



**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: **Redacted**

Business trading name: **Redacted**

**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 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

Tumour testing to detect somatic BRCA1 or BRCA2 gene mutations, in patients with platinum-sensitive, relapsed high grade serous ovarian cancer (HGSOC), to determine eligibility for PBS olaparib.

## 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.<sup>1</sup> The 5-year relative survival for women with ovarian cancer in Australia is low at 44.4%.<sup>1</sup> 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.<sup>2</sup> Ovarian cancer is a highly chemo-sensitive tumour type, but more than 70% of women with advanced disease initially responding 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. The HGSOC population who have platinum sensitive, relapsed disease is enriched for patients with BRCA1/2 germline and somatic mutations, in comparison to all ovarian cancer patients.

<sup>1</sup>Australian Institute of Health and Welfare Cancer in Australia 2017.

<sup>2</sup>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 BRCA1/2 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 from the time of diagnosis in ovarian cancer patients at >10% risk of having a pathogenic mutation became available on the MBS from November 2017 (Item 73296). Significant changes to the local and international tumour BRCA1/2 mutation testing environment and additional outcomes data (published and unpublished) warrants reconsideration of tumour testing for patients with somatic BRCA1/2 mutations at this time.

Tumour testing to detect somatic BRCA1/2 gene mutations is proposed to be **after** germline BRCA1/2 testing. There are two populations as follows:

- Patients with platinum-sensitive, relapsed HGSOC who were germline BRCA1/2 wild-type when first tested under MBS Item 73295; OR
- Patients with HGSOC who received germline BRCA1/2 testing under item 73296 and were found to be germline BRCA1/2 mutation wild-type, who are platinum sensitive and relapsed after platinum chemotherapy.

HGSOC patients who have no germline BRCA1/2 gene mutation but have a somatic BRCA1/2 gene mutation are not currently eligible for olaparib treatment. It is proposed that these patients should be eligible for olaparib treatment after completion of two lines of platinum chemotherapy and a response (complete or partial) after a platinum free interval of 6 months or greater. Patients who test wild-type for somatic BRCA1/2 gene mutations would receive “watch and wait” or no active anticancer treatment.

**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)

A new MBS item 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.

It is likely that there is overlap between the ovarian cancer population who would qualify for germline testing at diagnosis with Item 73296 and patients with HGSOC who demonstrate platinum sensitivity but eventually relapse. Germline BRCA1/2 testing under Item 73295 may be redundant if patients have already tested positive for germline BRCA1/2 at diagnosis.

The above germline testing methods are routinely performed using DNA extracted from blood samples, whereas the current Application requests a test of the tumour tissue itself to identify somatic only BRCA1/2 gene mutations not currently being detected. The current Application proposes to broaden the population being tested (germline BRCA1/2 testing then tumour BRCA1/2 testing on germline BRCA1/2 wild-types) and also broaden the PBS access to olaparib to include patients with only somatic BRCA1/2 gene mutations.

**(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):

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 tumour BRCA1/2 testing other than the MBS is sought, however in this co-dependent submission public funding for PBS access to olaparib in patients with somatic 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 tumour testing to determine PBS access to olaparib in patients with platinum sensitive, relapsed HGSOC with somatic BRCA1/2 gene mutations.

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

Trade name: LYNPARZA<sup>®</sup>

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:

**Redacted**

## 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: **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

- 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: *Olaparib 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.*

