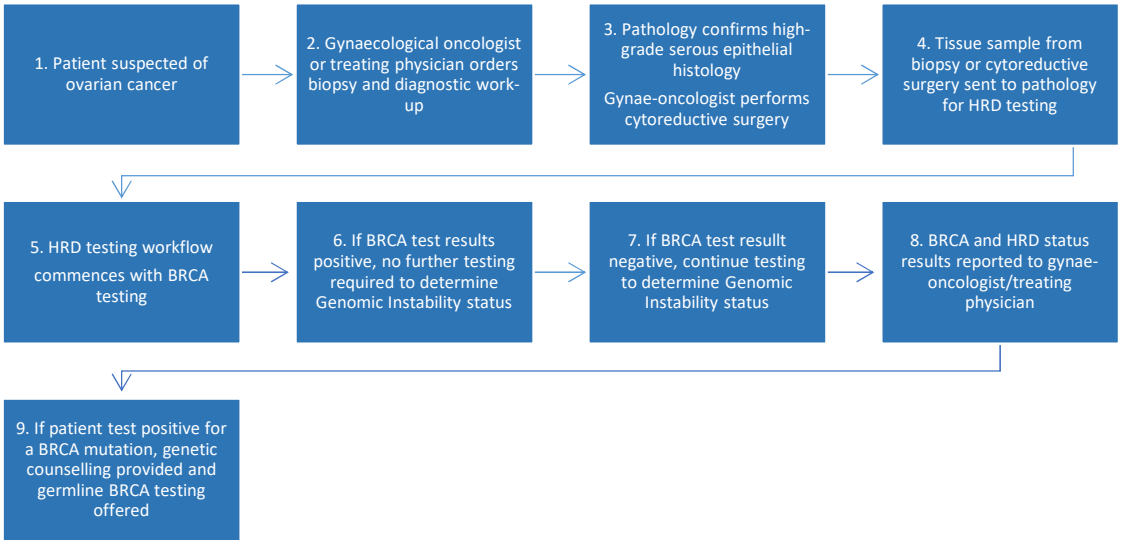
The key components and steps involved in delivering HRD testing is summarised and illustrated in Figure 3.

- Steps 1 to 4 are similar to the current referral pathway summarised in Figure 2. Tissue sample is retrieved under MBS item 72860 and DNA is extracted, purified and may be quantified using the laboratory's preferred methodology.
- Step 5 HRD workflow with tumour BRCA assay and GIS assay testing.
- Step 6 HRD (which includes BRCA and genomic instability) status results interpreted and reported by qualified/trained Pathologist and provided to gynae-oncologist, medical oncologist or treating physician
- Step 7 Patient informed of results. If BRCA positive, a patient will be offered genetic counselling and germline BRCA testing to inform of familial risk

At the time of this Application, (November 2020) **REDACTED** is the only laboratory developing a local HRD test. **REDACTED** offers a national service which provides high quality, timely service for all patients.

Besides **REDACTED**, three other laboratories have developed and validated their own in-house methods for tumour BRCA testing to detect germline and somatic BRCA1/2 pathogenic gene variants. It is anticipated that commercial kits will enter the market over the next 1-2 years.

Figure 3 Proposed future referral pathway for HRD (includes tumour BRCA) testing to determine eligibility for olaparib



28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Registered trademarks may be held by various commercial kits used at stages of the testing process, for example for DNA extraction, quality assurance, quantification, PCR amplification, as well as the NGS platform itself. It is also anticipated that commercial kits will enter the market over the next 1-2 years.

The HRD test used in the pivotal PAOLA1 clinical trial was Myriad MyChoice® HRD Plus which is not currently available in Australia.

HRD assays developed by individual laboratories will be remain their intellectual property.

The drug LYNPARZA has a registered trademark

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Germline BRCA testing is well established in Australia provided under MBS items 73296 and 73295.

Since August 2020, tumour BRCA testing to identify both germline and somatic BRCA pathogenic gene variants is funded under MBS item 73301.

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

HRD tumour testing is new to Australia, with a test being developed by **REDACTED**.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

No other medical services or healthcare resources need to be delivered at the same time as HRD testing.

