



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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Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/A

Corporation name: AstraZeneca Pty Limited

ABN: **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

Germline *BRCA* mutation testing to determine eligibility for olaparib treatment in patients with locally advanced or metastatic HER2 negative breast cancer (either hormone receptor positive or triple negative). It is proposed that only patients who are germline *BRCA* mutation positive and have received prior treatment with anthracycline and taxane and also refractory to hormone therapy will be eligible for olaparib treatment.

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)

In Australia, breast cancer is the most common cancer affecting women. In 2017, it is estimated that 17,586 women and 144 men will be diagnosed with breast cancer¹. On average, 48 Australians are diagnosed with breast cancer each day. The risk of being diagnosed with breast cancer increases with age, with 78% of new cases of breast cancer developing in women over the age of 50. A personal history of breast cancer or family history are contributing risk factors with approximately 5 to 10% of breast cancers due to a strong family history or genetic mutation; such as in *BRCA1* or *BRCA2* gene. Women with a *BRCA1* or *BRCA2* mutation are believed to have an intermediate risk of developing breast cancer.² The average cumulative risks of developing breast cancer by 70 years old has been reported as 57–65% for *BRCA1* mutation carriers and 45–49% for *BRCA2* mutation carriers.^{3,4,5}

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 *BRCA* mutation testing is currently well established in Australia especially for familial risk assessment and more recently to determine patient eligibility for olaparib in the ovarian cancer population.

Publically (state) funded *BRCA* genetic testing is available through public and some private Familial Cancer Centres (FCC) across Australia to those families who meet certain criteria. Self-funded gene testing can be arranged through a patient's general practitioner and available through private laboratories.

Germline mutations in *BRCA1* or *BRCA2* are present in around 5% of breast cancers overall⁶, and the eviQ guidelines currently recommend *BRCAM* testing in individuals with: TNBC age ≤ 50; high-grade non-mucinous ovarian cancer age ≤ 70; non-mucinous *ovarian cancer*, any age + family history; OR known *BRCA* mutation in a relative *BRCA* testing is not routinely recommended for all women diagnosed with the disease.⁷

Testing for germline *BRCA* mutation informs treatment choices and outcomes,^{8, 9, 10} and will ensure that targeted products such as olaparib are used for indications where patients are eligible for treatment and

¹ <https://www.bcna.org.au/understanding-breast-cancer/>

² Balmana J, Diez O, Rubio IT, Cardoso F, ESMO Guidelines Working Group. *BRCA* in breast cancer: ESMO Clinical Practice Guidelines. *Ann. Oncol.* 2011;22(Suppl 6):vi31-34.

³ Balmana J, Diez O, Rubio IT, Cardoso F, ESMO Guidelines Working Group. *BRCA* in breast cancer: ESMO Clinical Practice Guidelines. *Ann. Oncol.* 2011;22(Suppl 6):vi31-34.

⁴ Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am. J. Hum. Genet.* 2003;72(5):1117-1130.

⁵ Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J. Clin. Oncol.* 2007;25(11):1329-1333.

⁶ Villarreal-Garza C et al. *Cancer* 2015; February 1:372–378

⁷ eviQ Cancer Treatments Online. *Genetic Testing for Heritable Mutations in the BRCA1 and BRCA2 Genes* 2014; <https://www.eviq.org.au/Protocol/tabid/66/categoryid/440/id/620/Genetic%20Testing%20for%20Heritable%20Mutations%20in%20the%20BRCA1%20and%20BRCA2%20Genes.aspx>

⁸ Isakoff SJ, Mayer EL, He L, et al. TBCRC009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy With Biomarker Assessment in Metastatic Triple-Negative Breast Cancer. *J. Clin. Oncol.* 2015;33(17):1902-1909.

will get the most benefit. In addition, *BRCA* mutation testing can help identify and address increased cancer risk in family members through surveillance or prophylactic surgery.¹¹

This co-dependent submission requests public funding for germline *BRCA* mutation testing to determine eligibility of olaparib treatment in patients with locally advanced or metastatic HER2 negative breast cancer (which are either hormone receptor positive or triple negative). It is proposed that only patients who are germline *BRCA* mutation positive and have received prior treatment with anthracycline and taxane and are refractory to hormone therapy will be eligible for olaparib 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)

AstraZeneca will be guided by the Department of Health (DoH) and MSAC to assess whether an amendment to the existing MBS item or new MBS item is required.

(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:

MBS item # 73295

(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):

MBS item # 73295 is a medical service funded for the 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, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

This application seeks funding for the detection of germline *BRCA1* or *BRCA2* gene mutations but for a different patient population (a patient with advanced or metastatic HER2 negative breast cancer) to determine their eligibility to access olaparib. AstraZeneca will be guided by the DoH and MSAC to assess whether an amendment to the existing MBS item or new MBS item is required.

(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)

⁹ Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):235-244

¹⁰ Tutt A, Ellis PA, Kilburn LL, et al. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or *BRCA1/2* breast cancer. Presented at the San Antonio Breast Cancer Symposium (SABCS), 9-13 December, San Antonio, Tx. 2014.

¹¹ Petrucelli N, Daly MB, Feldman GL. *BRCA1* and *BRCA2* Hereditary Breast and Ovarian Cancer. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews(R)*. Seattle (WA)1993.