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

**Redacted.**

- 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

**Redacted**

Estimated date of submission to TGA: **Redacted**

Proposed indication(s), if applicable: **Redacted**

Proposed purpose(s), if applicable: **Redacted**

## 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***
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	<a href="http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(16)30376-X.pdf">http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(16)30376-X.pdf</a>  Ledermann JA, Harter P, Gourley C, Friedlander M, et. al. <i>Lancet Oncology</i> , 2016, <b>17</b> (November 2016): 1579-89.	November 2016
<b>Additional diagnostic studies</b>				
2.	Comparative diagnostic study	BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next generation sequencing	<a href="http://www.oncotarget.com/index.php?journal=oncotarget&amp;page=article&amp;op=view&amp;path[]&amp;path[]">http://www.oncotarget.com/index.php?journal=oncotarget&amp;page=article&amp;op=view&amp;path[]&amp;path[]</a>  Mafficini A, Simbolo M, Parisi A, Rusev B, et. al. <i>Oncotarget</i> , 2016 <b>7</b> (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. <i>Journal of Clinical Oncology</i> , 2017 <b>35</b> (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-embedded (FFPE)	Hahnen E, Baumann KH, Heimbach A, Reuss A, et. al. <i>Journal of Clinical Oncology</i> , 2016, <b>34</b> (Supplement 15 May 2016):	May 2016
5.	Comparative diagnostic study		DNA isolated from 42 ovarian tumour samples underwent full sequence and large rearrangement analysis using next generation sequencing	Wehnelt S, Timms K, Copeland K, Hayward C, et. al. <i>Oncology Research and Treatment</i> , 2016, <b>39</b> (Supplement 1) 95 February 2016	February 2016
6.	Comparative diagnostic study		Prevalence and clinical significance of BRCA1/2 germline and somatic mutations in Taiwanese patients with ovarian cancer	<a href="http://www.oncotarget.com/index.php?journal=oncotarget&amp;page=article&amp;op=view&amp;path[]1=13456&amp;path[]4=4022">http://www.oncotarget.com/index.php?journal=oncotarget&amp;page=article&amp;op=view&amp;path[]1=13456&amp;path[]4=4022</a>  Chao A, Chang T-C, Lapke N, Jung S-M, et. al. <i>Oncotarget</i> , 2016, <b>7</b> (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***
7.	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. <i>Cancer Medicine</i> , 2016, 5 (7 July):1640-1646.	April 2016
8.	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.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308695/pdf/oncotarget-07-61845.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308695/pdf/oncotarget-07-61845.pdf</a> Enyedi MZ, Jaksa G, Pinter L, Sukosd F, et.al. <i>Oncotarget</i> , 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***
9.	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.	<a href="https://watermark.silverchair.com/mdw392.28.pdf?token=AQEC_AHi208BE49Ooa9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAcgw_ggHEBgkqhkiG9w0BBwagggG1MIIBsQIBADCCAaoGCSqGS1b3DQE_HATAeBglghkgBZQMEAS4wEQQMCtq-AmJx8VpxAGGAAgEQgIBe0elSzaIDmXm09ni2EVWLfH_2tIJ2FF_Ovo6iZgsipC_cowGsg35w_BTEFPPuOUUn6kp_6jZfhzbD5OAnWI0KFzlu3t3Ex_TyJQTw6bDxCOTz5PbRcnfNNyBOvEj1sXbp1hVvf5IrCi-hALi9KGevCyOc8BY6XzfnvhQa6PuBeJaSt3oHEN-X-sgX9S0BnCEq5Pd6ZCFesicmlp8v-leAV10nyibQL0Q2BjBEH6rHOAOsOUTMv0KPJnYgEZybxIC6-R6E5tZi4BQogRwCZsyuDRdk4aTVAfM1kdKHQlfqaHAptGBz1MvAXrwipb41g-IfnJetKA5xOMNFQzHFQGGEZ0d7MEwFKCdS5EfdRjo3TWK5wcdY0l1t1HHT4e8Y9rgSZ56iQt_yDiLTaaq176gJNv3v6wsCi_ljf0NQB_DCeio-jPD08JUIFM_x0G3dTaAutRBtbaWT-mt8ZXVH8YsOHOamSzbN59v7GlgdV1GSAM950jh754YqR8QA">https://watermark.silverchair.com/mdw392.28.pdf?token=AQEC_AHi208BE49Ooa9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAcgw_ggHEBgkqhkiG9w0BBwagggG1MIIBsQIBADCCAaoGCSqGS1b3DQE_HATAeBglghkgBZQMEAS4wEQQMCtq-AmJx8VpxAGGAAgEQgIBe0elSzaIDmXm09ni2EVWLfH_2tIJ2FF_Ovo6iZgsipC_cowGsg35w_BTEFPPuOUUn6kp_6jZfhzbD5OAnWI0KFzlu3t3Ex_TyJQTw6bDxCOTz5PbRcnfNNyBOvEj1sXbp1hVvf5IrCi-hALi9KGevCyOc8BY6XzfnvhQa6PuBeJaSt3oHEN-X-sgX9S0BnCEq5Pd6ZCFesicmlp8v-leAV10nyibQL0Q2BjBEH6rHOAOsOUTMv0KPJnYgEZybxIC6-R6E5tZi4BQogRwCZsyuDRdk4aTVAfM1kdKHQlfqaHAptGBz1MvAXrwipb41g-IfnJetKA5xOMNFQzHFQGGEZ0d7MEwFKCdS5EfdRjo3TWK5wcdY0l1t1HHT4e8Y9rgSZ56iQt_yDiLTaaq176gJNv3v6wsCi_ljf0NQB_DCeio-jPD08JUIFM_x0G3dTaAutRBtbaWT-mt8ZXVH8YsOHOamSzbN59v7GlgdV1GSAM950jh754YqR8QA</a> Stjepanovic N, Wilson M, Mandrilaras V, Clarke B, et. al. <i>Annals of Oncology</i> , 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***
10	Diagnostic accuracy study		NEBNextDirect BRCA1/2 panel is a hybridisation-based method to enrich nucleic acid targets for detection of BRCA1/2 by next generation (Illumina MiSeq) sequencing. Differences in sensitivity and specificity for frozen tissue samples compared to FFPE samples were reported.	<a href="http://cancerres.aacrjournals.org/content/77/13_Supplement/5362">http://cancerres.aacrjournals.org/content/77/13_Supplement/5362</a>  Adams SM, Patel KM, Emerman AB, Bowman SK, et. al. <i>Cancer Research</i> , 2017, 77(13 Supplement 1 July): Abstract 5362	July 2017
11	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.	<a href="http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e23116">http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e23116</a>  Boulet G, Van Barel, Rotthier A, Goossens D, DelFavero J. <i>Journal of Clinical Oncology</i> , 2017, 35(15 Supplement):e23116	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***
12	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.	<a href="http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e17_060">http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e17_060</a>  Janikova K, Lasabova Z, Gredar M, Farkasova A, et.al. <i>Journal of Clinical Oncology</i> , 2017, <b>35</b> (15 Supplement):e17060	May 2017
13	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.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447142/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447142/</a>  Zhao Q, Yang J, Li L, Cao D, et. al. <i>Journal of Gynaecologic Oncology</i> , 2017, <b>28</b> (4):e39	July 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***
14	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.	<a href="http://mct.aacrjournals.org/content/16/10_Supplement/B29">http://mct.aacrjournals.org/content/16/10_Supplement/B29</a> Londono AI, Farrukh N, Smith MK, Tawfik CM, et.al. <i>Molecular Cancer Therapeutics</i> , 2017, <b>16</b> (10 Supplement 1): Abstract B29	January 2017
15	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.	<a href="https://www.sciencedirect.com/science/article/pii/S1525157817303380">https://www.sciencedirect.com/science/article/pii/S1525157817303380</a> Capone GL, Putignano AL, Saavedra ST, Paganini I, et.al. <i>Journal of Molecular Diagnostics</i> , 2018, <b>20</b> (1):87-94.	

