Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

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 in order 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.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

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

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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: Raewynne Tai, Senior Health Economics Associate

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

Alternative contact name: Rachael Anderson, Health Economics and Pricing Manager - Oncology

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

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

☐ Yes
☒ No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. (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

4. Application title

Testing of tumour tissue or blood to detect somatic or germline BRCA1 or BRCA2 gene mutations, in a patient with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy).

Please note that this population is broaden that the population in under MBS item 73295, ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component is a subset of advanced (FIGO III-IV) ovarian disease.

5. 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 1613 new cases in 2018.[1] The 5-year relative survival for women with ovarian cancer in Australia is low at 44.4%.[1] The most common and most aggressive histological subtype is high-grade serous ovarian cancer (HGSOC). Patients with fallopian tube or primary peritoneal cancer have similar serous features and are 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) so most women are diagnosed when their disease is advanced and widespread. Standard first line treatment of HGSOC is platinum-based chemotherapy.[2] Ovarian cancer is a highly chemo-sensitive tumour type, but more than 70% of women with advanced disease who initially respond to first-line chemotherapy will eventually relapse and require re-treatment. BRCA1 and BRCA2 mutational loss of function is a primary driver of ovarian cancer.

[1]Australian Institute of Health and Welfare Cancer in Australia 2017.

[2]Cancer Australia 2014 First line chemotherapy for the treatment of women with epithelial ovarian cancer. (https://canceraustralia.gov.au/publications-and-resources/clinical-practice-guidelines/first-line-chemotherapy-treatment-women-epithelial-ovarian-cancer)

6. 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)

Germline BRCA1 or BRCA 2 testing to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed high grade serous ovarian cancer (HGSOC) was listed on the MBS (Item 73295) and PBS (Items 11034R and 11050N) since 1 February 2017 (refer co-dependent MSAC/PBAC Application 1380). Subsequently, germline gene mutation testing, including BRCA1 and BRCA 2 testing at diagnosis of ovarian cancer in patients at >10% risk of having a pathogenic gene mutation became available on the MBS from November 2017 (Item 73296).

MSAC Application 1538 is currently being evaluated to include tumour tissue testing to detect somatic BRCA1 or BRCA 2 gene mutations to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed high grade serous ovarian cancer (HGSOC) and who have tested negative to germline BRCA 1 or BRCA 2 mutations. Application 1538 will be considered at the August 2019 PASC meeting.

This application for blood and tumour tissue testing to detect germline or somatic BRCA1 or BRCA2 gene mutations (referred to as BRCA mutation in this Application), is for newly diagnosed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, who do not met the eligibility criteria of MBS item 73295 or MBS item 73296, to determine PBS eligibility for olaparib as first-line maintenance therapy.

7. (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)

An amended MBS item number may be required. A number of existing MBS items are relevant, including the following:

- MBS Item 73295 Detection of germline BRCA1/2 gene mutations in patients with platinum sensitive HGSOC
- MBS Item 73296 Characterisation of germline gene mutations including BRCA1/2, STK11, PTEN, CDH1, PALB2 or TP53 in a patient with breast or ovarian cancer at >10% risk of having one or more of these mutations.
- MBS Item 73297 Characterisation of germline gene mutations in a biological relative of a patient with one or more of the gene mutations in Item 73296.

This Application proposes amending MBS Item 73295 such that germline BRCA 1 and BRCA 2 testing occurs when a patient newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy).
This Application also proposes amending the MBS Item proposed in Application 1538 such that tumour tissue testing to detect somatic BRCA1 or BRCA 2 mutations in a patient newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy).

A patient will only be tested for BRCA mutations once, either via MBS Items 73296 or 73295. The proposed amendments to the existing MBS Items are necessary for those patients who do not meet the current eligibility criteria for MBS Items 73296 or 73295.

(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:

May not be applicable, see above b).

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

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):

The this population in this application is broader that the population in under MBS item 73295, ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component is a subset of advanced (FIGO III-IV) ovarian disease (high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer).

Insert description of 'other' amendment here

(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 BRCA1/2mutation testing other than the MBS is sought, however in this co-dependent submission public funding for PBS access to olaparib in patients with BRCA1/2 gene mutations is also being sought.

(g) If yes, please advise:

Insert description of other public funding mechanism here

8. 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
☐ Hybrid health technology

9. 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
vi. ☐ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

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

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

11. (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 patients who have germline BRCA1/2 gene mutations are currently eligible for PBS olaparib (PBS Items 11034R and 11050N).

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

Insert PBS item code(s) here: 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

An integrated co-dependent submission to MSAC/PBAC is proposed for BRCA1/2 mutation testing to determine PBS access to olaparib as maintenance therapy in patients newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy.

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

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List? Not applicable

☐ Yes
☐ No

(b) If yes, please provide the following information (where relevant): Not applicable

Billing code(s): Insert billing code(s) here
Trade name of prostheses: Insert trade name here
Clinical name of prostheses: Insert clinical name here
Other device components delivered as part of the service: Insert description of device components here

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)? Not applicable

☐ 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? Not applicable

☐ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s): Not applicable

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables:
Multi-use consumables:
As per MSAC Application 1538, the only 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

14. (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: In-house developed
Manufacturer's name: N/A
Sponsor's name: Various, as follows at the time of this Application:

The medical services for BRCA mutation testing includes germline blood testing and tumour tissue somatic testing. Therefore, two MBS items are proposed.

Germline BRCA mutation testing in this application is an established service and there is no single sponsor for germline BRCAm testing in Australia. This test methodology remains unchanged to the methodology considered by MSAC in making its recommendation for the reimbursement of the test via MBS item #73295.

As for somatic BRCA mutation testing, AstraZeneca currently has a MSAC Application under consideration. MSAC Application 1538 will be discussed at the August 2018 PASC meeting. For further details on somatic testing please refer to this application. Therefore, an amendment to this service is proposed to include newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy). Please refer to MSAC Application 1538 for further information on somatic testing providers in Australia.

(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

15. (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

The pharmaceutical product LYNPARZA (olaparib) is registered on the ARTG and the registered indication already includes HGSOC patients with somatic BRCA1/2 gene mutations.
ARTG listing, registration or inclusion number: ARTG number 234008

TGA approved indication(s), if applicable:
Lynparza is indicated as monotherapy for the maintenance treatment of patients with platinum sensitive relapsed BRCA-mutated (germline or somatic) high grade serous 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.

Proposed new TGA indication AstraZeneca will be seeking is the following:
Redacted

TGA approved purpose(s), if applicable: Not applicable

16. 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

Date of submission to TGA: Not applicable
Estimated date by which TGA approval can be expected: Not applicable
TGA Application ID: Not applicable
TGA approved indication(s), if applicable: Not applicable
TGA approved purpose(s), if applicable: Not applicable

17. 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?

☒ Yes (please provide details below)
☐ No
As per MSAC Application 1538, the in-house developed somatic BRCA1/2 NGS assays have not yet been registered on ARTG. Registration will be sought prior to MSAC consideration of a submission based on this application.

