



**Australian Government**

**Department of Health**

# **Application Form**

**Germline BRCA mutation testing to determine eligibility for talazoparib treatment in patients with locally advanced or metastatic HER2-negative breast cancer (either hormone receptor positive or triple negative)**

**(New and Amended Requests for Public Funding)**

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.

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

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# PART 1 – APPLICANT DETAILS

## 1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: Pfizer Australia Pty Ltd

ABN: REDACTED

Business trading name: Pfizer Australia Pty Ltd

**Primary contact name: REDACTED**

Primary contact numbers

Mobile: REDACTED

Email: REDACTED

**Alternative contact name: REDACTED**

Alternative contact numbers

Email: REDACTED

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

Yes

No

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

Yes

No

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 3. Application title

Germline BRCA mutation testing to determine eligibility for talazoparib treatment in patients with locally advanced or metastatic HER2-negative breast cancer (either hormone receptor positive or triple negative).

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

Breast cancer is a major health burden worldwide, including in Australia, where over 16,500 new cases were diagnosed in 2014. In 2018, it is estimated that 18,235 new cases of breast cancer will be diagnosed in Australia (148 males and 18,087 females).<sup>1</sup>

Breast cancer is multifactorial and thought to result from interactions between a number of different environmental, lifestyle, hormonal and genetic factors, including a family history of breast cancer. “Hereditary” or “familial breast cancer” breast cancer suggests that there is a genetic predisposition to breast cancer associated with a particular gene or set of genes, within family groups. Within this group of high risk genes are mutations in the key tumour suppressor genes - the BREast CANcer susceptibility genes 1 or 2 (BRCA1/2). Such mutations may be inherited (germline) or arise de novo (somatic) as a result of combinatorial genetic and environmental factors.<sup>2</sup>

Specific subgroups of individuals have been identified as having a higher proportion of individuals who carry a BRCA mutation, including those who have been diagnosed with triple negative breast cancer (TNBC), men and those from different ethnic groups, including Black populations and those of Ashkenazi Jewish heritage.<sup>3-5</sup>

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

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. Pfizer notes a recent PICO confirmation for germline BRCA mutation testing to determine eligibility for olaparib in the metastatic HER2-negative breast cancer population.<sup>6</sup>

Publically (state) funded BRCA genetic testing and private Familial Cancer Centres (FCC) are available 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.<sup>6</sup>

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

- Yes  
 No

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

- Amendment to existing MBS item(s)  
 New MBS item(s)

### (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:

Amendment to MBS item number 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):

**(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

**(g) If yes, please advise:**

Insert description of other public funding mechanism here

**7. What is the type of service:**

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

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

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

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

- Pharmaceutical / Biological
- Prosthesis or device
- No

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

- Yes
- No

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

Insert PBS item code(s) here

**(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

Insert PBAC submission item number here

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

Trade name: TALZENNA

Generic name: Talazoparib

**11. (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):** N/A

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):**

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables: Blood sample collected in a single use disposable syringe

Multi-use consumables: Not applicable

## PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: Pharmaceutical  
Manufacturer's name: Pfizer Australia Pty Ltd  
Sponsor's name: Pfizer Australia Pty Ltd

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

- Class III  
 AIMD  
 N/A

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

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

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

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

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

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

- Yes (please provide details below)  
 No

Date of submission to TGA: **REDACTED**

Estimated date by which TGA approval can be expected: **REDACTED**

TGA Application ID: **REDACTED**

TGA approved indication(s), if applicable: Talzenna (talazoparib) is indicated for the treatment of patients with germline breast cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 (HER2) -negative locally advanced or metastatic breast cancer.