	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***
16	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.	<a href="https://ac.els-cdn.com/S1525157816301787/1-s2.0-S1525157816301787-main.pdf?_tid=7264e1e2-1065-11e8-93f3-00000aacb35d&amp;acdnat=1518489033_e391a79881ac337e09e02850e1a6d6d5">https://ac.els-cdn.com/S1525157816301787/1-s2.0-S1525157816301787-main.pdf?_tid=7264e1e2-1065-11e8-93f3-00000aacb35d&amp;acdnat=1518489033_e391a79881ac337e09e02850e1a6d6d5</a>  Lee W, Jo H, Yin X, Patel NM, et. al. <i>Journal of Molecular Diagnostics</i> , 2018, 20(1):87-94.	January 2018
17	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).	<a href="http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e17060">http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e17060</a>  Blanch S, Antonio F, Zaida GC, Igancio R, et.al. <i>Journal of Clinical Oncology</i> , 2016, 34(15 Supplement): Abstract e17060.	October 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***
18	Diagnostic study		Formalin fixed paraffin embedded tumour tissue samples from 695 patients with ovarian, peritoneal or fallopian tube cancer were analysed by next generation sequencing 300 cancer associated genes (Oncopanel test) including BRCA1/2.	<a href="http://cancerres.aacrjournals.org/content/76/14_Supplement/95">http://cancerres.aacrjournals.org/content/76/14_Supplement/95</a> Stover EH, Howitt B, Lindeman NI, Garraway LA, et.al. <i>Cancer Research</i> , 2016, 76(14 Supplement): Abstract 95.	April 2016
19	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	<a href="https://ac.els-cdn.com/S0959804916315374/1-s2.0-S0959804916315374-main.pdf?_tid=c92b7f60-1072-11e8-a2ad-00000aacb35f&amp;acdnat=1518494762_71d6c2d3dbb37743a5724d610d08a996">https://ac.els-cdn.com/S0959804916315374/1-s2.0-S0959804916315374-main.pdf?_tid=c92b7f60-1072-11e8-a2ad-00000aacb35f&amp;acdnat=1518494762_71d6c2d3dbb37743a5724d610d08a996</a> Herzog T, Xiu J, Bender R, Gatalica Z, et.al. <i>European Journal of Cancer</i> , 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***
20	Diagnostic study		Somatic mutation profiling of advanced breast and ovarian cancers according to germline BRCA1/2 mutation status. Targeted sequencing with Illumina MiSeq TruSeq Amplicon Cancer Panel was performed using archival tumour and germline DNA from advanced breast cancer and ovarian cancer patients. Somatic testing was completed in 151 ovarian cancer patients and germline BRCA1/2 testing in 83 ovarian cancer patients.	<a href="http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.1532">http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.1532</a> Stjepanovic N, Wilson MK, Oza AM, Clarke B, et.al. Journal of Clinical Oncology, 2015, 33(15 Supplement 1)	May 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***
21	Diagnostic study		Analysis of DNA extracted from FFPE ovarian and breast tumour tissue (including 64 serous ovarian cancer samples) to identify significant variants in BRCA1/2 using next generation sequencing methods (Illumina MiSeq). DNA extraction and enrichment with GeneRead DNaseq Targeted Exon Enrichment Panels, and Ion Ampliseq BRCA community panel and TruSeq DNA PCR-free HT Sample preparation Kit.	<p><a href="https://bmcclinpathol.biomedcentral.com/track/pdf/10.1186/s12907-015-0004-6?site=bmcclinpathol.biomedcentral.com">https://bmcclinpathol.biomedcentral.com/track/pdf/10.1186/s12907-015-0004-6?site=bmcclinpathol.biomedcentral.com</a></p> <p>Ellison G, Huang S, Carr H, Wallace A, et.al.  <i>BMC Clinical Pathology</i>, 2015, <b>15</b>(1):5.</p> <p>And</p> <p><a href="https://ac.els-cdn.com/S1525157814001731/1-s2.0-S1525157814001731-main.pdf?_tid=f2e15168-111c-11e8-864d-00000aacb362&amp;acdnat=1518567855_3f5d9a2aae98a7fef72138a5ae47fdag">https://ac.els-cdn.com/S1525157814001731/1-s2.0-S1525157814001731-main.pdf?_tid=f2e15168-111c-11e8-864d-00000aacb362&amp;acdnat=1518567855_3f5d9a2aae98a7fef72138a5ae47fdag</a></p> <p>Wallace A, Ellison G, Huang S, Carr H, et.al.  <i>Journal of Molecular Diagnostics</i>, 2014, <b>16</b>(6): 752 Abstract ST31.</p> <p>And</p> <p><a href="http://www.current-oncology.com/index.php/oncology/article/view/2077/1463">http://www.current-oncology.com/index.php/oncology/article/view/2077/1463</a></p> <p>Ellison G, Huang S, Carr H, Wallace A, et.al.  <i>Current Oncology</i>, 2014, <b>21</b>(2):752 (e378) Abstract P059</p>	<p>March 2015</p> <p>November 2014</p>

	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	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.	<p>Pennington KP, Walsh T, Harrell MI, Lee MK, et.al.  <i>Clinical Cancer Research</i>, 2014, 20(3):764</p> <p>And</p> <p><a href="https://ac.els-cdn.com/S0090825813009438/1-s2.0-S0090825813009438-main.pdf?_tid=8114155a-1146-11e8-aa19-0000aacb360&amp;acdnat=1518585695_8697136926bbdb45f1192c6fe89e843">https://ac.els-cdn.com/S0090825813009438/1-s2.0-S0090825813009438-main.pdf?_tid=8114155a-1146-11e8-aa19-0000aacb360&amp;acdnat=1518585695_8697136926bbdb45f1192c6fe89e843</a></p> <p>Pennington K, Walsh T, Harrell M, Lee M  <i>Gynecologic Oncology</i>, 2013, 131(1):257-58.</p> <p>And</p> <p><a href="https://ac.els-cdn.com/S0090825811009814/1-s2.0-S0090825811009814-main.pdf?_tid=d5dd19d8-11f0-11e8-9f9b-0000aab0f6b&amp;acdnat=1518658851_d764cadb5d00523acb1281dd36c70657">https://ac.els-cdn.com/S0090825811009814/1-s2.0-S0090825811009814-main.pdf?_tid=d5dd19d8-11f0-11e8-9f9b-0000aab0f6b&amp;acdnat=1518658851_d764cadb5d00523acb1281dd36c70657</a></p> <p>Pennington K, Walsh T, Casadei S, Lee M, et.al.  <i>Gynaecologic Oncology</i>, 2012, 125(Supplement 1):S5-6.</p>	<p>February 2014</p> <p>October 2013</p> <p>March 2012</p>