Estimated date of submission to TGA: July 2018
Proposed indication(s), if applicable: Not applicable
Proposed purpose(s), if applicable: To be determined

PART 4 – SUMMARY OF EVIDENCE

18. **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 (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
Pivotal study					

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Comparative diagnostic study based on randomised, double blind, placebo-controlled trial	Study 19	Biological and clinical evidence for somatic mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high grade serous ovarian cancers. Planned retrospective analysis of tumours from Study 19. Next generation sequencing (NGS) of BRCA1/2 to detect mutations in tumour tissue. High concordance was demonstrated with Sanger sequenced germline BRCA1/2 mutations in matched blood samples. Comparison of clinical outcomes between placebo and olaparib treated patients with somatic and germline BRCA1/2 mutations	http://www.oncotarget.com/index.php?journal=oncotarget&page=article&op=view&path[]=17613&path[]=56383 Dougherty BA, Lai Z, Hodgson DR, Orr MCM *et al*. *OncoTarget*, 2017, **8**(27):43653-43661 plus online Supplement. https://ac.els-cdn.com/S0959804916303008/1-s2.0-S0959804916303008-main.pdf?_tid=59a4120e-106f-11e8-a11a-00000aab0f26&acdnat=1518493287_2db02025f85bc68a9039ff1576f3e963 Timms K, Neff C, Morris B, Hodgson D, et.al. *European Journal of Cancer*, 2015, 51 (Supplement 3):S100-S101.	May 2017 September 2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
	Randomised, placebo controlled, double blind Phase II trial	Study 19	Overall survival in patients with platinum sensitive, recurrent, serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo controlled double blind Phase II trial. This report includes the final overall survival results for the intent to treat and BRCA1/2 mutant subgroups as well as additional analyses in BRCA mutant subgroups	http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(16)30376-X.pdf Ledermann JA, Harter P, Gourley C, Friedlander M, *et. al.* *Lancet Oncology*, 2016, **17** (November 2016): 1579-89.	November 2016
Additional diagnostic studies					
2.	Comparative diagnostic study		BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next generation sequencing	http://www.oncotarget.com/index.php?journal=oncotarget&page=article&op=view&path[]=6834&path[]=19269 Mafficini A, Simbolo M, Parisi A, Rusev B, *et. al.* *Oncotarget,* 2016 **7**(2):1076	January 2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	Comparative diagnostic study		Comprehensive analysis of germline and somatic BRCA1/2 mutations in ovarian cancer population: Interim results of OVATAR prospective study	Tyulyandina A, Kekeeva T, Karaseva V, Gorbunova V, *et. al.* *Journal of Clinical Oncology,* 2017 **35**(15 Suppl. 1 May):Abstract e23109	May 2016
4.	Comparative diagnostic study		Cohort study of primary and recurrent ovarian cancer patients using next generation sequencing of DNA derived from blood samples and a customised Agilent gene panel for formalin-fixed paraffin-embeded (FFPE)	Hahnen E, Baumann KH, Heimbach A, Reuss A, et. al. Journal of Clinical Oncology, 2016, **34**(Supplement 15 May 2016):	May 2016
5.	Comparative diagnostic study		Prevalence and clinical significance of BRCA1/2 germline and somatic mutations in Taiwanese patients with ovarian cancer	http://www.oncotarget.com/index.php?journal=oncotarget&page=article&op=view&path[]=13456&path[]=44022 Chao A, Chang T-C, Lapke N, Jung S-M, et. al. *Oncotarget*, 2016, **7**(51):85529-85541.	November 2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6.	Comparative diagnostic study		This study aimed to identify the frequency and spectrum of germline and somatic BRCA1/2 gene mutations in a cohort of 100 women with serous ovarian cancer. Mutational analysis of BRCA1/2 genes was performed on tumour tissue (FFPE) using next generation sequencing. Germline BRCA1/2 mutation status of non-neoplastic tissue was determined using bidirectional Sanger sequencing.	Koczkowska M, Zuk M, Gorczynski A, Ratajska M, *et. al.* *Cancer Medicine*, 2016, **5** (7 July):1640-1646.	April 2016
7.	Comparative diagnostic study		Simultaneous detection of BRCA mutations and large genomic rearrangements in germline DNA and FFPE tumour samples. Ten ovarian cancer samples were included in this study which also reported results for a similar number of breast cancer samples. Two different next generation sequencing platforms were compared.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308695/pdf/oncotarget-07-61845.pdf Enyedi MZ, Jaksa G, Pinter L, Sukosd F, et.al. Oncotarget, 2016, **7**(38):61845-61859.	August 2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8.	Comparative diagnostic study		Germline and somatic multi-gene sequencing in patients with advanced high grade serous ovarian cancer (HGSOC). DNA extracted from matched blood and tumour samples (from FFPE) were tested using a lab developed next generation sequencing method.	https://watermark.silverchair.com/mdw392.28.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAcgwggHEBgkqhkiG9w0BBwagggG1MIIBsQIBADCCAaoGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMCtq-AmJx8VpxAGGAAgEQgIIBe0eIdSzalDmXm09ni2EVWLfH_2tlJJ2FFOvo6jZgsjpC_cowGsg35w_BTEFPPuOUn6k-p_6jZFhzbD5OAnWI0KFzIu3t3Ex_TyJQTw6bDx-COTz5PbRcnfNNyBOvEj1sXbp1hVvf5IrC-ihALl9KGevCyOc8BY6XzfnvhQa6PuBeJaSt3oHEN-X-sgX9S0BnCEq5Pd6ZCFesicmlp8v-leAV10nyibQL0Q2BjBEH6rHOAOsOUtMv0KPJnYgEZybxlC6-R6E5tZi4BQoqRwCZsyuDRdk4aTVAfM1kdKHQlfqaHAptGBz1MvAXrwipb41g-IfnJetKA5xOMNFQzHFQGGEZ0d7MEwFKCdS5EfdRjo3TWK5wcdY0l1t1HHT4e8Y9rgSZ56iQt_yDiLTaag176gJNv3v6wsCi_ljf0NQB_DCeio-jPD08JUIFM_x0G3dTaAutRBtbaWT-mt8ZXVH8YsOHOamSzbN59v7GIgdV1GSAM950jh754YqR8QA Stjepanovic N, Wilson M, Mandrilaras V, Clarke B, et. al. *Annals of Oncology,* 2016, 27(Supplement 6):Abstract 1547P	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
9.	Diagnostic accuracy study		This multicentre study evaluated the analytical performance of BRCA Tumor MASTR Plus Dx (Multiplicom) for diagnosis of somatic and germline BRCA mutations in formalin-fixed paraffin embedded tumour tissue derived DNA. 51 clinical and 3 reference samples were used. The clinical samples were characterised by next generation sequencing.	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e23116 Boulet G, Van Barel, Rotthier A, Goossens D, DelFavero J. *Journal of Clinical Oncology*, 2017, **35**(15 Supplement):e23116	May 2017
10.	Diagnostic accuracy study		Testing of BRCA1/2 gene mutations in FFPE samples of patients with high-grade serous ovarian cancer and the limits of its bioinformatic interpretation.	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e17060 Janikova K, Lasabova Z, Gredar M, Farkasova A, *et.al.* *Journal of Clinical Oncology*, 2017, **35**(15 Supplement):e17060	May 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
11.	Comparative diagnostic study		Next generation sequencing was used to detect deleterious mutations through all exons in 31 core homologous recombination genes. Paired whole blood and frozen tumour samples from 50 chinese women diagnosed with epithelial ovarian carcinomas were tested to identify both germline and somatic variants.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447142/ Zhao Q, Yang J, Li L, Cao D, *et. al.* *Journal of Gynaecologic Oncology*, 2017, **28**(4):e39	July 2017
12.	Comparative diagnostic study		Patients diagnosed with recurrent ovarian cancer underwent next generation sequencing of archival tumour specimens using a 65 gene panel or a 315 gene panel (Foundation Medicine). Some patients also underwent NGS of circulating free DNA from blood specimens. Genomic alterations identified from the blood based testing were compared to the archival tumour tissue.	http://mct.aacrjournals.org/content/16/10_Supplement/B29 Londono AI, Farrukh N, Smith MK, Tawfik CM, *et.al.* Molecular Cancer Therapeutics, 2017, **16**(10 Supplement 1): Abstract B29	January 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
13.	Diagnostic accuracy study		Validation of the Devyser BRCA kit, for next generation sequencing of high risk breast/ovarian cancer susceptibility genes BRCA1 and BRCA2. The assay of 48 samples including nucleotide substitutions, small deletions/insertions and large deletions/duplications and showed 100% concordance with gold standards.	https://www.sciencedirect.com/science/article/pii/S1525157817303380 Capone GL, Putignano AL, Saavedra ST, Paganini I, *et.al.* *Journal of Molecular Diagnostics,* 2018*,* **20**(1):87-94.	
14.	Comparative diagnostic study		496 patient tumour samples, including 68 ovarian cancer patients with peripheral blood and archival FFPE samples were analysed to detect germline and somatic sequence variants of DNA repair genes. Enrichment of targets was carried out using the Agilent SureSelect hybrid capture baits. Next generation sequencing was carried out on Illumina platforms.	https://ac.els-cdn.com/S1525157816301787/1-s2.0-S1525157816301787-main.pdf?_tid=7264e1e2-1065-11e8-93f3-00000aacb35d&acdnat=1518489033_e391a79881ac337e09e02850e1a6d6d5 Lee W, Jo H, Yin X, Patel NM, et. al. *Journal of Molecular Diagnostics*, 2018, 20(1):87-94.	January 2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
15.	Comparative diagnostic study		This study included 9 patients with high grade serous ovarian cancer with known germline BRCA1/2 mutations. Somatic mutations were detected using the BRCA Tumor MASTR Plus (Multiplicom) and next generation sequencing (Illumina platform).	http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e17060 Blanch S, Antonio F, Zaida GC, Iganacio R, et.al. *Journal of Clinical Oncology*, 2016, 34(15 Supplement): Abstract e17060.	October 2016
16.	Diagnostic study		A total of 1691 epithelial ovarian cancer tumour samples (63% serous histology) were analysed by multi-platform molecular analysis including next generation sequencing, immunohistochemistry of protein expression and/or gene amplification (FISH/CISH) to determine if there was any difference by histology in frequency of BRCA1 and BRCA2 mutations	https://ac.els-cdn.com/S0959804916315374/1-s2.0-S0959804916315374-main.pdf?_tid=c92b7f60-1072-11e8-a2ad-00000aacb35f&acdnat=1518494762_71d6c2d3dbb37743a5724d610d08a996 Herzog T, Xiu J, Bender R, Gatalica Z, et.al. *European Journal of Cancer*, 2015, **51**(Supplement 3):S554-S555.	September 2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
17.	Diagnostic and comparative clinical outcomes study.		Germline and somatic mutations in homologous recombination genes were detected using targeted capture (BROCA panel) and massively parallel genomic sequencing (next generation sequencing) in 390 ovarian carcinomas, including 239 high grade serous carcinomas. For all suspected loss of function variants PCR amplification and Sanger sequencing were performed both on lymphocyte derived (germline) and neoplastic DNA to confirm and classify the mutation as somatic or germline. The presence of these gene mutations predicts platinum response and survival in ovarian, fallopian tube and peritoneal carcinomas.	Pennington KP, Walsh T, Harrell MI, Lee MK, et.al. *Clinical Cancer Research*, 2014, 20(3):764 And https://ac.els-cdn.com/S0090825813009438/1-s2.0-S0090825813009438-main.pdf?_tid=8114155a-1146-11e8-aa19-00000aacb360&acdnat=1518585695_8697136926bbdb45f1192c6efe89e843 Pennington K, Walsh T, Harrell M, Lee M Gynecologic Oncology, 2013, 131(1):257-58. And https://ac.els-cdn.com/S0090825811009814/1-s2.0-S0090825811009814-main.pdf?_tid=d5dd19d8-11f0-11e8-9f9b-00000aab0f6b&acdnat=1518658851_d764cadb5d00523acb1281dd36c70657 Pennington K, Walsh T, Casadei S, Lee M, et.al. Gynaecologic Oncology, 2012, 125(Supplement 1):S5-6.	February 2014 October 2013 March 2012