TGA approved purpose(s), if applicable: N/A

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

- 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

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

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
1	Study of diagnostic accuracy  Meta-analysis	Next-Generation Sequencing-Based Detection of Germline Copy Number Variations in BRCA1/BRCA2: Validation of a One-Step Diagnostic Workflow.	This meta-analysis reports the use of NGS gene panel sequencing on the Illumina MiSeq platform and JSI SeqPilot SeqNext software to call germline CNVs in BRCA1 and BRCA2. For validation 18 different BRCA1/BRCA2 CNVs previously identified by MLPA in 48 Danish breast and/or ovarian cancer families were analyzed. 120 patient samples previously determined as negative for BRCA1/BRCA2 CNVs by MLPA were included in the analysis. Comparison of the NGS data with the data from MLPA revealed that the sensitivity was 100%, whereas the specificity was 95%. Taken together, this study validates a one-step bioinformatics work-flow to call germline BRCA1/2 CNVs using data obtained by NGS of a breast cancer gene panel.	<a href="https://www.sciencedirect.com/science/article/pii/S1525157817300776">https://www.sciencedirect.com/science/article/pii/S1525157817300776</a>	Schmidt et al, 2017 Nov.  Journal of Molecular Diagnostics. 19(6):809-816.
2	Study of diagnostic accuracy	Development and validation of a variant detection workflow for BRCA1 and BRCA2 genes and its clinical application based on the Ion Torrent technology.	This study evaluated the performance of a panel for BRCA1 and BRCA2, using the Ion Torrent PGM (Life Technologies) platform in a customized workflow and multiplex ligation-dependent probe amplification for detection of mutations, insertions, and deletions in these genes. The panel was validated with 26 samples previously analyzed by Myriad Genetics Laboratory, and our workflow showed 95.6% sensitivity and 100% agreement with Myriad reports, with 85% sensitivity on the positive control sample from NIST. 68 clinical samples were also screened and found 22 distinct mutations.	<a href="https://humgenomics.biomedcentral.com/articles/10.1186/s40246-017-0110-x">https://humgenomics.biomedcentral.com/articles/10.1186/s40246-017-0110-x</a>	Buzolin et al, 2017 June.  Human Genomics. 11(1):14, 2017 Jun 26.
3	Study of diagnostic accuracy	Current guidelines for BRCA testing of breast cancer patients are insufficient to detect all mutation carriers.	1371 newly diagnosed BC patients were tested with sequencing and Multi Ligation Probe Amplification (MLPA). A pathogenic BRCA mutation was identified in 3.1%. Carriers differed from non-carriers in terms of age at diagnosis, family history, grade, ER/PR-status, triple negativity (TNBC) and Ki67, but not in HER2 and TNM status. One mutation positive female relative was identified per mutation positive BC patient. Using age of onset below 40 or TNBC as criteria for testing	<a href="https://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3422-2">https://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3422-2</a>	Grindedal et al, 2017 June.  BMC Cancer. 17(1):438.

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
			identified 32-34% of carriers. Common guidelines for testing identified 45-90%, and testing all below 60 years identified 90%. Thirty-seven percent of carriers had a family history of cancer that would have qualified for predictive BRCA testing. A Variant of Uncertain Significance (VUS) was identified in 4.9%.		
4	Study of diagnostic accuracy	Validation and optimization of the Ion Torrent S5 XL sequencer and Oncomine workflow for BRCA1 and BRCA2 genetic testing	This study validated the analytical performance of BRCA1/2 sequencing using Ion Torrent's new bench-top sequencer with amplicon panel with optimized bioinformatics pipelines. Using 43 samples that were previously validated by Illumina's MiSeq platform and/or by Sanger sequencing/multiplex ligation-dependent probe amplification, we amplified the target with the Oncomine™ BRCA Research Assay and sequenced on Ion Torrent S5 XL (Thermo Fisher Scientific, Waltham, MA, USA). The study compared two bioinformatics pipelines for optimal processing of S5 XL sequence data: the Torrent Suite with a plug-in Torrent Variant Caller (Thermo Fisher Scientific), and commercial NextGENe software (Softgenetics, State College, PA, USA). The sensitivity, specificity, false positive rate, and accuracy for detection of single nucleotide variant and small indels of S5 XL sequencing were 99.85%, 100%, 0%, and 99.99% for the Torrent Variant Caller and 99.85%, 99.99%, 0.14%, and 99.99% for NextGENe, respectively. The reproducibility of variant calling was 100%, and the precision of variant frequency also showed good performance with coefficients of variation between 0.32 and 5.29%.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5471017/pdf/oncotarget-08-34858.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5471017/pdf/oncotarget-08-34858.pdf</a>	Shin et al, 2017 May.  Oncotarget. 8(21):34858-34866.
5	Study of diagnostic accuracy	Evaluation of the Ion Torrent PGM sequencing workflow for the routine rapid detection of BRCA1 and BRCA2 germline mutations.	The study validated the NGS approach in a cohort of 33 patients who had previously undergone genetic diagnosis in our laboratory by conventional methods. 29 newly diagnosed and uncharacterized patients by NGS, and Sanger sequencing was used to confirm results from the NGS platform. In the validation cohort, all previously identified single nucleotide variants, insertions and deletions were identified by NGS in their correct zygosity status except for variants in a complex multinucleotide region within intron 7 of BRCA1 gene. NGS approach was further able to identify previously undetected variants. In the prospective cohort, almost all (99.3%) called variants were confirmed by Sanger. In both cohorts, in addition to the false positive	<a href="https://www.sciencedirect.com/science/article/pii/S0014480016302970">https://www.sciencedirect.com/science/article/pii/S0014480016302970</a>	Zanella et al, 2017 April  Experimental & Molecular Pathology. 102(2):314-320.