	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	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.	<a href="https://www.nature.com/articles/ncomms4156.pdf">https://www.nature.com/articles/ncomms4156.pdf</a> Kanchi KL, Johnson KJ, Lu C, McLennan MD, et.al. Nature Communications, 2014, 5:3156	January 2014
24	Diagnostic study		A study investigating temporal heterogeneity, in particular the stability of somatic mutations over time, in paired primary and recurrent ovarian carcinomas. Neoplastic and germline DNA was extracted by targeted capture (BROCA panel) from 23 paired samples primary and recurrent ovarian, fallopian tube and peritoneal carcinomas and mutations were detected using massively parallel genomic sequencing (next generation sequencing).	<a href="https://ac.els-cdn.com/S0090825813009438/1-s2.0-S0090825813009438-main.pdf?_tid=8114155a-1146-11e8-aa19-0000aacb360&amp;acdnat=1518585695_8697136926bbdb45f1192c6efe89e843">https://ac.els-cdn.com/S0090825813009438/1-s2.0-S0090825813009438-main.pdf?_tid=8114155a-1146-11e8-aa19-0000aacb360&amp;acdnat=1518585695_8697136926bbdb45f1192c6efe89e843</a> Pennington K, Walsh T, Harrell M, Lee M Gynecologic Oncology, 2013, 131(1):258.	October 2013

	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***
25	Diagnostic study		Massively parallel DNA sequencing was used to characterise base substitutions, short insertions and deletions (indels) copy number alterations and selected fusions across 287 cancer-related genes from routine FFPE clinical specimens (5% ovarian cancer). DNA was extracted from FFPE specimens and then after whole genome library construction there was hybridisation-based capture of 4557 exons from 287 cancer related genes (including BRCA1/2). The hybrid-capture-selected libraries were sequenced to high uniform depth using the Illumina MiSeq platform.	<a href="https://www.nature.com/articles/nbt.2696">https://www.nature.com/articles/nbt.2696</a> Frampton GM, Fichtenholz A, Otto GA, Wang K, et.al. <i>Nature Biotechnology</i> , 2013, <b>31</b> (11):1023	November 2013

	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***
26	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.	<a href="https://academic.oup.com/annonc/article/25/suppl_4/iv308/2241599">https://academic.oup.com/annonc/article/25/suppl_4/iv308/2241599</a>  Yates M, Timms K, Daniels M, Batte B, et.al. <i>Annals of Oncology</i> , 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***
27	Diagnostic and clinical outcome study		BRCA1/2 was sequenced in 235 unselected ovarian cancer specimens. Frozen tumour tissue had DNA extracted using a Qiagen DNA kit followed by amplification with quantitative polymerase chain reaction (Applied Biosystems TaqMan). Primers for BRCA1/2 (Myriad Genetics BRCAnalysis) were used. Sequence products were run on an Megabace4500 automated sequencer. Progression free survival (PFS) was determined for patients found to have a BRCA1/2 mutation, compared to those without mutation.	<a href="http://ascopubs.org/doi/full/10.1200/JCO.2009.27.2997">http://ascopubs.org/doi/full/10.1200/JCO.2009.27.2997</a> Hennessey BTJ, Timms KM, Carey MS, Gutin A, et.al <i>Journal of Clinical Oncology</i> , 2010, <b>28</b> :3570-3576.	July 2010

	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***
28	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).	<a href="https://www.sciencedirect.com/science/article/pii/S0140673617324406">https://www.sciencedirect.com/science/article/pii/S0140673617324406</a>  Coleman RL, Oza AM, Lorusso D, Aghajanian C, et.al. <i>Lancet</i> , 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***
29	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).	<a href="https://www.sciencedirect.com/science/article/pii/S1470204516305599">https://www.sciencedirect.com/science/article/pii/S1470204516305599</a> Swisher EM, Lin KK, Oza AM, Scott CL, et.al. <i>Lancet Oncology</i> , 2017, <b>18</b> :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***
30	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).	<a href="http://www.nejm.org/doi/full/10.1056/NEJMoa1611310">http://www.nejm.org/doi/full/10.1056/NEJMoa1611310</a> 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***
31	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.	<a href="http://ascopubs.org/doi/full/10.1200/JCO.2011.39.8545">http://ascopubs.org/doi/full/10.1200/JCO.2011.39.8545</a> Alsop K, Fereday S, Meldrum C, DeFazio A, et.al. <i>Journal of Clinical Oncology</i> , 2012, <b>30</b> :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***
	Redacted	Redacted	Redacted	Redacted	Redacted
	Redacted	Redacted	Redacted	Redacted	Redacted
	Redacted	Redacted	Redacted	Redacted	Redacted

\* 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 (tumour testing to detect somatic BRCA1/2 gene mutations) are the Royal College of Pathologists of Australasia (RCPA). A statement from the RCPA on the clinical relevance of the test is provided as an attachment to this Application.

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

Not applicable, the comparator for tumour testing to detect somatic BRCA1/2 gene mutations is no tumour testing. Genetic counselling services would not be required for patients who have somatic BRCA1/2 gene mutations.

- 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 is provided as an attachment to this Application.

- 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):**

Name of expert 1: Redacted

Telephone number(s): Redacted

Email address: Redacted

Justification of expertise: Redacted

Name of expert 2: Redacted

Telephone number(s): Redacted

Email addresses: Redacted

Justification of expertise: Redacted

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

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. In Study 19<sup>3</sup> 86% of the study population comprised primary ovarian cancer and patients with primary fallopian tube or primary peritoneal cancer comprised 3 and 11%, respectively. 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.<sup>4</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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. 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,<sup>6</sup> with somatic BRCA1/2 mutations representing up to 30% of all BRCA1/2 mutations.<sup>7</sup> 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.

<sup>1</sup>Australian Institute of Health and Welfare Cancer in Australia 2017.

<sup>2</sup>Australian Institute of Health and Welfare Australian Burden of Disease Study 2011.

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

<sup>4</sup>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>)

<sup>5</sup>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.

<sup>6</sup>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.

<sup>7</sup>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. This may also be significantly before HGSOC patients relapse following treatment with two or more lines of platinum based chemotherapy.

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.

*Proposed patients for tumour testing*

Tumour testing to detect somatic BRCA1/2 gene mutations is proposed to be **after** germline BRCA1/2 testing (whether this is determined at diagnosis or when patients have been shown to be platinum sensitive and have relapsed). There are two populations proposed for tumour testing to detect somatic BRCA1/2 mutations as follows:

- Patients with platinum-sensitive, relapsed HGSOC who were germline BRCA1/2 wild-type when first tested under MBS Item 73295; OR
- Patients with HGSOC who received germline BRCA1/2 testing under item 73296 and were found to be gBRCA1/2 mutation wild-type, who are platinum sensitive and relapsed after platinum chemotherapy.