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Testing to identify HRD status should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

At the time of this Application, (November 2020) **REDACTED** is the only laboratory developing a local HRD test. **REDACTED** offers a national service and provides timely service for all patients.

It is expected that once HRD testing is MBS funded more laboratories will have capability and accreditation for HRD testing.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Testing to identify HRD status in patients with advanced ovarian cancer should be based on a referral request from a specialist or consultant physician and should not be pathologist determinable.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Testing to identify HRD status should be conducted and the results interpreted and reported by suitably qualified and trained pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☐ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

The proposed medical service will be conducted in pathology laboratories which may be private companies or may be domiciled within private or public research institutes or hospitals. All laboratories are accredited to the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs. For further information please refer to the website: https://www.rcpaqap.com.au/home-page

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:
N/A

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

The Test

Currently tumour BRCA 1 or BRCA 2 testing is funded under MBS item 73301 for women newly diagnosed with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer.

Therefore tumour BRCA 1 or BRCA 2 testing is the main comparator for the proposed medical service: tumour HRD testing

The drug

As of 1 November 2020, women newly diagnosed with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer and BRCA pathogenic gene variant are eligible for treatment with olaparib on the PBS.

For patients who are non BRCA the current treatment option is bevacizumab.

Prior, to 1 June 2021 Bevacizumab was PBS listed 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 sub-optimally debulked and have a WHO performance status of 2 or less. Otherwise treatment was 'watch and wait' if PBS criteria was not met. However, it is assumed that the majority of patients are treated with drug rather than 'watch and wait'.

Following the expansion of the bevacizumab PBS criteria, patients who test negative for BRCA1 or BRCA 2 bevacizumab will continue to be treatment option with some patients continuing to receive 'watch & wait'.

For patients identified as HRD+BRCAwt via tumour HRD testing the treatment is the addition of olaparib to their current bevacizumab treatment (i.e. olaparib + bevacizumab).

Therefore placebo + bevacizumab is the main drug comparator.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☒ Yes (please list all relevant MBS item numbers below)
☐ No

MBS items numbers: 73295, 73296, 73301

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

Treatment of advanced ovarian cancer

First-line treatment for women with newly diagnosed advanced HGEOC is curative in intent, aiming to achieve and maintain complete remission (Raja FA, 2012); (Ledermann JA, 2017). The mainstay of treatment involves cytoreductive surgery, platinum-based doublet chemotherapy. Currently, patients who harbour a BRCA-variant ovarian cancer receive the same first-line maintenance treatment as those with non-BRCA-variant disease.

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 progression-free survival (PFS) and overall survival (OS) (Ledermann, et al., 2013); (du Bois A, 2009); (van der Burg ME, 1995); (Vergote I, 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 C, 2017); (Ledermann, et al., 2013); (AIHW, 2018) (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, et al., 2013) (NICE, Clinical Guideline 122, 2011). Bevacizumab in combination with carboplatin and paclitaxel is used in patients with sub-optimally debulked Stage III or Stage IV ovarian cancer.

Prior to 1 June 2021, Bevacizumab was PBS listed as maintenance treatment for patients with advanced (FIGO Stage IIIB, IIIC or Stage IV) epithelial ovarian, fallopian tube or primary peritoneal cancer who are sub- optimally debulked and have a WHO performance status of 2 or less. Treatment was limited to a lifetime total of 18 cycles of bevacizumab. Patients eligible for bevacizumab treatment rarely harbour a BRCA pathogenic gene variant and their clinical features tend to be distinct from patients who do.

Based on current ovarian cancer guidelines it is recommended that women newly diagnosed with ovarian cancer be referred for BRCA testing.