- 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 germline *BRCA* mutation testing other than the MBS is sought, however in this co-dependent submission public funding for PBS access to olaparib is also being sought.

(g) If yes, please advise: Not applicable

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

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

MBS item # 73295

(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 germline *BRCA* mutation testing to determine PBS access to olaparib.

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

Trade name: LYNPARZA®

Generic name: olaparib

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Protheses 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 Protheses 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: Peripheral blood sample collected in a single use syringe

Multi-use consumables: Insert description of multi use consumables here

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:**

The proposed medical service, germline *BRCA* mutation testing in this application is an established service and there is no single sponsor for germline *BRCAM* testing in Australia. At present, there are several different Australian molecular pathology service providers that offer *BRCAM* testing on a commercial basis. AstraZeneca has contacted a number of providers to obtain information about the methods that are used for *BRCAM* testing in current clinical practice. The majority (90%) of laboratories are using MiSeq - NGS platform (Illumina). Other platforms in use are Ion Torrent - NGS platform (Life Technologies – Thermo Fisher) and Applied biosystems – Sanger Sequencing (Life Technologies – Thermo Fisher).

All molecular pathology service providers that currently perform germline *BRCAM* testing services in Australia use in-house developed testing methods (as opposed to commercial test kits). Under the 2010 TGA regulatory framework, *BRCAM* tests that are used to determine eligibility for olaparib are classified as in-house developed Class 3 in vitro diagnostic medical devices (IVDs)¹². Recent reforms to the TGA framework require laboratories that deal with Class 3 IVDs to provide the TGA with a declaration of conformity that the in-house IVDs comply with the essential principles and describe the 'kinds' of IVDs manufactured. It is understood that a transition period is in place until 30 June 2017.

The test methodology proposed in this application remains unchanged to the methodology considered by MSAC in making its recommendation for the reimbursement of the test via MBS item #73295.

Type of therapeutic good: Insert description of single use consumables here

Manufacturer's name:

Sponsor's name: Insert description of single use consumables here

- (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?**

The proposed medical service involves the use of an in-vitro diagnostic test to detect *BRCA* mutations in patients with advanced/metastatic cancer, in order to determine eligibility for olaparib treatment. Because this is a human genetic test intended to identify patients who may benefit from treatment with olaparib, all manufactured and in-house laboratory tests that are intended for use in *BRCA* mutation testing are classified as Class 3 in vitro diagnostic medical devices (IVDs).

- 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?** Not applicable see response in # 14 above

- 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)?** Not applicable see response above

- Yes (if yes, please provide details below)
 No

¹² Therapeutic Goods Administration. *Overview of the new regulatory framework for in vitro diagnostic medical devices (IVDs) 2011*; <http://www.tga.gov.au/industry/ivd-framework-overview.htm>

ARTG listing, registration or inclusion number: Insert ARTG number here
TGA approved indication(s), if applicable: Insert approved indication(s) here
TGA approved purpose(s), if applicable: Insert approved purpose(s) here

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? Not applicable

- Yes (please provide details below)
 No

Date of submission to TGA: Insert date of submission here
Estimated date by which TGA approval can be expected: Insert estimated date here
TGA Application ID: Insert TGA Application ID here
TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here
TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

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? Not applicable

- Yes (please provide details below)
 No

Estimated date of submission to TGA: Insert date of submission here
Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)
Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

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***
1	Observational	Detection of inherited mutations for hereditary cancer using target enrichment and next generation sequencing	Next generation sequencing (NGS) has been rapidly evolving to increase testing sensitivity and throughput. It can be potentially used to identify inherited mutation in clinical diagnostic setting. This demonstrate that the target enrichment combined with NGS method provides the accuracy, sensitivity, and high throughput for genetic testing for patients with high risk of hereditary or familial cancer	https://rd.springer.com/article/10.1007/s10689-014-9749-9	Guan Y. <i>et al.</i> Fam Cancer. 2015 14(1):9-18
2	Study of diagnostic accuracy	Genetic Testing in Hereditary Breast and Ovarian Cancer Using Massive Parallel Sequencing	The aim of this study was to develop a workflow for the detection of BRCA1 and BRCA2 mutations using massive parallel sequencing in a 454 GS Junior bench top sequencer. The investigators workflow was first validated in a panel of 23 patients previously Sanger sequenced. Subsequently, 101 patients with familial breast and ovarian cancer were studied. We found 18 pathogenic mutations and 10 variants with unknown clinical significant effect (VUS). We show here that our workflow performs as Sanger sequencing in terms of sensitivity and specificity with the advantage of taking less time and cost consuming being suitable for genetic diagnosis.	https://www.hindawi.com/journals/bmri/2014/542541/	Ruiz A. <i>et al.</i> Biomed Res Int. 2014:542541