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
			(31) and false negative (110) results in the intron 7 of BRCA1 gene, the NGS method detected 10 false positives, that were solved by Sanger.		
6	Study of diagnostic accuracy	BRCA1/2 missense mutations and the value of in-silico analyses.	This single-centre study aimed to evaluate the impact of in-silico analyses in a spectrum of different BRCA1/2 missense variants. Overall 201 different variants, 68 of which constituted missense variants were ranked as pathogenic, neutral, or unknown. The classification of missense variants by in-silico tools resulted in a higher amount of pathogenic mutations (25% vs. 13.2%) compared to the GC-HBOC-classification. Altogether, more than fifty percent (38/68, 55.9%) of missense variants were ranked differently. Sensitivity of in-silico-tools for mutation prediction was 88.9% (PPH2), 100% (SIFT) and 100% (MT2).	<a href="https://www.sciencedirect.com/science/article/pii/S1769721216305687">https://www.sciencedirect.com/science/article/pii/S1769721216305687</a>	Sadowski et al, 2017 Nov.  European Journal of Medical Genetics. 60(11):572-577.
7	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.	<a href="https://www.ncbi.nlm.nih.gov/pubmed/27848044">https://www.ncbi.nlm.nih.gov/pubmed/27848044</a>	Suryavanshi et al, 2017. Fam Cancer;16(3):311-317.
8	Study of diagnostic accuracy	Simultaneous detection of BRCA mutations and large genomic rearrangements in germline DNA and FFPE tumor samples	This study describes the development of a methodology based on next-generation sequencing and a new bioinformatics software for data analysis. The diagnostic method was initially developed on an Illumina MiSeq NGS platform using germline-mutated stem cell lines and then adapted for the Ion Torrent PGM NGS platform as well. They also investigated the usability of NGS coverage data for the detection of copy number variations and exon deletions as a replacement of the conventional MLPA technique. They also tested the developed workflow on FFPE samples from breast and ovarian cancer patients. The method meets the sensitivity and specificity requirements for the genetic diagnosis of breast and ovarian cancers both from germline and FFPE samples.	<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 et al, 2016 September  Oncotarget. 7(38):61845-61859.
9	Study of diagnostic accuracy	Performance of multiplicom's BRCA MASTR Dx kit on the	This study evaluated Multiplicom's BRCA MASTR Dx assay on a set of 97 FFT derived DNA samples, in combination with the MID for Illumina MiSeq for BRCA1 and BRCA2 mutation detection. We obtained	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5348397/pdf/oncotarget-07-81357.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5348397/pdf/oncotarget-07-81357.pdf</a>	Badoer et al, 2016 Dec.