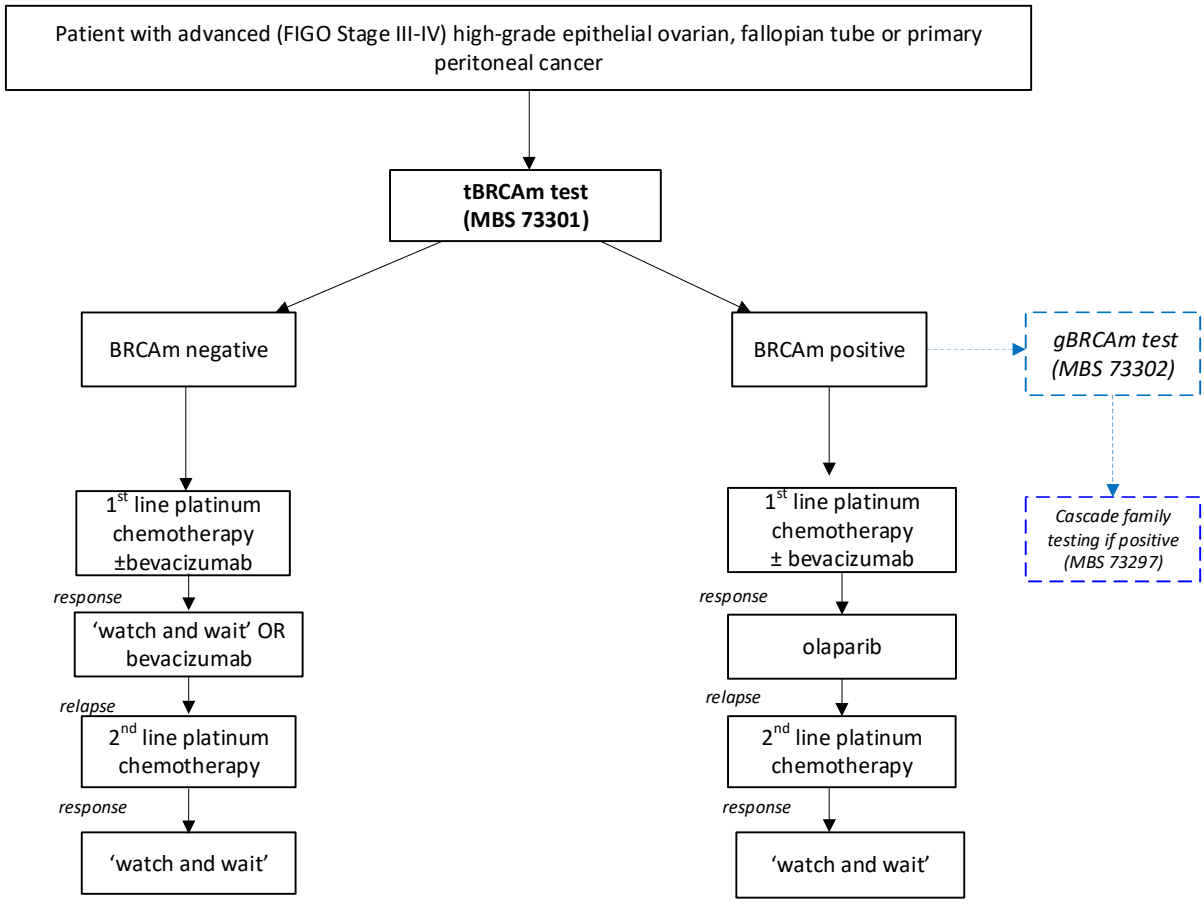
BRCA testing is MBS funded under MBS item 73296 for germline testing or MBS item 73301 for tumour testing to determine eligibility to olaparib as maintenance treatment. Patients with a positive BRCA pathogenic gene variant will be eligible for olaparib after first completing and responding to a course of platinum-based chemotherapy.

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

Germline BRCA testing is offered to those patients with a positive tumour BRCA result to determine if the mutation originated from germline mutation and thus will provide information of any familial risk. Cascade testing is also under MBS item 73297 to family members who wish to be informed of their BRCA status.

Refer to Figure 4 for the current clinical management pathway for patients after they have received tumour BRCA testing (the main comparator). A small proportion of patients may be tested with a germline BRCA test, if there is no available or quality tumour tissue sample.