	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	Study of diagnostic accuracy	Development and Validation of a Next-Generation Sequencing Assay for <i>BRCA1</i> and <i>BRCA2</i> Variants for the Clinical Laboratory	The objective of this study was to design and validate a next-generation sequencing assay (NGS) to detect <i>BRCA1</i> and <i>BRCA2</i> mutations. The investigators developed an NGS <i>BRCA1/2</i> sequencing assay, MiSeq/QSAP, with 100% analytic sensitivity and specificity in the validation set consisting of 379 variants. The MiSeq/QSAP combination has sufficient performance for use in a clinical laboratory.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546651/	Strom CM et al. PLoS One. 2015 Aug 21;10(8):e0136419. doi: 10.1371/journal.pone.0136419.
4	Study of diagnostic accuracy	Detection of false positive mutations in BRCA gene by next generation sequencing.	New age sequencing platforms have revolutionized massively parallel sequencing in clinical practice by providing cost effective, rapid, and sensitive sequencing. This study critically evaluates the false positives in multiplex panels and suggests the need for careful analysis.	https://www.ncbi.nlm.nih.gov/pubmed/27848044	Fam Cancer. 2017 Jul;16(3):311-317. doi: 10.1007/s10689-016-9955-8.
5	Study of diagnostic accuracy	Validation of an NGS Approach for Diagnostic BRCA1/BRCA2 Mutation Testing	The aim of the study was to evaluate the sensitivity and specificity of the Ion Torrent PGM™ for diagnostic mutation screening of BRCA1/2 genes. The study validated a quick and accurate diagnostic test, with an overall specificity of 95.9% and sensitivity of up to 100% followed by confirmation of the identified variants by Sanger sequencing. The results showed that the Ion AmpliSeq™ BRCA1/2 Community Panel used with the PGM™ platform was able to detect all sequence variants discovered by Sanger sequencing.	https://www.ncbi.nlm.nih.gov/labs/articles/25893891/	Dacheva D. et al. Mol Diagn Ther. 2015 19(2):119-30

	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	Study of diagnostic accuracy	Pilot Study of Validation of Testing BRCA 1/2 Mutation Using Next Generation Sequencing	<p>Testing BRCA 1/2 mutation is important for patients with breast cancer, and Sanger sequencing is a standard method to identify BRCA 1/2 mutation. Next generation sequencing (NGS) is a high-throughput parallel sequencing that can provide genetic information with high accuracy. NGS is a faster and cost-effective method to detect gene mutations compared to Sanger sequencing. In this study, we evaluated the clinical role of NGS testing for BRCA 1/2 compared to Sanger sequencing.</p> <p>Twenty-four paired samples from 12 patients were analyzed in this prospective study to compare the performance of NGS to the Sanger method. Both NGS and Sanger sequencing were performed in 2 different laboratories using blood samples from patients with breast cancer. We then analyzed the accuracy of NGS in terms of variant calling and determining concordance rates of <i>BRCA1/2</i> mutation detection.</p>	<p>https://clinicaltrials.gov/ct2/show/NCT02151747</p> <p>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5416916/</p>	Ann Surg Treat Res. 2017 May; 92(5): 331–339.

	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	Randomised trial	Olaparib for metastatic breast cancer in patients with a Germline BRCA Mutation NCT02000622	<p>A randomised open-label, phase 3 trial in which olaparib monotherapy was compared with standard therapy in patients with a germline BRCA mutation and human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease. Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles). The primary end point was progression-free survival.</p> <p>Results demonstrated Median progression-free survival was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval, 0.43 to 0.80; P<0.001). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group. The rate of grade 3 or higher adverse events was 36.6% in the olaparib group and 50.5% in the standard-therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9% and 7.7%, respectively.</p>	http://www.nejm.org/doi/full/10.1056/NEJMoa1706450#t=article	Robson et al 2017 DOI: 10.1056/NEJMoa1706450

* 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 trial	Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA)	Olaparib treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy . Primary Outcome Measures: Invasive Disease Free Survival (IDFS) [Time Frame: Up to 10 years] Time from randomisation to date of first treatment failure that is loco-regional or distant recurrence or new cancer or death from any cause	ClinicalTrials.gov Identifier: NCT02032823	Yet to be published

* 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 Royal College of Pathologist of Australasia

A statement of clinical relevance for the proposed medical service has been request and will be send separately to this application

List all professional bodies here

- 21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):** Not applicable

List professional bodies here

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

The Breast Cancer Network of Australia (BCNA).

BCNA is the peak national organisation for Australians affected by breast cancer, and consists of a network of more than 120,000 members and 288 Member Groups. More than 90 per cent of members have had a diagnosis of breast cancer. BCNA works to ensure that Australians affected by breast cancer receive the very best support, information, treatment and care appropriate to their individual needs.

A letter of support from BCNA is attached to this application

List relevant consumer organisations here

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

There is no single sponsor for germline *BRCAm* testing in Australia.

List relevant sponsor/s and or manufacturer/s here

- 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 email correspondence with MSAC Secretariat.