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
18.	Diagnostic study		Analysis of germline and somatic genetic alterations in 429 ovarian cancer cases and 557 controls. Germline and tumour DNA were sequenced by exome capture followed by next generation sequencing on Illumina or SOLiD platforms.	https://www.nature.com/articles/ncomms4156.pdf Kanchi KL, Johnson KJ, Lu C, McLennan MD, et.al. Nature Communications, 2014, 5:3156	January 2014
19.	Diagnostic study		263 patients with previously untreated high grade ovarian cancer were offered germline and somatic BRCA1/2 mutation screening. Germline mutation screening was performed on DNA from blood via custom amplicon assay and next generation sequencing. DNA from FFPE tumour samples was sequenced using custom hybridisation enrichment and next generation sequencing. 100% concordance was demonstrated between the blood and tumour based NGS assays.	https://academic.oup.com/annonc/article/25/suppl_4/iv308/2241599 Yates M, Timms K, Daniels M, Batte B, et.al. *Annals of Oncology*, 2014, 25(Supplement 4):iv305-iv326.	March 2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
20.	Phase III randomised, double blind, placebo controlled trial with diagnostic testing and subgroup analyses	ARIEL 3	Patients with platinum sensitive, high grade serous or endometrioid ovarian, primary peritoneal or fallopian tube carcinoma were randomised to the PARP inhibitor rucaparib (n=375) or placebo (n=189). Central testing of DNA derived from patient archival tissue samples was conducted using Foundation Medicine T5 NGS assay. Germline mutations were identified with BRCAnalysis CDx test (Myriad Genetics). A pre-specified cohort of BRCA mutant patients were included in the study. Clinical outcomes included progression-free survival in subgroups by BRCA mutation status (BRCA1, BRCA2, germline, somatic).	https://www.sciencedirect.com/science/article/pii/S0140673617324406 Coleman RL, Oza AM, Lorusso D, Aghajanian C, et.al. *Lancet*, 2017, 390:1949-61.	September 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
21.	Phase II open-label single arm trial with diagnostic testing and subgroup analyses	ARIEL 2	Patients with platinum sensitive, high grade ovarian carcinoma were randomised to the PARP inhibitor rucaparib (N=206). Central testing of DNA derived from patient archival tissue samples was conducted using Foundation Medicine T5 NGS assay. The most recent specimen was used (pre-treatment biopsy if available or archival biopsy). Mutations detected in tumour tissue were identified as germline or somatic by analysis of genomic DNA from blood using the BROCA-homologous recombination sequencing assay. Clinical outcomes included overall response rate in subgroups by BRCA mutation status (BRCA1, BRCA2, germline, somatic).	https://www.sciencedirect.com/science/article/pii/S1470204516305599 Swisher EM, Lin KK, Oza AM, Scott CL, et.al. *Lancet Oncology*, 2017, **18**:75-87.	January 2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
22.	Randomised, double-blind, Phase III trial with diagnostic testing and subgroup analyses	NOVA	Patients with platinum sensitive, recurrent ovarian cancer were randomised to the PARP inhibitor niraparib (n=372) or placebo (n=181) with each treatment group containing a germline BRCA cohort and a non-germline BRCA cohort using BRCAnalysis testing (Myriad Genetics). Prior to database lock tumour testing from archived samples was performed using myChoice homologous recombination deficiency (HRD) test (Myriad Genetics). Clinical outcomes included progression-free survival in subgroups by BRCA mutation status (germline BRCA, no germline HRD positive, no germline).	http://www.nejm.org/doi/full/10.1056/NEJMoa1611310 Mirza MR, Monk BJ, Herrstedt J, Oza AM, et.al. New England Journal of Medicine, 2016, 375(22): 2154-64.	December 2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
23.	Population-based case-control study with BRCA testing	Australian Ovarian Cancer Study	Patients comprised 1409 women with newly diagnosed invasive epithelial ovarian, peritoneal or fallopian tube cancer. The majority of patients had high grade tumours with serous histology. Germline testing was completed using sequencing and multiplex ligation dependent probe amplification (MPLA). Tumour DNA samples were screened for somatic mutations in all coding exons of BRCA1 and BRCA2 using high resolution melt analysis. Treatments were captured in the analysis and clinical outcomes, including time to progression and time to death, were reported.	http://ascopubs.org/doi/full/10.1200/JCO.2011.39.8545 Alsop K, Fereday S, Meldrum C, DeFazio A, et.al. *Journal of Clinical Oncology*, 2012, **30**:2654-2663.	July 2012