Figure 4 Current clinical treatment management for patients with advanced ovarian cancer (updated)



Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline BRCA1 or BRCA2 mutation, tBRCA = tumour BRCA 1 or BRCA2 mutation

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

HRD test will be used instead of tumour BRCA testing as it provides both BRCA and GIS status.

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

It is assumed that 95% of eligible patients are able to provide a quality tumour sample for testing. Of these patients 100% will take up HRD testing (which include testing for both BRCA and GIS status determination).

The remaining 5% of patients will be able to access germline BRCA testing.

Refer to Section 7 for further details of the utilisation of HRD test.

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

The 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 proposed medical Service HRD test provides both BRCA and GIS status and will replace the tumour BRCA test (MBS item 733301) as the one test will identify HRD (defined as BRCA or GIS) status.

At the PASC meeting (15 April 2021), the Department of Health suggested that HRD testing to identify HRD positive-BRCAwt status could be performed in advanced high grade serous ovarian cancer (HGSOC) patients determined upon eligibility for bevacizumab maintenance therapy. AstraZeneca recognise 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 turn-around 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

In Figure 5, HRD testing identifies patients with a positive BRCA status and also HRD. The treatment algorithm for those patients with a positive BRCA status will remain unchanged as current practice described above in Q40 (i.e. they will be eligible to access olaparib in the first-line maintenance treatment after first completing and responding to platinum-based chemotherapy).

For those patients with a negative BRCA (i.e. BRCAwt) status and a positive GIS status, first-line treatment will include platinum based chemotherapy and with or without bevacizumab. Patients who are in response after initial chemotherapy are then maintained with treatment with olaparib in combination with bevacizamub. This new combination maintenance regimen is based on the pivotal clinical trial PAOLA1.

Patients who are HRD negative will receive similar treatment to those patients who are BRCA negative described above in Q40. These patients will either be actively monitored ('watch and wait') or receive bevacizumab as maintenance therapy.

PAOLA-1/ENGOT-ov25 (Ray-Coquard et al 2019) is the first phase III trial to investigate the efficacy and safety of a PARP inhibitor with bevacizumab as first-line maintenance therapy in patients with ovarian cancer with and without a BRCA mutation. This international, academic-led trial enrolled 806 patients with stage III/IV ovarian cancer and 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. Patient's 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.

The median follow-up was 24 months in the olaparib arm and 22.7 months in the placebo arm. Median progression free survival was 22.1 months in the olaparib group and 16.6 months in the placebo group (hazard ratio 0.59; 95% confidence interval 0.49–0.72; p<0.0001).