Name of expert 1: Insert name here

Telephone number(s): Insert phone number/s here

Email address: Insert email address here

Justification of expertise: Insert a justification of expertise here

Name of expert 2: Insert name here

Telephone number(s): Insert phone number/s here

Email address: Insert email address here

Justification of expertise: Insert a justification of expertise here

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:

In Australia, breast cancer is the most common cancer affecting women. In 2017, it is estimated that 17,586 women and 144 men will be diagnosed with breast cancer¹³. On average, 48 Australians are diagnosed with breast cancer each day. Advanced breast cancer includes both locally advanced and metastatic breast cancer. Although treatable, metastatic breast cancer remains an incurable disease with a median overall survival of about 2 to 3 years and a 5 year survival of only about 25%.^{14,15}

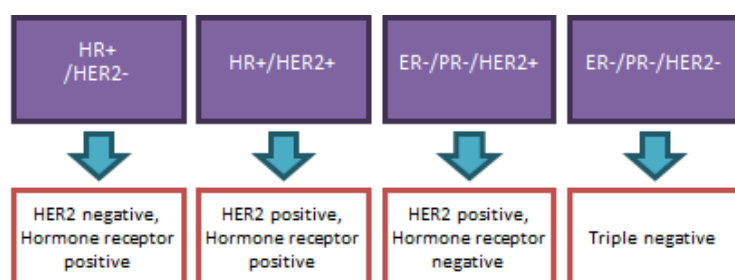
The risk of being diagnosed with breast cancer increases with age, with 78% of new cases of breast cancer developing in women over the age of 50. A personal history of breast cancer or family history are contributing risk factors with approximately 5 to 10% of breast cancers due to a strong family history or genetic mutation; such as *BRCA1* and *BRCA2*. Women with a *BRCA1* or *BRCA2* mutation are believed to have an intermediate risk of developing breast cancer.¹⁶ The average cumulative risks of developing breast cancer by 70 years old has been reported as 57–65% for *BRCA1* mutation carriers and 45–49% for *BRCA2* mutation carriers.^{17,18}

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:

Treatment decisions are impacted not only by receptor status / molecular subtype, but also tumour stage and grade, symptoms and patient factors. Determination of the molecular subtype is a standard part of the workup of breast cancer diagnosis as it provides valuable prognostic information and determines the treatment pathway the patient will follow. In general, the expression of three receptors on the tumour are routinely determined in clinical practice:

- estrogen (ER)
- progesterone (PR)
- human epidermal growth factor receptor 2 (HER2)

Major clinical groups of breast cancer are as follows:



¹³ <https://www.bcna.org.au/understanding-breast-cancer/>

¹⁴ Global Status of Advanced/metastatic breast cancer 2005-2015 Decade report. www.breastcancerrevision.com

¹⁵ Sundquist M et al. trends in survival in metastatic breast cancer. *Cancer Eur J Cancer* 2010; 8(3)191 Abstract 453

¹⁶ Balmana J, Diez O, Rubio IT, Cardoso F, ESMO Guidelines Working Group. *BRCA* in breast cancer: ESMO Clinical Practice Guidelines. *Ann. Oncol.* 2011;22(Suppl 6):vi31-34.

¹⁷ Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am. J. Hum. Genet.* 2003;72(5):1117-1130

¹⁸ Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J. Clin. Oncol.* 2007;25(11):1329-1333.

The majority of breast cancers are HR+/HER2 negative (72.7%) based on histological subtypes; whereas approximately 12% are triple negative (TNBC)¹⁹. In particular, TNBC has been associated with more aggressive disease and worse survival versus non-TNBC.^{20,21,22}

Epidemiology data show a high prevalence of *BRCA1* mutations in TNBC patients and that these mutations are not restricted to young women or patients with a positive family history.^{23,24,25,26} TNBC has been incorporated into *BRCA1/2* genetic testing guideline recommendations from NICE and NCCN,^{27,28} although the guidelines vary on the age group for this cancer subtype. While the frequency of *BRCA1/2* mutations is higher among women with TNBC than in those with HR+/HER2 negative disease, the latter comprises a much larger proportion of the total breast cancer population. This means there are potentially more women harbouring *BRCA1/2* mutations who have HR+/HER2 negative disease than have TNBC.

In current clinical practice, *BRCA* mutation testing is performed for the main purpose of determining whether an individual is genetically predisposed to developing breast, ovarian or other BRCA-related cancers.²⁹

In Australia, many Genetic /Familial Cancer Centres use the criteria outlined in the eviQ '*Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes*'³⁰, to identify suitable candidates for BRCAm testing for the purpose of familial cancer risk assessment. EviQ is an online point of care cancer treatment information resource that provides health professionals with current evidence-based, peer-reviewed, best practice cancer treatment protocols relevant to the Australian clinical environment. It is designed to support a busy work flow in all clinical and geographical settings, providing rural, remote and metropolitan health professionals, patients, carers and their families with access to the same standard evidence-based information. The eviQ guidelines currently recommend BRCAm testing for the purpose of familial cancer risk assessment in individuals with a greater than 10% probability of carrying a mutation, based on their personal or family history of cancer. This includes a recommendation for BRCAm testing in individuals with: TNBC age ≤ 50; high-grade non-mucinous ovarian cancer age ≤ 70; non-mucinous ovarian cancer, any age + family history; OR known BRCA mutation in a relative.

AstraZeneca notes a submission by the Royal College of Pathologist of Australasia (Application No. 1411.1) which is seeking MBS funding of diagnostic testing of hereditary mutations (including *BRCA* mutations) predisposing to breast and/or ovarian cancer. The outcome of this submission is currently pending.

Refer to #27 and #28 for further detail how a patient would be investigated and managed within the Australian Health Care System.