A revision to the item descriptor for Item 73295 and consistency for the new item number for tumour testing is requested so that BRCA1/2 testing can occur for HGSOC patients who are platinum sensitive and relapsed after their first line of chemotherapy, that is, in parallel with their 2<sup>nd</sup> line of chemotherapy. It is important to allow time after germline BRCA1/2 testing for the more complex tumour testing to detect somatic BRCA1/2 mutations (which can take 6-8 weeks for completion) while 2<sup>nd</sup> line chemotherapy is delivered. This will ensure that patients who then go on to qualify for olaparib avoid delays that could compromise the benefit of olaparib treatment.

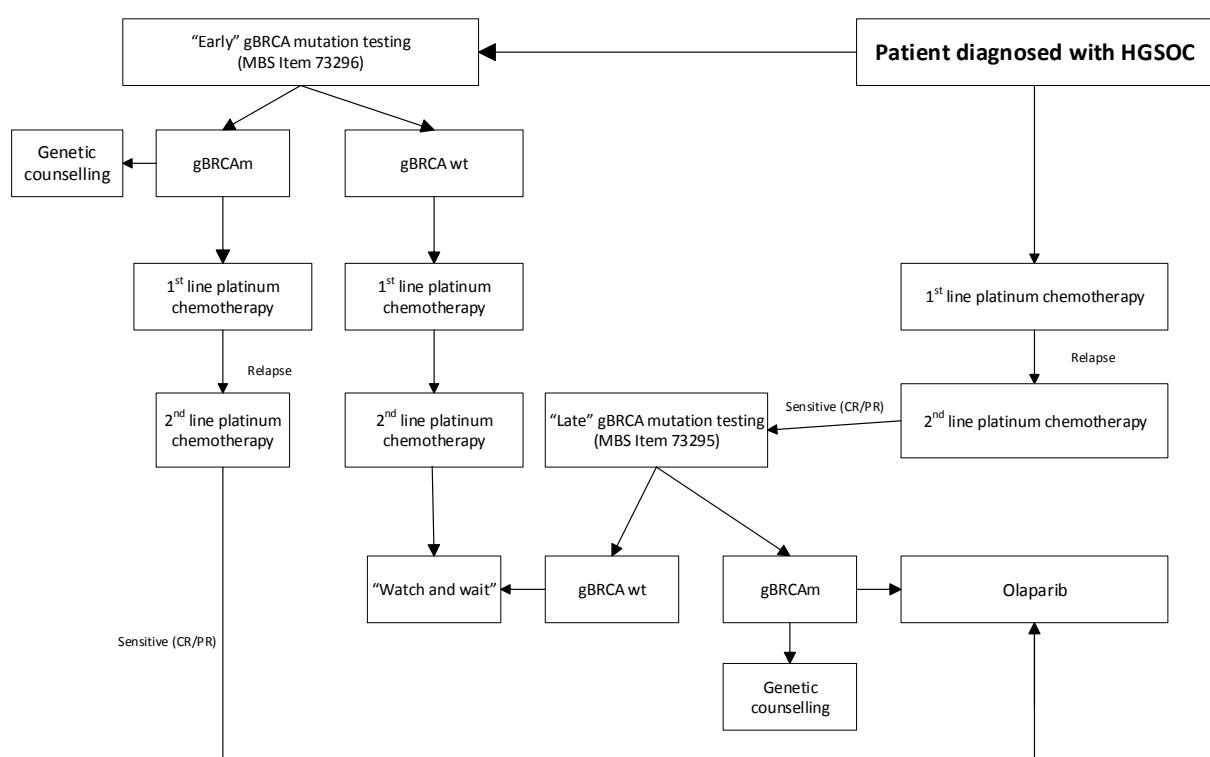
*Proposed patients for olaparib treatment*

It is proposed that HGSOC patients should be eligible for olaparib treatment after completion of two lines of platinum chemotherapy and a response (complete or partial) after a platinum free interval of 6 months

or greater. Patients who are found to have no germline BRCA1/2 gene mutation but have a somatic BRCA1/2 gene mutation are not currently eligible for olaparib treatment. It is proposed that these patients should be eligible for olaparib treatment. Patients who test wild-type for somatic BRCA1/2 gene mutations would receive no active anticancer 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 Visio Attachment to this application, “PSR HGSOC Algorithms”, and “Current” drawing for an editable version of the flowchart below.



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

The majority of patients who are diagnosed with high grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSOC) would currently be eligible for germline BRCA1/2 testing “early” under MBS Item 73296 from the time of diagnosis (ie. 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). First line chemotherapy with a platinum-based chemotherapy regimen is then standard of care 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. 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 received early germline BRCA1/2 testing and were found to be gBRCA1/2 wild type would

still undergo the same treatment of tumour debulking surgery (with or without neo-adjuvant chemotherapy) followed by several rounds of platinum-based chemotherapy, however these patients are not currently eligible for olaparib treatment even if they have relapsed and have demonstrated sensitivity to platinum-based treatment. The next step for these patients is “watch and wait”, or no active anticancer treatment.

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 “late” 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. Patients who are germline BRCA1/2 wild-type are not eligible for olaparib and currently have “watch and wait”, or no active anticancer treatment.

**PART 6b – INFORMATION ABOUT THE INTERVENTION**

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

*Tumour BRCA1/2 testing*

For the substantial majority of patients with platinum sensitive, relapsed HGSOC tumour specimens to provide tissue for BRCA1/2 testing will be available as formalin-fixed paraffin-embedded blocks archived following primary tumour debulking surgery. However, HGSOC patients proposed for testing will have relapsed following two or more lines of platinum based chemotherapy, consequently 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.

Blood-based germline BRCA1/2 testing will have been determined prior to tumour BRCA1/2 testing and since the nature of the specimen is different tumour BRCA1/2 testing should be requested by a specialist or consultant physician. In addition, the HGSOC patients proposed for testing will need to have relapsed after 1<sup>st</sup> line platinum-based chemotherapy, as assessed by the treating specialist or consultant physician, so they are best placed to order the test.