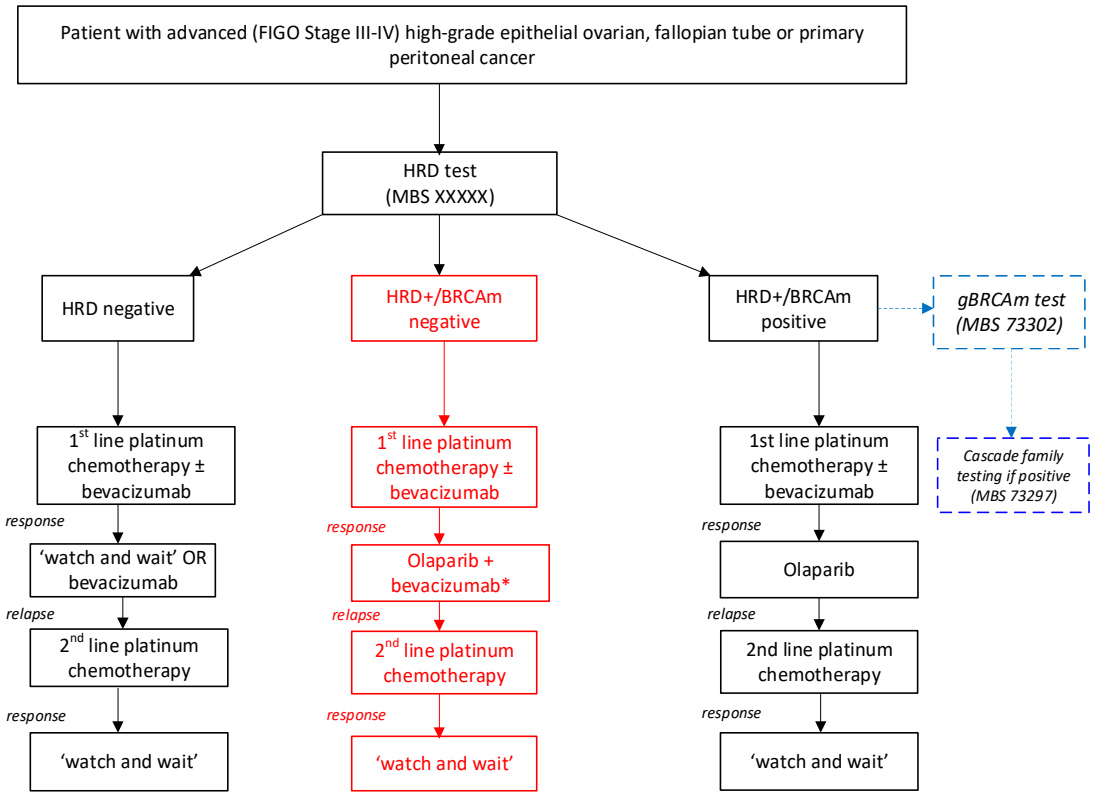
In prespecified subgroup analyses, the progression free survival benefit of olaparib + bevacizumab versus bevacizumab alone was even more pronounced in patients with a BRCA mutation and in those with homologous recombination deficiency (HRD), with hazard ratios of 0.31 and 0.33, respectively. Median progression free survival with olaparib + bevacizumab reached 37.2 months in patients with HRD including a BRCA mutation.

These results supports adding olaparib to maintenance bevacizumab therapy improves progression-free survival for advanced ovarian cancer regardless of BRCA mutation.

Please note that the target population for the upcoming co-dependent MSAC/PBAC submission are those patients identified with HRD positive BRCA wildtype tumours which is a subgroup of the population covered in PAOLA1 study.

Figure 5 illustrates the proposed future clinical management pathway for patients after they have received tumour HRD testing.

Figure 5 Clinical treatment pathway with proposed medical service - HRD test (includes BRCA and GIS status) – updated



Abbreviations: FIGO = the International Federation of Gynaecology and Obstetrics; gBRCAm = germline BRCA1 or BRCA2 mutation, HRD = homologous recombination deficiency

Note: *BRCA*m negative is the same as *BRCA*wt, * olaparib + bevacizumab anticipated to be used in the majority of HRD+BRCAwt patients based on the PAOAL1 trial results however, a small proportion of patients may use bevacizumab monotherapy or 'watch and wait'.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Please advise if the overall clinical claim is for:

☒ Superiority
☒ Non-inferiority

Overall, the clinical claim is that the proposed co-dependent technologies; 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 *BRCA* 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.

44. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

The below table is from the PASC ratified minutes and outcomes from the PASC meeting in April 2021.

Safety Outcomes:

- physical and/or psychological harms from testing or no testing, adverse events from testing
- adverse events associated with biopsy/re-biopsy for patients with inadequate tissue

Analytical validity:

- test failure rate
- sensitivity and specificity of test and of the test compared to the evidentiary standard used in the PAOLA-1 trial
- unsatisfactory or uninterpretable results
- diagnostic yield
- concordance with tumour-based somatic and blood-based germline BRCA1/2 testing methods and other tumour tissue BRCA1/2 test methods

Clinical validity – differential prognostic effect of being HRD positive (with no BRCA pathogenic variant) or not, in patients with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer

Clinical utility – treatment effect modification of olaparib in patients with advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer

Effectiveness (primary outcomes)

- health-related quality of life
- mortality

Other test-related considerations

- re-biopsy rates
- test turn-around time

Treatment-related outcomes

- overall survival
- progression-free survival
- health-related quality of life
- adverse events

Healthcare system outcomes

- cost of testing per patient treated, cost-effectiveness of genetic testing
- financial implications

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

45. Estimate the prevalence and/or incidence of the proposed population:

It is anticipated that HRD testing will be MBS funded in **REDACTED**. Based on the Australian Institute of Health and Welfare projections the incidence of ovarian cancer in **REDACTED** is estimated at 1,765 cases. Of these new cases, approximately 84% are epithelial tumours only (AIHW 2010) .