¹⁹ Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J. Natl. Cancer Inst.* 2014;106(5)

²⁰ Hudis CA, Gianni L. Triple-negative breast cancer: an unmet medical need. *Oncologist.* 2011;16(Suppl 1):1-11

²¹ Li X, Yang J, Peng L, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. *Breast Cancer Res. Treat.* 2017;161(2):279-287

²² Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J. Clin. Oncol.* 2008;26(8):1275-1281.

²³ Muendlein A, Rohde BH, Gasser K, et al. Evaluation of BRCA1/2 mutational status among German and Austrian women with triple-negative breast cancer. *J. Cancer Res. Clin. Oncol.* 2015;141(11):2005-2012.

²⁴ Gonzalez-Rivera M, Lobo M, Lopez-Tarruella S, et al. Frequency of germline DNA genetic findings in an unselected prospective cohort of triple-negative breast cancer patients participating in a platinum-based neoadjuvant chemotherapy trial. *Breast Cancer Res. Treat.* 2016;156(3):507-515

²⁵ Wong-Brown MW, Meldrum CJ, Carpenter JE, et al. Prevalence of BRCA1 and BRCA2 germline mutations in patients with triple-negative breast cancer. *Breast Cancer Res. Treat.* 2015;150(1):71-80

²⁶ Fostira F, Tsilaidou M, Papadimitriou C, et al. Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. *Breast Cancer Res. Treat.* 2012;134(1):353-362

²⁷ National Institute for Health and Care Excellence (NICE). Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2017;

<https://www.nice.org.uk/guidance/cg164/chapter/1-recommendations>; . Accessed 16 January 2017.

²⁸ National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology - Genetic/familial high-risk assessment: breast and ovarian. 2013;v4 http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed 3 February 2014

²⁹ Lau C, Suthers G. BRCA testing for familial breast cancer. *Australian Prescriber.* 2011;34(2):49-51

³⁰ eviQ Cancer Treatments Online. *Genetic Testing for Heritable Mutations in the BRCA1 and BRCA2 Genes* 2014; <https://www.eviq.org.au/Protocol/tabid/66/categoryid/440/id/620/Genetic%20Testing%20for%20Heritable%20Mutations%20in%20the%20BRCA1%20and%20BRCA2%20Genes.aspx>

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):

There are no definitive treatment guidelines for HER2 negative, metastatic breast cancer patients with a germline *BRCA* mutation, and these patients are typically treated in the same way as patients with non-hereditary metastatic breast cancer.³¹ In the *BRCA* mutation setting, patients additionally require genetic counselling and testing prior to initiation of treatment.

As surgery is rarely suitable for patients with metastatic disease, the three main treatment options for patients with HER2 negative metastatic breast cancer, regardless of *BRCA* mutation status, tend to include endocrine therapy, chemotherapy and where suitable, targeted therapy.

Clinical management guidelines for metastatic breast cancer is complex with the main treatment goal to maximise length of life and quality of life for patients. Therefore, selection of specific agents is based on a number of factors such as, tumour stage and grade, symptoms and patient factors such tolerability levels.

ER+/HER2 negative

For patients who are ER+/HER2 negative, chemotherapy therapy may include both combination or sequential single agents. Based on the ESMO³²/NCCN³³ guidelines, sequential monotherapy is the preferred choice for metastatic breast cancer. Combination chemotherapy should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

In the absence of any medical contraindications or patient concerns, anthracycline and taxane based regimens, preferably as single agents are considered as first line chemotherapy for HER2 negative metastatic breast cancer, in those patients who have not received these regimens as (neo)adjuvant treatment and for whom chemotherapy is appropriate. For patients who have progressed, other options include capecitabine and vinorelbine (particularly if avoiding alopecia is a priority for the patient).

In patients with taxane-naïve and anthracycline resistant metastatic breast cancer or when anthracycline maximum cumulative dose or toxicity has occurred, taxane-based therapy as a single agent would be considered. Other options include capecitabine and vinorelbine (particularly if avoiding alopecia is a priority for the patient).

In patients pre-treated in the (adjuvant and/or metastatic setting) with an anthracycline and a taxane, and who do not need combination chemotherapy, a single agent capecitabine, vinorelbine or eribulin are preferred choices. Additional agents may include gemcitabine, platinum agents, taxanes and liposomal anthracyclines. Treatment decisions need to be individualised with the consideration of different toxicity profiles, previous exposure and patient preferences.

HR negative/HER2 negative (TNBC)

Triple negative breast cancer patients remain the patient group with the largest unmet need within advanced metastatic breast cancer. Anthracyclines and taxane-based chemotherapy is recommended as initial treatment.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

Based on the guidelines discussed above in #26, germline *BRCA* mutation testing is generally limited to high risk patients (young, family history of breast or ovarian cancer or TNBC). The stage of disease at which *BRCA* testing is offered is also determined by the histological subtypes of the disease. For example,

³¹ Schurer M, Chapman A-M, Beard S. A structured review of published guidelines/recommendations on treatment options for patients with HER2- metastatic breast cancer (with a specific focus on germline BRCA1/2 mutations. Version 2.0 (final). BresMed. 2016.