NOTE: There are now many published studies reporting methods for detection of somatic mutations in BRCA1/2 in ovarian tumour tissue, or comparison of somatic versus germline BRCA1/2 testing in patients with ovarian cancer. A selection of key papers is outlined above and a comprehensive, current overview of the published evidence will be presented in the submission.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

*** *If the publication is a follow-up to an initial publication, please advise.*

19. 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.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Randomised controlled trial	SOLO1 ClinicalTrials.gov Identifier: NCT01844986	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer Following First Line Platinum Based Chemotherapy.	https://clinicaltrials.gov/ct2/show/NCT01844986 Unpublished, AstraZeneca data on file	Q4,2018

Abbreviations: PARPi poly (ADP-ribose) polymerase inhibitors

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. 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):

The group of health professionals who would provide the medical service are the Royal College of Pathologists of Australasia (RCPA). A statement from the RCPA on the clinical relevance of the test will be provided directly by the RCPA.

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

Not applicable

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

The main consumer organisation representing patients with ovarian cancer is Ovarian Cancer Australia (OCA). A letter from OCA supporting this Application will be provided directly by OCA.

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

The most similar tests to the proposed service would be MBS Items 73295 (germline BRCA1/2 testing to determine eligibility for olaparib) and MBS Items 73296 & 73297 (which includes germline BRCA1/2 testing in patients with ovarian cancer at high risk (>10%) of harbouring a mutation, and testing for their biological relatives).

24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s): Not required as per correspondence with MSAC Secretariat

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. 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 1613 new cases in 2018.[1] The 5-year relative survival for women with ovarian cancer in Australia is low at 44.4%.[1] Ovarian cancer is estimated as the 6th highest cause of cancer related deaths for women in Australia in 2017, with 1047 deaths.[1] Among Australian women, ovarian cancer is the eleventh highest contributor to fatal burden of disease (18,789 years of life lost).[2]

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.[4] 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.[4] Ovarian cancer (EOC) 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.[5] Subsequent treatment options for patients with relapsed HGSOC involve repeat courses of platinum-based chemotherapy, with ever-decreasing treatment-free (remission) intervals.

BRCA1 and BRCA2 mutational loss of function is a primary driver of ovarian cancer. If a lifetime risk for ovarian cancers among women in the general population is estimated to be 1.4 percent (14 out of 1,000), a woman with BRCA1 or BRCA2 deleterious mutation has a lifetime risk of 15 to 40 percent (150–400 out of 1,000). BRCA mutated ovarian cancer patients can also develop ovarian cancer earlier in their life than those without the mutation.

The high grade serous ovarian cancer population is enriched for patients with BRCA1/2 germline and somatic mutations, in comparison to all ovarian cancer patients. In HGSOC patients with BRCA1/2 gene mutations comprise up to 25% of patients,[6] with somatic BRCA1/2 mutations representing up to 30% of all BRCA1/2 mutations.[7] Germline/somatic BRCA mutated ovarian cancers are associated with an improved response to platinum based chemotherapy (standard of care) and longer-term prognosis than non-BRCA-associated ovarian cancers. Identification of BRCA- mutated ovarian cancer is important to identify those at further cancer risk, at-risk family members and to plan individual treatment decisions.

The target population for this application are those enrolled into the pivotal trial SOLO1; a Phase 3 double blind randomised placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO Stage III-IV) ovarian cancer following first line platinum based chemotherapy. The study population comprised of:

- Female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian - tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal).

- Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery.
- Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function).
- Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation:
- Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post treatment scan or rising CA-125 level, following completion of this chemotherapy course. Patients with stable disease on the post-treatment scan at completion of first line platinum-containing therapy are not eligible for the study.

https://clinicaltrials.gov/ct2/show/record/NCT01844986

[1]Australian Institute of Health and Welfare Cancer in Australia 2017.

[2]Australian Institute of Health and Welfare Australian Burden of Disease Study 2011.

[3]Lederman J, Harter P, Gourley C, Friedlander M, et.al. New England Journal of Medicine, 2012, **366**:1382-92.

[4]Cancer Australia 2014 First line chemotherapy for the treatment of women with epithelial ovarian cancer. (https://canceraustralia.gov.au/publications-and-resources/clinical-practice-guidelines/first-line-chemotherapy-treatment-women-epithelial-ovarian-cancer)

[5]Lederman JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, et.al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 2013, **24**(Supplement 6):vi24-32.