**Redacted.**

Macro- or micro-dissection of the specimen may be required to increase the proportion of tumour tissue. DNA is extracted, purified and may be quantified using the laboratory's preferred commercially available kits. PCR amplification methods, including multiplex ligation dependent probe amplification (MLPA) may be used. Hybridisation capture baits may also be used. Libraries for sequencing are prepared and library quality may be evaluated at this step. Some gene panels (eg BROCA) identify all classes of mutations including single base substitutions, small insertions and deletions and large gene re-arrangements. Variants are called using comparison to reference libraries. Next generation sequencing is performed at most Australian laboratories using the Illumina MiSeq platform, although some laboratories have moved to Illumina NextSeq. Sequencing results are then reported to the requesting specialist or consultant physician.

*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.

Eligibility for PBS treatment with olaparib is proposed in HGSOC patients who are found to have no germline BRCA1/2 gene mutations but have a somatic BRCA1/2 gene mutation identified by tumour BRCA1/2 testing as described above. HGSOC patients need to have completed two lines of platinum based chemotherapy and have a response (complete or partial) after a 6 months or greater platinum free interval. HGSOC Patients who test wild-type for somatic BRCA1/2 gene mutations would receive best supportive care/no active anticancer treatment.

**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?**

The tumour testing approach to identify somatic BRCA1/2 mutations is relatively new and is not yet reimbursed on the MBS. Using this approach to testing could identify new patients with somatic BRCA1/2 mutations who could potentially benefit from PARP inhibitor treatment with LYNPARZA. These platinum sensitive, relapsed HGSOC patients are not currently eligible for reimbursed LYNPARZA and have no treatment alternatives. Therefore, this approach represents a new approach to both testing and treatment.

**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):**

It is unlikely that patients would require more than one somatic BRCA1/2 test in their lifetime. There are a number of DNA quality assurance checks during the process outlined in Q28 above to determine if the sample is adequate to progress to the next step, minimising re-testing.

**32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:**

No genetic counselling services are required for platinum sensitive, relapsed HGSOC patients who test positive for somatic BRCA1/2 gene mutations. No additional medical services are required at the same time as tumour BRCA1/2 testing.

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

Tumour testing to identify BRCA1/2 gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Tumour 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:**

Tumour testing to identify BRCA1/2 gene mutations in patients with platinum sensitive, relapsed HGSOC 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:**

Tumour testing to identify BRCA1/2 gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Tumour 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 tumour testing to detect somatic BRCA1/2 gene mutations in patients with platinum sensitive, relapsed HGSOC and no germline BRCA1/2 mutations is **no testing**. Patients with platinum sensitive, relapsed HGSOC are eligible for MBS BRCA1/2 testing to detect germline BRCA1/2 gene mutations, but there is no MBS subsidy for tumour testing to detect somatic only BRCA1/2 mutations. Similar MBS item numbers exist for blood-based testing for germline BRCA1/2 mutations (Items 73295, 73296, 73297), but the proposed tumour testing is in addition to, and after germline BRCA1/2 status has been determined, rather than in place of these tests.

The nominated comparator for olaparib treatment in patients with platinum sensitive, relapsed HGSOC 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

Specify item number/s here:

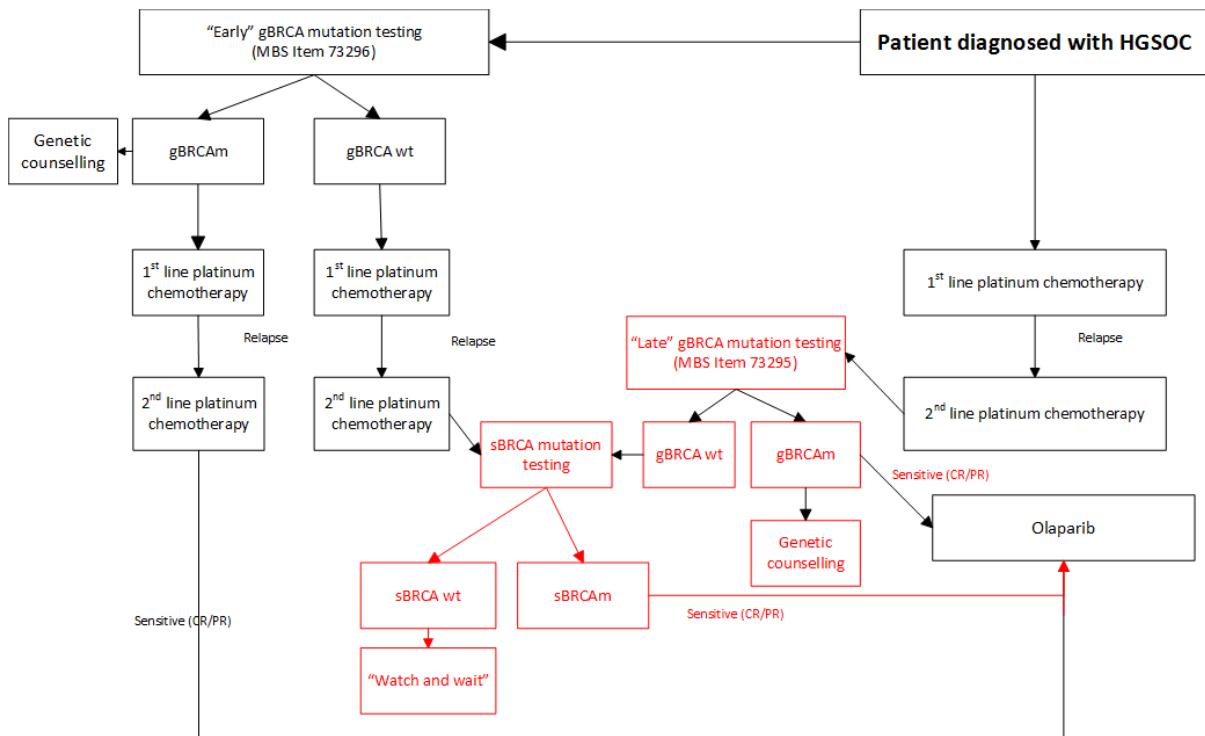
- 41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical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

Please refer to the Microsoft Visio Attachment to this application, “HGSOC Algorithms”, and “Proposed” drawing for an editable version of the flowchart below.