³² Cardoso et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Annals of Oncology 2016; 1-17 (doi:10.1093/annonco/mdw544)

³³ NCCN National Comprehensive Cancer Network Guidelines Version 2.2017 accessed 22 May 2017
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

patients who are hormone receptor positive may be offered BRCA testing when they are resistant to endocrine therapy, while patients who are diagnosed with TNBC may be offered BRCA testing after their diagnosis.

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.
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. If the results do not detect a mutation, but a VUS (variant of unknown significant result) or strong family history will also result in a face-to-face appointment.
5. Based on a positive BRCAm result the medical practitioner will consider prescribing Olaparib to the patient with metastatic breast cancer if they meet the PBS criteria to access treatment.

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

The test does not have a registered trademark
OLAPARIB® is a registered trade mark

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?

Yes, inclusion of germline BRCA mutation testing on the MBS to determine eligibility for PBS access to olaparib treatment would present a new approach to advanced / metastatic breast cancer patient management particularly for patients who are hormone receptor positive (and includes HER2 negative and triple negative patients).

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):

BRCA testing is currently well established in Australia. It is performed by at least 8 public and 1 private pathology laboratories in Australia. A testing centre is available in each state/territory (except for the Northern Territory). All states/territories in Australia have at least one publically funded Genetic Service centre available to patients and their families.

Because BRCAm testing provides prognostic information that can have an impact on family members, testing is ordinarily preceded and followed by genetic counselling. Pre-test genetic counselling is important to ensure that individuals understand the likelihood of a BRCAm being identified and the risks and benefits of being tested. Post-test genetic counselling helps patients understand the practical meaning of the

results including implications for family members, including risk-reducing strategies that are available if a BRCAm is identified.³⁴

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:

Not applicable. No other medical services or healthcare resources need to be delivered at the same time as germline BRCA mutation testing.

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

Germline BRCA mutation testing is currently conducted and the results interpreted and reported by suitably qualified and trained pathologists.

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: Refer to response in #31 above

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:

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. All laboratories are accredited to the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs. For further information please refer to the website: <https://www.rcpaqap.com.au/home-page>

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

Specify further details here

(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

³⁴ Lau C, Suthers G. BRCA testing for familial breast cancer. *Australian Prescriber*. 2011;34(2):49-51

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):**

Currently germline *BRCA* mutation testing is not funded by the Commonwealth for patients with advanced/metastatic breast cancer to determine their status of the *BRCA 1* and *2* gene. Therefore ‘no testing’ is the comparator.

As discussed in #27, patients with metastatic breast cancer irrespective of a known *BRCA* status are treated with anthracycline and/or taxane therapy. For a HER2 negative metastatic breast cancer patient who has progressed after anthracycline and/or taxane therapy; single agent chemotherapy is a treatment option among the conventional chemotherapies capecitabine, vinorelbine and eribulin.³⁵

- 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#73295 is being sought with this application. MBS item #73295 pertains to a different patient population. This application requests either a new MBS item or an amendment to MBS item #73295, whichever is most appropriate.

- 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 treat with standard of care.

As discussed in #27 and #39 above, patients with metastatic breast cancer irrespective of a known *BRCA* status are treated with anthracycline and/or taxane therapy. For a HER2– metastatic breast cancer patient who has progressed after anthracycline and/or taxane therapy, there is no clear superior agent among the conventional chemotherapies capecitabine, vinorelbine and eribulin.³⁶

- 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 (ie germline *BRCA* mutation testing) will be used instead of the comparator (no germline *BRCA* mutation testing).

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

The comparator (no germline *BRCA* mutation test) will be substituted with a germline *BRCA* mutation test to determine patient eligibility to treatment with olaparib. The availability of a new treatment option will increase uptake of germline *BRCA* mutation testing. A patient can only access olaparib based on a positive *BRCA*m status. Up to 100% substitution of ‘no testing’ with *BRCA* mutation testing could be assumed. However, not all patients may take up testing. Reasons for patients not taking up the test could be cultural

³⁵ NICE. *Advanced breast cancer: diagnosis and treatment. Full guidelines. Developed for NICE by the National Collaborating Centre for Cancer. Last modified July 2014. 2009.*

³⁶ NICE. *Advanced breast cancer: diagnosis and treatment. Full guidelines. Developed for NICE by the National Collaborating Centre for Cancer. Last modified July 2014. 2009.*

or religious³⁷ beliefs. Current uptake of germline BRCA mutation testing in patients with ovarian cancer is approximately 70%.

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):

Of the patients taking up germline *BRCA1/2* mutation testing, approximately 15%³⁸ will test positive for a *BRCA1/2* mutation. Therefore, these patients will be eligible for treatment with Olaparib. The remaining 75% of patients will be treated with the current of standard of care.

Olaparib (Lynparza[®]) will be the first poly ADP-ribose polymerase (PARP) inhibitor to be available as a treatment option for HER2 negative metastatic breast cancer patients with a germline *BRCA* mutation after treatment with anthracyclines or taxanes (suitable as a single chemotherapy agent when hormonal therapy is considered inappropriate).