[6]Pennington KP, Walsh T, Harrell MI, Lee MK, et.al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube and peritoneal carcinomas. *Clinical Cancer Research*, 2014, **20**:764-775.

[7]Dougherty BA, Lai Z, Hodgson DR, Orr MCM, et.al. Biological and clinical evidence for somatic mutations in BRCA1/2 as predictive markers for olaparib response in high grade serous ovarian cancers in the maintenance setting. *Oncotarget*, 2017, **8**(27):43653-43661.

26. 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:

Germline BRCA1/2 testing to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed high grade serous ovarian cancer (HGSOC) has been listed on the MBS (Item 73295) and PBS (Items 11034R and 11050N) since 1 February 2017 (refer co-dependent MSAC/PBAC Application 1380).

Subsequently germline gene mutation testing, including BRCA1/2 testing in ovarian cancer patients at >10% risk of having a pathogenic mutation identified, became available on the MBS from November 2017 (Item 73296). Germline BRCA1/2 gene mutation testing (Item 73297) is also available to biological relatives of patients who have pathogenic mutations identified according to Item 73296. Ovarian cancer patients may qualify for BRCA1/2 testing under Item 73296 & 73297 at the time of ovarian cancer diagnosis. Although the listings are much broader and include testing in breast cancer patients, the utilisation of services for MBS Items 73296&7 in the first few months of listing has already substantially exceeded the utilisation of services under Item 73295 during the entire first year of MBS listing. Consequently, the germline BRCA1/2 mutation status of patients may be known at an earlier stage in disease management and patients with detected mutations can receive genetic counselling services

At the time of MSAC first consideration of Application 1380 in March 2016, the MSAC recognised that germline BRCA1/2 testing would not identify all women who could benefit from olaparib therapy. The MSAC also noted that *"if access to somatic testing was requested in future there may be an incremental cost to the MBS because patients without an identified germline BRCA mutation would need additional tumour testing." "As such, MSAC would require a new application before considering the addition of somatic BRCA testing to the MBS." [Public Summary Document Application 1380 MSAC Consideration March & November 2016]*

Over two years later germline BRCA1/2 gene mutation testing is established in Australian clinical practice and some Australian laboratories have developed assays for tumour testing to detect somatic BRCA1/2 gene mutations. There have been other significant changes to the local and international tumour BRCA1/2 mutation testing environment and additional outcomes data (published and unpublished) to warrant reconsideration of tumour testing for patients with somatic BRCA1/2 mutations at this time. Based on this, MSAC Application 1538 was lodged and will be considered at the August 2018 PASC meeting.

Proposed patients for BRCA mutation testing

The current Application is an amendment to MSAC Application1538 and MBS item 73295.

Cancer Australia recommends that women newly diagnosed with invasive epithelial ovarian, fallopian tube or primary peritoneal 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 at their next follow-up visit.

A woman with invasive epithelial ovarian cancer should be offered genetic testing for a heritable mutation in BRCA1 or BRCA2, if she meets any of the following criteria:

- has high grade (Grade 2 or 3) invasive non-mucinous ovarian cancer, diagnosed at 70 years or younger.
- 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).
- has relapsed platinum- sensitive ovarian cancer, is a candidate for treatment with PARP inhibitors and meets MBS criteria.

This recommendation aligns to the current Application which propose testing to detect BRCA1/2 gene mutations when patients are newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy). This will ensure that patients who then go on to qualify for olaparib as maintenance therapy (after first line platinum based chemotherapy) avoid delays that could compromise the benefit of olaparib treatment.

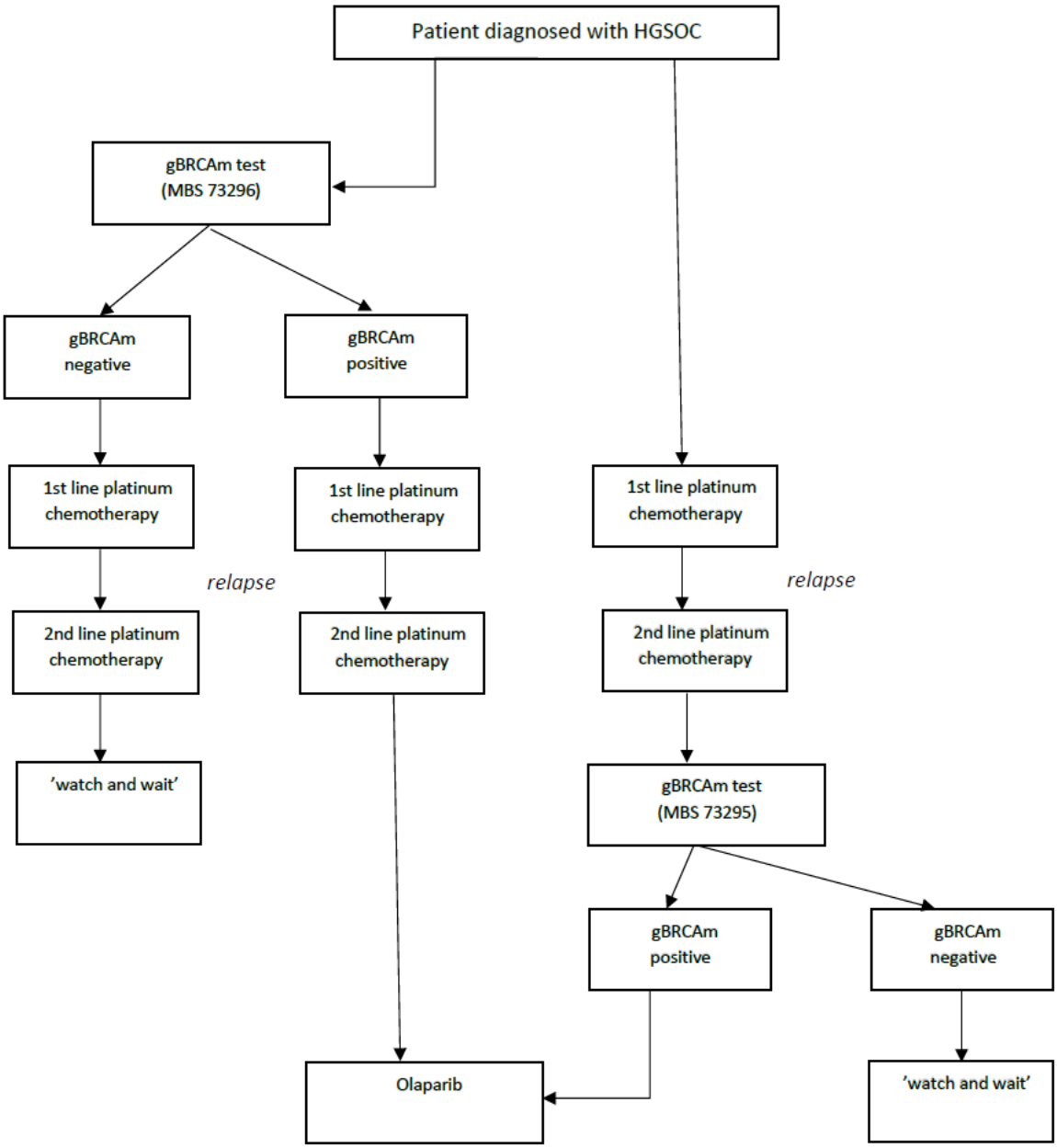
https://canceraustralia.gov.au/publications-and-resources/position-statements/genetic-testing-women-diagnosed-ovarian-cancer/recommendations

Proposed patients for olaparib treatment

Eligible patients in the pivotal trial, SOLO1 were those patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III-IV) BRCA mutated high grade serous or high grade endometrioid (based on local histopathological findings) ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who are in clinical complete response or partial response following completion of first line platinum-based chemotherapy. This is the proposed patient for PBS listed olaparib treatment.