Based on Alsop et al 2012, ~70% of patients are diagnosed at the advanced stage. It is assumed that 95% of patients will take up tumour testing, with the remaining 5% unable to provide a tumour tissue sample or poor quality sample. The sponsor has assumed that all 95% of patients are eligible and take up testing.

In total it is estimated that approximately 986 women will take up HRD testing in **REDACTED**. Refer to Table 2 below.

46. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Tumour testing to determine HRD (BRCA and GIS) status would be conducted only once per patient in most cases.

47. How many years would the proposed medical service(s) be required for the patient?

Tissue tumour testing to determine HRD status does not require routine monitoring of a patient. The substantial majority of patients should only require testing once to determine HRD (BRCA and GIS) status and positivity/deficiency.

48. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

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 **REDACTED**, however only 1,482 are epithelial tumours (line 2 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 women diagnosed at advanced stage, data from the Australian Ovarian Cancer Study registered (AOCS, Alsop et al 2012) was used. AOCS assumes that 70% of women are diagnosed with advanced disease (line 3).

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

In total approximately 986 women will utilise tumour HRD testing to determine their HRD and BRCA status (line 5). Table 2 provides a summary of the estimated utilisation of tumour testing.

Table 2 Estimated utilisation of tumour HRD testing

	Description	Estimated number of patients in REDACTED
1	Incidence of ovarian cancer in Australia	1,765
2	Ovarian, Primary peritoneal & fallopian tube cancer-epithelial Tumour only	1,482
3	Diagnosed with advanced ovarian cancer	1,038
4	Eligible patients for tumour testing	986
5	Patients taking up HRD testing	986

49. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

A detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

It is not anticipated that there would be any supply or demand issues as the overall number of patients requiring testing to detect HRD status is manageable even if the number of laboratories conducting testing does not increase. Risk of leakage is expected to be low given the specific details of the proposed MBS item descriptor.

PART 8 – COST INFORMATION

50. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The current MBS fee for detection of germline or tumour BRCA1 or BRCA2 mutations according to Item 73295, Item 73296 and item 73301 is $1,200.00.

The proposed cost of HRD testing determined by **REDACTED** is approximately to be in the range of **REDACTED** to **REDACTED**. As per the MSAC application and pre-PASC document **REDACTED** has advised that testing of tumour tissue to identify HRD status has additional complexity over tumour BRCA testing alone as a number of including but not limited to the development of a quantitative assessment of genomic instability in tumour tissue.

Given the PASC concerns with regards to the propose price of the test, AstraZeneca seeks guidance from MSAC to advise an appropriate pricing structure to support a cost-effective price of the HRD test

51. Specify how long the proposed medical service typically takes to perform:

Tumour testing to detect somatic BRCA1/2 mutations takes 4-6 weeks from request to reporting. This includes time for the request and time to transport the tumour specimen to a specialist laboratory, if needed (7-10 days). Testing in the laboratory may require several hours of activity to perform plus run time for automated processes depending on instrumentation and procedures being followed and could take up to 4 weeks. Reporting results to the requesting specialist or consultant physician takes a further 1-2 days. A similar timeframe would apply to HRD testing.

52. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

This MSAC application request the following MBS items for the medical service Homologous Recombination Deficiency testing.

Table 3 Proposed MBS item description for HRD test which includes BRCA1 or BRCA2 identification

Category 6 – Pathology Services	
MBS item XXXXX	Group P7 - Genetics
Proposed item descriptor: A test of tumour tissue from a patient with advanced (FIGOIII-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 BRCA 1 or BRCA2 pathogenic or likely pathogenic gene variants to determine patient eligibility to access olaparib with or without bevacizumab under the Pharmaceutical Benefits Scheme (PBS). Once per primary tumour diagnosis Fee: $ TO BE CONFIRMED	

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