Olaparib is an oral, potent inhibitor of PARP-1, PARP-2 and PARP-3.³⁹ These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During this repair process, PARP auto-modifies itself and dissociates from the DNA to facilitate access for other repair enzymes. Olaparib inhibits the action of PARP-1 and PARP-2 by preventing their dissociation, trapping PARP on the DNA and blocking repair of the single-strand break. In replicating cells, this then leads to double-strand DNA breaks. In normal cells, DNA double-strand breaks are repaired by homologous recombination repair, which requires functional BRCA1 and BRCA2 proteins. In *BRCA1* or *2*-mutated tumour cells, whereby both copies of the *BRCA* gene have lost function, the non-functional BRCA proteins mean that DNA double-strand breaks cannot be repaired by homologous recombination repair and, instead, alternative and error-prone pathways such as the non-homologous end-joining pathway must be used by the cell. This results in increased genomic instability that, after a number of rounds of cell-cycle replication, can reach insupportable levels and result in cancer cell death.

Olaparib will therefore be a substitute for the current reimbursed standard of care single chemotherapy agents (capecitabine, vinorelbine or eribulin). Olaparib offers patients and medical specialist a targeted treatment for biomarker defined metastatic breast cancer HER2 negative patients with a clinically meaningful efficacy, more favourable safety, toxicity and Health related quality of life profile and ease of administration compared to chemotherapy regimens.

The pivotal clinical study, OlympiAD is a randomised, open-label, phase 3 trial in which olaparib monotherapy was compared with 'standard therapy' in patients with a *gBRCA* mutation and HER2 negative (either hormone receptor positive or triple negative) breast cancer. Patients must also have received no more than two previous chemotherapy regimens for metastatic breast cancer and had received neoadjuvant or adjuvant treatment or treatment for metastatic disease with an anthracycline and a taxane.

Of the 302 patients randomised, 205 were assigned treatment with either olaparib or 'standard of care'. The results demonstrated statistically and clinically significant increase in progression free survival (PFS) /death of 7 months in patients on olaparib compared to 4.2 months in patients on 'standard of care' (capecitabine, vinorelbine or eribulin). Median PFS hazard ratio: 0.58, 95% confidence interval 0.43 to 0.80; $p < 0.001$. The median time from randomisation to a second progression event or death (PFS2) was also significantly increased with olaparib treatment versus 'standard of care' indicating benefit beyond first progression (hazard ratio, 0.57; 95% confidence interval, 0.40 to 0.83; $p = 0.003$). Patients treated with olaparib had a significantly better HRQoL compared with those on 'standard of care', a clinically meaningful benefit for patients. Olaparib tablets were generally well tolerated with the majority of

³⁷ Cohen PA et al Impact of clinical genetics attendance at a gynecologic oncology tumor board on referrals for genetic counselling and BRCA mutation testing. *Int. J Gynecological Cancer* 2016; 26(5):892-897

³⁸ Economic Evaluation Report of MSAC application 1411.1 page 2.

<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1411.1-public>

³⁹ AstraZeneca data on file. Olaparib monotherapy as maintenance treatment of patients with platinum-sensitive relapsed BRCA mutated ovarian cancer. 2.5 Clinical Overview. 15 January 2014

adverse events being mild or moderate in severity and consistent with the safety profile seen in previous studies.⁴⁰

As a consequence of olaparib being listed on the PBS, germline *BRCA* testing will increase as access to olaparib treatment is dependent on a positive *BRCA* status. That is, prior to prescribing olaparib as a treatment option for patients with advanced metastatic HER2 negative breast cancer (either hormone receptor positive or triple negative), patients will require a germline *BRCA* mutation test and must also meet the PBS criteria to access treatment (prior anthracycline and taxane therapy and refractory to hormone therapy).

Other medical services which will also increase as a consequence will be post-test genetic counselling (MBS item # 73295) for patients found to have a *BRCA1/2* mutation.

⁴⁰ Robson et al. N Engl J Med. 2017

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):

Based on the results of OlympiAD described in #43 above.

The overall clinical claim is that the proposed co-dependent technologies (germline *BRCA* mutation testing and olaparib) are superior in terms of comparative effectiveness versus the main comparator (i.e. no testing with the standard care single agent chemotherapy) in patients who harbour a *gBRCA* mutation with locally advanced or metastatic HER2- breast cancer which are hormone receptor positive, or triple negative.

Summarise clinical claims here

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:

The safety and tolerability of olaparib monotherapy treatment assessed by adverse events. Physical examination, vital signs including blood pressure, pulse, electrocardiogram and laboratory findings.

Clinical Effectiveness Outcomes:

Test Outcomes:

Trial based (evidentiary standard) germline BRCA1/2 mutation assay analytical performance:

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Comparative performance of germline BRCA1/2 testing methods:

Concordance with other commercially available germline BRCA1/2 mutation platforms

Concordance with other commercially available germline BRCA1/2 mutation assays

Re-testing rates

Drug Outcomes:

Progression free survival (PFS) (according to RECIST)- Independent Review

Overall Survival (OS)

Time from randomisation to second progression-free event/death after first progression event (PFS2)

Health related quality of life (according to European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C30])

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

It is proposed that patients would be tested for a *BRCA* mutation when the clinician has determined the patient may benefit from treatment with olaparib and have therefore met the PBS criteria to access treatment. The proposed PBS criteria for olaparib is for patients with locally advanced metastatic breast cancer whom are hormone receptor positive (either HER2 negative or triple negative) with a germline *BRCA* mutation. Patients must also have received prior treatment with an anthracycline and a taxane in either the adjuvant or metastatic setting.