27. 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):

Please refer to the Microsoft Word attachment to this application, 'Advanced (FIGO III-IV) OC Algorithm' and 'Current algorithm' for an editable version of this flowchart below.



Abbreviations: gBRCA germline BRCA1 or BRCA2; HGSOC high grade serous ovarian cancer

Treatment for newly diagnosed advanced (FIGO III-IV) ovarian cancer is first line chemotherapy with a platinum-based chemotherapy regimen for these patients. Ovarian cancer is generally a chemotherapy-sensitive tumour type, however patients who do initially respond to treatment eventually relapse. Standard of care at the point of relapse is another round of platinum-based chemotherapy.

The majority of patients who are newly diagnosed with advanced (FIGO III-IV) ovarian cancer would currently be eligible for germline BRCA1/2 testing under MBS Item 73296 from the time of diagnosis (i.e. most HGSOC have >10% risk of having a mutation according to the quantitative algorithm used in practice). These patients may have pre-test genetic counselling and, if found to carry a germline BRCA1/2

mutation will be eligible for post-test genetic counselling. These patients would also have tumour debulking surgery after neo-adjuvant chemotherapy at some institutions. For HGSOC patients with known germline BRCA1/2 gene mutations who have completed at least two courses of platinum-based chemotherapy and demonstrated they are sensitive [had an objective response (complete response or partial response) to their most recent regimen], maintenance treatment with olaparib is the next treatment option.

HGSOC patients who are not eligible or are not tested for germline BRCA1/2 testing under MBS item 73296 at diagnosis also undergo the same treatment of tumour debulking surgery (with or without neo-adjuvant chemotherapy) followed by first line platinum-based chemotherapy and, after relapse another round.

HGSOC patients who have completed at least two courses of platinum-based chemotherapy and demonstrated they are sensitive [had an objective response (complete response or partial response) to their most recent regimen] are eligible for germline BRCA1/2 testing under Item 73295 and, if they have a germline BRCA1/2 mutation, would then be eligible for maintenance olaparib treatment. Germline BRCA1/2 testing takes approximately 4 weeks so there is currently a delay before olaparib can be started even for patients who will ultimately qualify. If germline BRCA1/2 testing could be completed earlier then the next treatment for patients could be planned without a delay.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

BRCA mutation testing

Patients who meet the criteria for *BRCA* testing can be referred for testing by a clinical geneticist or genetic counsellor. Cancer patients are usually referred for genetic counselling by a medical oncologist. At-risk relatives are usually referred for genetic counselling by a general practitioner. *BRCA* testing is generally limited to "high risk" patients (young, family history of breast or ovarian cancer, TNBC) as specified by country guidelines.

The current key components and clinical steps involved in delivering a germline *BRCA* mutation test are as follows:

1. Patient is referred to Genetic Services/Familial Cancer Centre by a medical practitioner for a pre-test consultation.
2. Genetic counselling with Genetic Services/Familial Cancer Centre team and patient. Genetic Services/Familial Cancer Centre team provides information about genetics, inheritance (family risk) and genetic testing. The patient decides to take a genetic test i.e. the germline *BRCA* mutation test. The patient will provide a signed consent form to Genetic Services who will order the *BRCA* test and order the collection of a blood sample to be taken. Oncology teams are currently being trained in genetic mainstreaming the oncologist or "treating specialist" can also sign the pathology request form and arrange for the blood collection.
3. Patient's blood sample is taken and send to a pathology laboratory where *BRCA* testing is performed. The turnaround for test results is around 3 to 8 weeks.
   For somatic BRCAm test, tumour specimens to provide tissue for BRCA1/2 testing will be available as formalin-fixed paraffin-embedded blocks archived following primary tumour debulking surgery. Tumour specimens may have been archived for many months or even years. In some circumstances (such as a long period in archive or issues with the FFPE process) there may be degradation of the DNA in the specimen and a re-biopsy may be necessary. A fresh biopsy may also be required in a minority of cases where initial neo-adjuvant chemotherapy resulted in significant tumour shrinkage and tumour debulking surgery did not provide any viable tumour tissue. Costs will be incurred for retrieving samples from archive and possibly for forwarding them on to the specialist molecular diagnostic laboratories who are able to perform the tissue BRCA1/2 test.
   For further information on somatic testing please refer to MSAC Application 1538.
4. The results are send to the Genetic Services/ Familial Cancer Centre and treating medical practitioner. If a *BRCA* mutation is detected, a face to face post-test counselling appointment with the patient and their family is arranged to deliver the results.
5. Based on a positive *BRCA*m result the medical practitioner will consider prescribing Olaparib to the patient if they meet the PBS criteria to access treatment.

LYNPARZA® (olaparib) treatment

Olaparib is a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor. Olaparib traps PARP at sites of DNA damage, blocking base-excision repair and resulting in the collapse of DNA replication forks and the accumulation of DNA double-strand breaks. Induced "synthetic lethality" is seen with olaparib in tumours that are deficient in homologous recombination repair pathways, such as those with BRCA1/2 gene mutations.

As described earlier in Q25, the pivotal trial SOLO1 included patients newly diagnosed advanced (FIGO III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian - tube cancer who have completed first line platinum based chemotherapy (intravenous or intraperitoneal).

Eligibility for PBS treatment with olaparib as maintenance therapy is proposed in newly diagnosed advanced (FIGO III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer disease

with a BRCA 1/2mutation. Patients must also with have completed first line of platinum based chemotherapy and have a response (complete or partial).

29. **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 outlined in Q28 above, for example for DNA extraction, quality assurance, quantification, PCR amplification, as well as the NGS platform itself. The drug LYNPARZA has a registered trademark.

30. **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?**

    BRCAm testing for patients newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy) is proposed to be tested earlier in the treatment algorithm. This approach could be considered as new. However, BRCA testing is currently being performed as per MBS item 73296 and 73295.

    The tumour testing approach to identify somatic BRCA1/2 mutations is relatively new and is not yet reimbursed on the MBS. As per MSAC application 1538 using this approach to testing could identify new patients with somatic BRCA1/2 mutations who could potentially benefit from PARP inhibitor treatment with olaparib.