In Q27 it was outlined in the current treatment algorithm that patients who are germline BRCA1/2 wild type (whether this is determined by an “early” or “late” blood-based test) 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). These patients are not eligible for tumour tissue testing to detect somatic BRCA1/2 gene mutations and are also not eligible for olaparib maintenance treatment.

In the proposed clinical treatment algorithm below, the different treatment pathway for patients who might otherwise receive no tumour tissue testing and “watch and wait” treatment is highlighted in red.

HGSOC patients who are germline BRCA1/2 mutant may be tested “early” from diagnosis or may be tested “late” following relapse after 1<sup>st</sup> line platinum chemotherapy. These patients will become eligible for olaparib after completion of 2<sup>nd</sup> line platinum chemotherapy if they have a response (complete or partial) after a 6 month or greater platinum free interval. HGSOC patients who are germline BRCA1/2 wild-type (whether this is determined by an “early” or “late” blood-based test) and have relapsed after 1<sup>st</sup> line platinum chemotherapy would then become eligible for tumour testing to detect somatic BRCA1/2 gene mutations. If a somatic BRCA1/2 mutation is detected the patient would be eligible for PBS olaparib treatment after completion of second line therapy if they have a response (complete or partial) after a 6 month or greater platinum free interval. Patients who are wild-type for a somatic BRCA1/2 gene mutation would receive “watch and wait” or no active anticancer treatment after completion of second line chemotherapy.



Abbreviations: gBRCA germline BRCA1 or BRCA2; wt wild type; sBRCA somatic BRCA1/2; HGSOC high grade serous 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 in addition to the similar MBS services of blood-based testing to detect germline BRCA1/2 mutations. The proposed medical service will be used instead of no tumour testing to detect somatic mutations for these patients. Olaparib treatment will be used instead of watch and wait, or 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 tumour testing for somatic BRCA1/2 mutations with testing for somatic BRCA1/2 mutations. Up to 100% substitution of no active anticancer treatment for patients with somatic BRCA1/2 mutations with olaparib treatment. Patients who are somatic BRCA1/2 wild-type will continue to receive no active anticancer treatment.

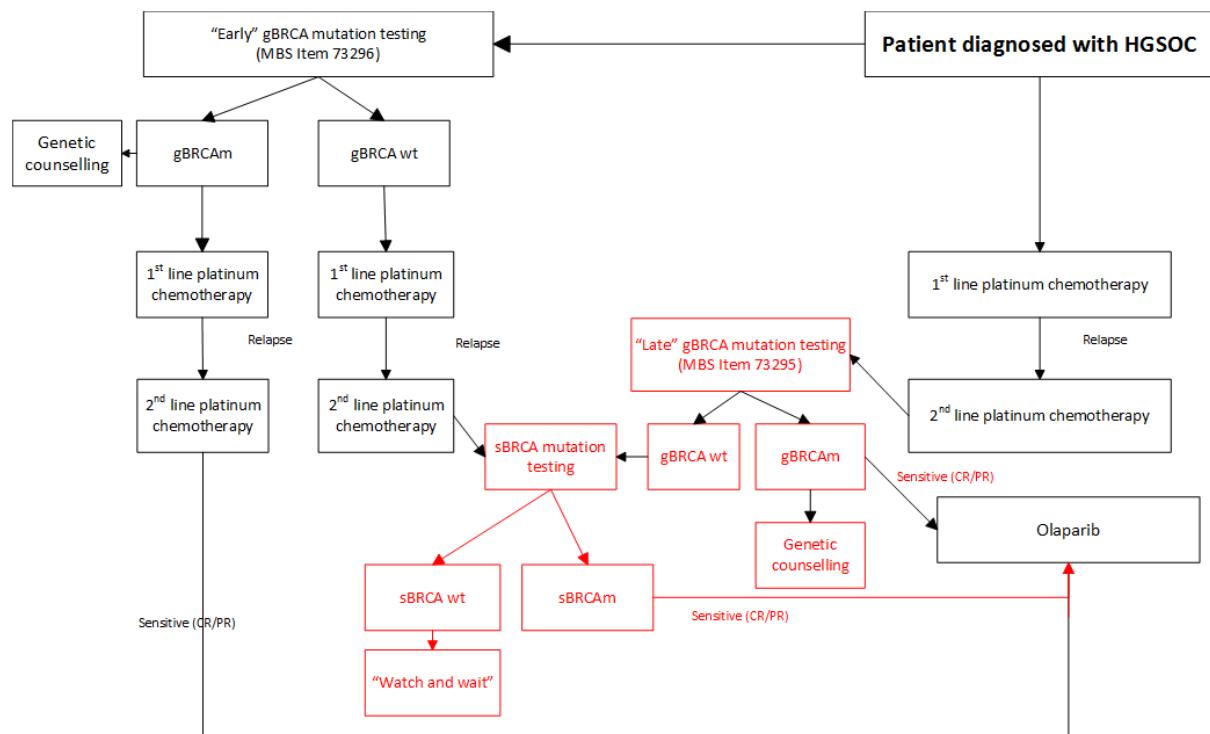
- 43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):**

Please refer to the Microsoft Visio Attachment to this application, HGSOC Algorithms, and "Proposed" drawing for an editable version of the flowchart below.

In the proposed clinical treatment algorithm, reproduced again below, the different treatment pathway for patients who might otherwise receive no tumour tissue testing and "watch and wait" treatment is highlighted in red.