Based on current information to date, the best estimate of the population to be tested is based on assumptions presented in **Table 1** below. The estimated incidence is based on the Australia Institute of Health and Welfare (AIHW) projected figures for 2019 (the proposed year that *BRCA* test and olaparib would be funded on the MBS and PBS). AIHW estimated that in 2019 there will be approximately 18066 Australians newly diagnosed with breast cancer.

Please note that the co-dependent MSAC/PBAC submission will include further detailed information to these estimates.

Table 1 Estimated eligible population in 2019

Projected new cases of breast cancer (2019) ⁴¹	18066
Proportion HR+/HER2 negative ⁴²	63%
Proportion TNBC ⁴⁵	17%
Proportion with prior treatment with anthracycline/taxane and not suitable for hormone therapy*	80%
Uptake rate of <i>BRCA</i> test in HR+/HER2 negative population at Year 1, Year 2, Year 3*	30%, 40%, 50%
Uptake rate of <i>BRCA</i> test in TNBC population at Year 1, Year 2, Year 3*	60%, 75%, 80%

*Assumption based on internal market research

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

It is proposed that *BRCA* testing would be delivered once to a patient to determine their eligibility to olaparib treatment. One lifetime germline *BRCA* mutation test is required per patient.

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

BRCA mutation test is not required for routine monitoring of a breast cancer patient. One lifetime germline *BRCA* mutation test is required per patient

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

The projected number of patients estimated to utilise germline *BRCA*m test is based on the number of patients newly diagnosed with breast cancer per year i.e. approximately 18066. Germline *BRCA*m test is most likely to be offered to patients who are HER2 negative (includes the HR+ and TNBC population) and who are refractory to anthracycline/taxane therapy.

The estimated number of eligible patients who will utilise germline *BRCA*m test in 2019 is 3960.

⁴¹ AIHW Cancer incidence projections: Australia 2011-2020 p.21-32, <http://www.aihw.gov.au/publication-detail/?id=10737421461>

⁴² Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J. Natl. Cancer Inst.* 2014;106(5).

Refer to **Table 2** below for the calculation of this estimation.

Table 2 Estimated number of patients estimated to utilise gBRCAm test in Year 1 of listing

	Year 1 (2019)
Projected new cases of breast cancer (2019) ⁴³	18066
Estimated number of HR+/HER2 negative patients treated with prior anthracycline/taxanes and not suitable for hormone therapy (18066 x 63% x 80%)	9105
Estimated number of Triple negative patients treated with prior anthracycline/taxanes and not suitable for hormone therapy (18066 x 17% x 80%)	2457
Uptake of gBRCAm test in eligible HR+/HER2 patients (9105 x 30%)	2732
Uptake of gBRCAm test in eligible triple negative patients (2457 x 50%)	1228
Total eligible patients taking up gBRCAm test (2732 + 1228)	3960

51. 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:

Refer to **Table 1** above which presents the estimated uptake rate of *BRCAm* testing for the eligible patients from Year 1 to Year 3 of listing. It is expected that there will be an increase in future *BRCA* testing rates compared to the current *BRCA* testing rate. A detailed utilisation analysis will be presented in the co-dependent MSAC/PBAC submission.

In order to reduce the risk of leakage to other populations it is proposed that the MBS restriction should specify germline *BRCA1/2* mutation testing from patients with locally advanced or metastatic breast cancer which are *HER2* negative who meet the PBS criteria. This will be clarified in the co-dependent PBS criteria, however the additional clarification in the MBS criteria would reduce the risk of leakage in populations where the clinical and cost effectiveness of germline *BRCA* mutation testing has not yet been determined.

⁴³ AIHW Cancer incidence projections: Australia 2011-2020 p.21-32, <http://www.aihw.gov.au/publication-detail/?id=10737421461>

PART 8 – COST INFORMATION

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

The current cost of germline *BRCA* mutation test for MBS item # 73295 is \$1200 per test. It is anticipated that the cost will be the same for metastatic breast cancer patients. Only one test is required per lifetime.

53. 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.

54. 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.

Category 6 – PATHOLOGY SERVICES

Proposed item descriptor:

Detection of germline *BRCA1* or *BRCA2* gene mutation, in patients with human epidermal growth factor-2 (*HER2*) negative locally advanced or metastatic breast cancer who have received prior treatment with an anthracycline and a taxane in either the adjuvant or metastatic setting. Hormone receptor positive patients must be refractory or inappropriate for treatment with endocrine therapy. Request for medical service is by a specialist or consultant physician to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Maximum on test per lifetime

Fee: \$ 1200 (insert proposed fee here)

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

6 weeks

Insert approximate duration here

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

- Yes
 No

(b) If no, provide areas of concern:

Describe areas of concern here

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

Did not need to refer to the guidelines, most of the questions were self-explanatory. Also useful that we could contact the MSAC Secretariat for clarification of any issues.

- Yes
 No

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

Insert feedback here

58. (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:

Insert feedback here