31. **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):**

    gBRCA testing is currently well established in Australia. Only one germline BRCA test is required for a patient in their lifetime. It is also unlikely that a patient would require more than one somatic BRCA1/2 test in their lifetime.

32. **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 BRCA mutation testing.

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

    Testing to identify BRCA1/2 gene mutations 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.

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

    Not applicable.

35. **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 BRCA1/2 gene mutations in patients with advanced (FIGO III-IV) ovarian cancer should be based on a referral request from a specialist or consultant physician and should not be pathologist determinable.

36. **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 BRCA1/2 gene mutations 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.

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

☐ Inpatient private hospital
☐ Inpatient public hospital
☐ Outpatient clinic
☐ Emergency Department
☐ Consulting rooms
☐ Day surgery centre
☐ Residential aged care facility
☐ Patient's home
☒ Laboratory
☐ Other – please specify below

The 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.

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

Not applicable.

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

☒ Yes
☐ No – please specify below

Specify further details here. Not applicable

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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 nominated comparator for the medical service of testing to detect BRCA1/2 gene mutations in patients newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy) is **no testing**.

Some patients with advanced advanced (FIGO stage III-IV) disease may also be eligible for MBS 73296 to detect germline BRCA1/2 gene mutations. Similarily, MBS item numbers exist for blood-based testing for germline BRCA1/2 mutations (Items 73295, 73296, 73297).

The nominated comparator for olaparib as maintenance treatment in patients following first line platinum therapy is '**watch and wait', or no active anticancer treatment**.

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

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

No MBS item has been nominated as the comparator A similar medical service to MBS item 73295 pertains to a subset of the target patient population and brings forward BRCA testing. This application requests an amendment to MBS item #73295.

Specify item number/s here:

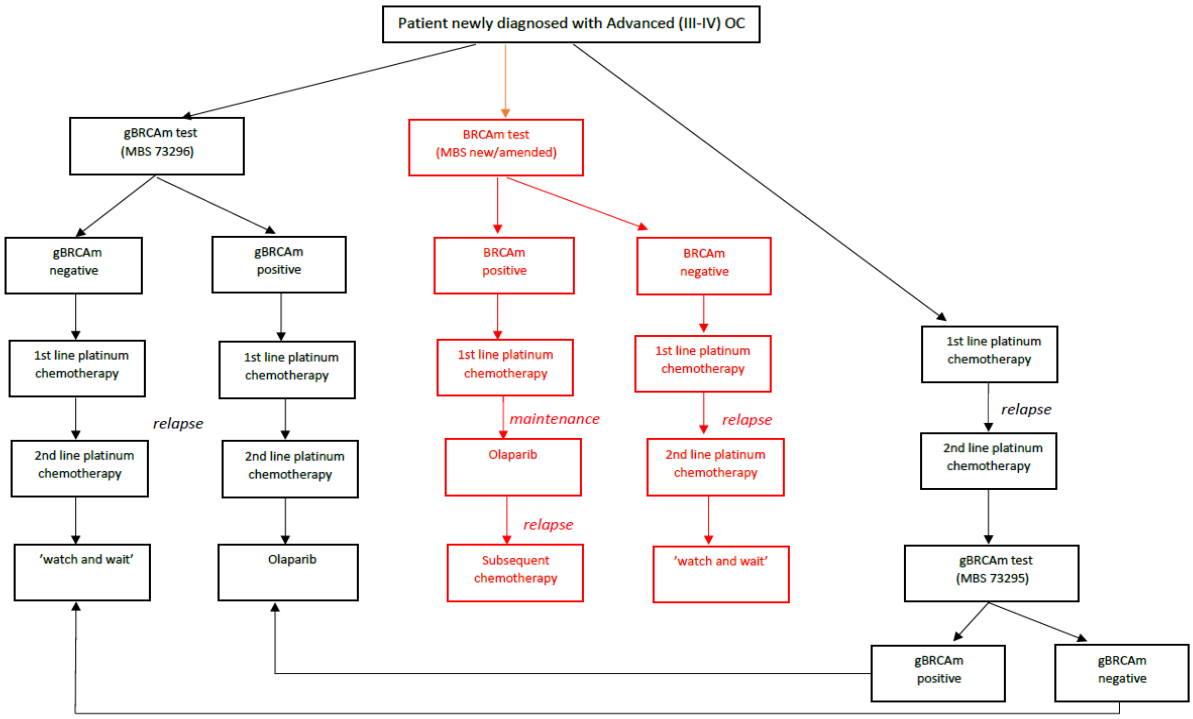
41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical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

The nominated comparator is 'no test' and 'no active treatment'

As discussed in #27 and #39 above, patients newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy). However, based on current ovarian guidelines, it is recommended that newly diagnosed patients be referred for BRCA testing.

In Q27 it was outlined in the current treatment algorithm that patients who are BRCA1/2 (whether this is determined by MBS 73296 or MBS 73295) and have a tumour sensitive to chemotherapy but have relapsed, and have completed at least two courses of platinum-based doublet chemotherapy currently need to "wait and wait" (no active anticancer treatment). In the proposed clinical treatment algorithm, patients newly diagnosed advanced (FIGO III-IV) ovarian cancer could be tested earlier than MBS 73295 if they do not meet the criteria for MBS 73296, therefore bringing forward BRCA testing by one line of therapy. If patient are BRCA mutation positive they are able to access PBS listed olaparib as maintenance therapy after first line platinum base therapy (partial or complete response). Those patients who test negative for BRCA will not receive active treatment or 'watch and wait'.

Please refer to the Microsoft Word attachment to this application, 'Advanced (FIGO III-IV) OC Algorithm' and 'Proposed algorithm' for an editable version of this flowchart below. The proposed change to the current algorithm with the addition of the new medical service is high-lighted in red.



Abbreviations: gBRCA germline BRCA1 or BRCA2; BRCAm germline or somatic BRCA1/2; HGSOC high grade serous ovarian cancer; OC ovarian cancer

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

☒ Yes
☐ No

The proposed medical service will be used instead of no BRCA mutation testing to detect BRCA mutations for these patients who currently do not meet the criteria for currently funded MBS item 73296. After first line platinum based therapy, olaparib maintenance treatment will be used instead of no active anticancer treatment in these patients.

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

Up to 100% substitution of no testing for BRCA1/2 mutations with testing for BRCA1/2 mutations. Up to 100% substitution of no active anticancer treatment for patients with BRCA1/2 mutations with olaparib as maintenance therapy in newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy). Patients who are non BRCA mutated will continue to receive no active anticancer treatment or 'watch wait'.

43. 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):

Please refer to the above "Proposed" flowchart in Q41.

Patients who do not meet the criteria to access MBS 73296 will be tested for BRCA mutation at diagnosis of advanced (FIGO III-IV) ovarian disease. After receiving first line platinum based therapy (partial or complete response), these patients are eligible to access PBS-listed olaparib as maintenance therapy. Based on the pivotal trial SOLO1, patients could receive olaparib treatment for up to 2 years or to disease progression, whichever occurs earlier. After this point patients may receive subsequent therapies, such as second line platinum therapy. Consequently, there may be a decrease in utilisation of MBS 73295.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. 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):

The overall clinical claim is that the proposed co-dependent technologies (BRCA mutation testing and olaparib as maintenance therapy) are **superior** in terms of comparative effectiveness versus the main comparator (i.e. no testing with no active treatment or 'watch and wait) in patients newly diagnosed advanced (FIGO stage III-IV) BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy.

45. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

46. 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:

Safety Outcomes:

Safety and tolerability of olaparib treatment assessed by adverse events (AEs), physical examinations, laboratory findings, and vital signs

Clinical Effectiveness Outcomes:

Test outcomes

Trial based (evidentiary standard) analytical performance:

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Clinical utility of test:

Prognostic effect of BRCA1/2 mutation newly diagnosed advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy).

Treatment effect modification of olaparib in patients newly diagnosed with advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy).

Other test-related considerations:

Re-biopsy rates

Test turn-around time

Estimated number of patients being tested

Cost of testing per patient

Drug outcomes

Overall survival (OS)

Progression-free survival (PFS)

Health-related quality of life

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Testing to determine germline BRCA1/2 gene mutation status would be conducted only once per patient in most cases.

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

Tissue testing to determine BRCA1/2 gene mutation status is not required for routine monitoring of a patient. The substantial majority of patients should only require testing once to detect BRCA1/2 gene mutations.

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

Utilisation of testing to detect BRCA1/2 mutations

The incidence of ovarian cancer in Australia is estimated at 1613 new cases in 2018.[1] The number of new cases including the number of fallopian tube or primary peritoneal cancer can be estimated by increasing by an additional 14% in alignment with the proportions reported in Study 19[2] to give 1839 new cases. A large Australian epidemiological survey indicated the proportion of cases with high grade serous histology is 71%, or 1306 cases.[3] Therefore, it is estimated that approximately 1306 patients would require BRCA testing per year.

This study also included an analysis of response to treatment by BRCA1/2 mutation status (germline or somatic). A high proportion (835/918 = 91%) of patients had primary treatment (tumour debulking surgery and received 1st line platinum-based chemotherapy). [3] It is estimated that 1081 (0.91 x 1188) patients would require BRCA testing per year.

Incidence of ovarian cancer in Australia[1]	1613 patients
Adjustment to include fallopian tube and primary peritoneal cancer based on Study 19[2]	1839 patients
High grade serous histology[3]	1306 patients
Receive primary treatment (surgery, platinum-based chemotherapy)[3]	1188 patients
Receive primary platinum based chemotherapy[3]	1081 patients
Response after 1st line chemotherapy (BRCA1/2)[3]	918 patients

Patients eligible for olaparib

In BRCA 1/2 mutation positive subgroup that proportion of patients who responded after first line platinum chemotherapy was 85%. This give a total of 918 patients (0.85 x 1081) who would respond after first line platinum therapy.

In a study of somatic and germline mutations in ovarian, fallopian tube and peritoneal carcinomas including a high grade serous histology subgroup, 26% of HGSOC patients were found to have germline loss-of function mutations in homologous recombination genes, with 75% found in BRCA1/2 (.26 x .75 = 19.5%).[4] Using this approach, if approximately 20% of patients have germline BRCA1/2 mutations this leaves 80% of patients (404 patients per year) who are wild-type and are proposed for tumour testing to

detect somatic BRCA1/2 gene mutations. In this same study only approximately 4% (5% somatic x 71% BRCA1/2) of patients were found to have somatic only BRCA1/2 mutations. Therefore, approximately 220 (24%) of patients could test positive for a BRCA mutation and be eligible for olaparib treatment each year.

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

[1]Australian Institute of Health and Welfare Cancer in Australia 2017.

[2]Lederman J, Harter P, Gourley C, Friedlander M, et.al. *Lancet Oncology*, 2014, **15**:852-61.

[3]Alsop K, Fereday S, Meldrum C, DeFazio A, et.al. *Journal of Clinical Oncology*, 2012, 30(21):2654-2663.

[4]Pennington KP, Walsh T, Harrell MI, Lee MK, et.al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube and peritoneal carcinomas. *Clinical Cancer Research*, 2014, **20**:764-775.

[5]Dougherty BA, Lai Z, Hodgson DR, Orr MCM, et.al. Biological and clinical evidence for somatic mutations in BRCA1/2 as predictive markers for olaparib response in high grade serous ovarian cancers in the maintenance setting. *Oncotarget*, 2017, **8**(27):43653-43661.

50. 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:

It is not anticipated that there would be any supply or demand issues as the overall number of patients requiring testing to detect BRCA1/2 gene mutations 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 item descriptor.

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

PART 8 – COST INFORMATION

51. 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 BRCA1 or BRCA2 mutations according to Item 73295 or Item 73296 is $1,200.00.

Please note that for MSAC Application 1538 the MBS fee of $1400.00 is proposed for tumour testing to detect somatic BRCA1/2 mutations.

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

Testing turnaround time from when the blood sample is collected to test result is between 3 to 8 weeks. The tumour testing to detect somatic BRCA1/2 mutations takes 6-8 weeks from request to reporting.

53. 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 submission requests a modification to the MBS Item 73295 item descriptor to include newly diagnosed advanced (FIGO III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer disease, please note that this is a broader population to the population described in the current MBS item 73295.

Category 6 – Pathology Services	
MBS item 73295	Group P7 - Genetics
Detection of germline BRCA1 or BRCA2 gene mutations, in a patient with newly diagnosed advanced (FIGO III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer disease, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib as maintenance therapy after first line platinum based therapy (partial or complete response) under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime Fee: $1200.00 Benefit: 75% = $900.00 85% = $1020.00	

The proposed MBS descriptor for MSAC Application 1538 has been modified below to include newly diagnosed advanced (FIGO III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer disease.

Category 6 – Pathology Services	
MBS item number	Group P7 - Genetics
Tumor testing for detection of somatic BRCA1 or BRCA2 gene mutations, in a patient with newly diagnosed advanced (FIGO III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer disease, and has been tested for germline BRCA1/2 gene mutations under MBS Item 73295 or 73296 and was found to be germline BRCA1/2 wild-type requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib as maintenance therapy after first line platinum based therapy (partial or complete response) under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime Fee: $1400.00 Benefit: 75% = $1,50.00 85% = $1,190.00	

PART 9 – FEEDBACK

The Department is interested in your feedback.

54. How long did it take to complete the Application Form?

Approximately 2 weeks.

55. (a) Was the Application Form clear and easy to complete?

☒ Yes
☐ No

(b) If no, provide areas of concern:

The application can be readily completed if all the requested information is available.

56. (a) Are the associated Guidelines to the Application Form useful?

☒ Yes
☐ No
Being able to contact the Pathology Services Section staff is also helpful.

(b) If no, what areas did you find not to be useful?

Insert feedback here

57. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☒ Yes
☐ No

(b) If yes, please advise:

There is still a significant amount of repetition in the line of questions within and between the Parts of this Application.