HGSOC patients who are germline BRCA1/2 mutant may be tested "early" from diagnosis or may be tested "late" following relapse after 1<sup>st</sup> line platinum chemotherapy. These patients will become eligible for

olaparib after completion of 2<sup>nd</sup> line platinum chemotherapy if they have a response (complete or partial) after a 6 month or greater platinum free interval. HGSOC patients who are germline BRCA1/2 wild-type (whether this is determined by an “early” or “late” blood-based test) and have relapsed after 1<sup>st</sup> line platinum chemotherapy would then become eligible for tumour testing to detect somatic BRCA1/2 gene mutations. If a somatic BRCA1/2 mutation is detected the patient would be eligible for PBS olaparib treatment after completion of second line therapy if they have a response (complete or partial) after a 6 month or greater platinum free interval. Patients who are wild-type for a somatic BRCA1/2 gene mutation would receive “watch and wait” or no active anticancer treatment after completion of second line chemotherapy.



Abbreviations: gBRCA germline BRCA1 or BRCA2; wt wild type; sBRCA somatic BRCA1/2; HGSOC high grade serous ovarian cancer

**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):**

Overall, tumour testing to identify somatic BRCA1/2 gene mutations in patients with platinum sensitive, relapsed high grade serous ovarian cancer who do not have germline BRCA1/2 gene mutations, and olaparib treatment for patients found to have somatic BRCA1/2 gene mutations and “watch and wait” for patients who do not, is **superior** in terms of comparative effectiveness versus the main comparator (no tumour testing and “watch and wait” for all of these patients).

- 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

Adverse events associated with biopsy/re-biopsy for patients with inadequate tissue

**Clinical Effectiveness Outcomes:**

**Test outcomes**

*Trial based (evidentiary standard) analytical performance:*

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Concordance with blood-based germline BRCA1/2 test methods

*Clinical utility of test:*

Prognostic effect of BRCA1/2 mutation in platinum sensitive, relapsed HGSOC

Treatment effect modification of olaparib in platinum sensitive, relapsed HGSOC

*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:

Tumour tissue testing to determine somatic 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?

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

The incidence of ovarian cancer in Australia is estimated at 1613 new cases in 2018.<sup>1</sup> 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<sup>2</sup> 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.<sup>3</sup> 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 1<sup>st</sup> line platinum-based chemotherapy).<sup>3</sup> In the BRCA1/2 mutation wild-type subgroup (701/835 = 84% of patients) the proportion who demonstrated platinum sensitivity (>6months response to first progression) was 68% (.84 x .68 x 1188 = 679 patients).<sup>3</sup> This is an estimate of the number of patients who would require tumour testing per year.

Incidence of ovarian cancer in Australia <sup>1</sup>	1613 patients
Adjustment to include fallopian tube and primary peritoneal cancer based on Study 19 <sup>2</sup>	1839 patients
High grade serous histology <sup>3</sup>	1306 patients
Receive primary treatment (surgery, platinum-based chemotherapy) <sup>3</sup>	1188 patients
Response after 1 <sup>st</sup> line chemotherapy (BRCA1/2 wild-type subgroup) <sup>3</sup>	679 patients

#### **Redacted.**

<sup>1</sup>Australian Institute of Health and Welfare Cancer in Australia 2017.

<sup>2</sup>Lederman J, Harter P, Gourley C, Friedlander M, et.al. *Lancet Oncology*, 2014, **15**:852-61.

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

### 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 tumour testing to detect somatic BRCA1/2 gene mutations is manageable even if the number of laboratories conducting testing does not increase. **Redacted**.

## 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. Tumour testing to detect somatic BRCA1/2 may have additional complexity over blood-based tumour testing as FFPE tumour specimens may need to be retrieved from archive and transported to the testing laboratory. Macro or micro-dissection of the tumour specimen may be required and DNA quality assurance may be carried out prior to next generation sequencing. Depending on the quality and quantity of the specimen, multiplex ligation-dependent probe amplification (MLPA) may be required. To make provision for these costs an MBS fee of **Redacted** is proposed for tumour testing to detect somatic BRCA1/2 mutations.

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

Tumour testing to detect somatic BRCA1/2 mutations takes 6-8 weeks from request to reporting. This includes time to request and transport 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. 1-2 days to report the results to requesting specialist or consultant physician.

**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, and also the creation of a new MBS item for tumour testing to detect somatic mutations, as follows:

Category 6 – Pathology Services	
Item 73295	Group P7 - Genetics
Detection of germline BRCA1 or BRCA2 gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, <b>and who has responded to subsequent platinum-based chemotherapy</b> , requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Maximum one test per lifetime	
Fee: \$1200.00 Benefit: 75% = \$900.00      85% = \$1020.00	

Category 6 – Pathology Services	
MBS item number	Group P7 - Genetics
Proposed item descriptor:	
Tumour tissue testing for detection of somatic BRCA1 or BRCA2 gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or high grade serous component, 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 eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
Fee: <b>Redacted</b> Benefit: 75% = <b>Redacted</b> 85% = <b>Redacted</b>	

The proposed PBS Item descriptors for olaparib in ovarian, fallopian tube or primary peritoneal cancer would also require modification as follows:

**High grade serous ovarian cancer**

Treatment Phase: Initial treatment

Clinical criteria:

The condition must be platinum sensitive,

AND

Patient must have received at least two previous platinum-containing regimens,

AND

Patient must have relapsed following a previous platinum-containing regimen,

AND

Patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen,

AND

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

The treatment must be maintenance therapy,

AND

Patient must not have previously received PBS-subsidised treatment with this drug for this condition.

Population criteria:

Patient must have evidence of a germline **or somatic** class 4 or 5 BRCA1 or BRCA2 gene mutation.

Platinum sensitivity is defined as disease progression greater than 6 months after completion of the penultimate platinum regimen.

A response (complete or partial) to the platinum-based chemotherapy regimen is to be assessed using either Gynaecologic Cancer InterGroup (GCIG) or Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

Evidence of a BRCA1 or BRCA2 gene mutation must be derived through germline **or somatic** testing.

**High grade serous ovarian cancer**

Treatment Phase: Continuing treatment

Clinical criteria:

Patient must have previously received PBS-subsidised treatment with this drug for this condition,

AND

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

The treatment must be maintenance therapy,

AND

Patient must not have progressive disease.

Olaparib PBS list and net pricing is proposed to be the same as current.

## PART 9 – FEEDBACK

The Department is interested in your feedback.

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

Approximately four weeks.

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

- Yes
- No

**(b) If no, provide areas of concern:**

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

- Yes
- No

**(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:**