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
		detection of BRCA1 and BRCA2 mutations in fresh frozen ovarian and breast tumor samples.	interpretable NGS results for all tested samples and showed > 99.7% sensitivity, specificity and accuracy.		Oncotarget. 7(49):81357-81366.
10	Study of diagnostic accuracy	Implementation of next-generation sequencing for molecular diagnosis of hereditary breast and ovarian cancer highlights its genetic heterogeneity	The aim of this work was to validate the use of next-generation sequencing (NGS) for the detection of BRCA1/BRCA2 point mutations in a diagnostic setting and to study the role of other genes associated with HBOC in Portuguese families. . A total of 506 variants in the BRCA1/BRCA2 genes were detected by both methodologies, with a 100 % concordance between them. This strategy allowed the detection of a total of 39 deleterious mutations in the 94 index patients, namely 10 in BRCA1 (25.6 %), 21 in BRCA2 (53.8 %), four in PALB2 (10.3 %), two in ATM (5.1 %), one in CHEK2 (2.6 %), and one in TP53 (2.6 %), with 20.5 % of the deleterious mutations being found in genes other than BRCA1/BRCA2. These results demonstrate the efficiency of NGS for the detection of BRCA1/BRCA2 point mutations and highlight the genetic heterogeneity of HBOC.	<a href="https://link.springer.com/article/10.1007%2Fs10549-016-3948-z">https://link.springer.com/article/10.1007%2Fs10549-016-3948-z</a>	Pinto et al, 2016 Sep.  Breast Cancer Research & Treatment. 159(2):245-56
11	Study of diagnostic accuracy	Evaluation of an amplicon-based next-generation sequencing panel for detection of BRCA1 and BRCA2 genetic variants.	This study tested samples from 88 patients using the TruSeq custom panel (Illumina Inc, USA) and a MiSeq sequencer (Illumina) and compared the results to the outcomes of conventional Sanger sequencing. All 1015 sequence variations identified by Sanger sequencing were detected by NGS, except for one missense variant that might have been missed due to a rare mutation on a primer-binding site. One deletion variation, c.1909 + 12delT of BRCA2, was falsely called in all samples due to a homopolymer error. In addition, seven different single-nucleotide substitutions with low variant frequencies were falsely called by NGS. In a separate batch, 10 different false-positive variations were found in five samples. The overall sensitivity and positive predictive value of NGS were estimated to be 99.9 and 87.5 %, respectively. Targeted NGS panel for BRCA1 and BRCA2 showed an excellent agreement with Sanger sequencing results.	<a href="https://link.springer.com/article/10.1007%2Fs10549-016-3891-z">https://link.springer.com/article/10.1007%2Fs10549-016-3891-z</a>	Shin et al, 2016 Aug.  Breast Cancer Research & Treatment. 158(3):433-40

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
	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.	<a href="https://www.ncbi.nlm.nih.gov/labs/article/s/25893891/">https://www.ncbi.nlm.nih.gov/labs/article/s/25893891/</a>	Dacheva D. et al. Mol Diagn Ther. 2015 19(2):119-30
12	Observational study	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 demonstrates 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.	<a href="https://rd.springer.com/article/10.1007/s10689-014-9749-9">https://rd.springer.com/article/10.1007/s10689-014-9749-9</a>	Guan Y. et al. 2015 Fam Cancer. 14(1):9-18
13	Study of diagnostic accuracy	Massive Parallel Sequencing for Diagnostic Genetic Testing of BRCA Genes--a Single Center Experience	The aim of this study was to implement massive parallel sequencing (MPS) technology in clinical genetics testing. A total of 16 random DNA samples were characterized using standard Sanger sequencing and applied to optimize the variant calling process and evaluate the accuracy of the MPS-method. The best bioinformatics workflow included the filtration of variants using GATK with the following cut-offs: variant frequency >14%, coverage (>25x) and presence in both the forward and reverse reads. The MPS method had 100% sensitivity and 94.4% specificity. Similar accuracy levels were achieved for DNA obtained from the different sample types	<a href="http://journal.waocp.org/?sid=Entrez:PubMed&amp;id=pmid:26625824&amp;key=2015.16.17.7935">http://journal.waocp.org/?sid=Entrez:PubMed&amp;id=pmid:26625824&amp;key=2015.16.17.7935</a>	Ermolenko et al, 2015 Asian Pacific Journal of Cancer Prevention: Apjcp. 16(17):7935-41.
14	Study of diagnostic accuracy	Development and Validation of a Next-Generation Sequencing Assay for BRCA1 and BRCA2 Variants for the Clinical Laboratory.	The objective of this study was to design and validate a next-generation sequencing assay (NGS) to detect BRCA1 and BRCA2 mutations. Both the MiSeq/QSAP combination and PGM/Torrent Suite combination had 100% sensitivity for the 379 known variants in the validation series. However, the PGM/Torrent Suite combination had a lower intra- and inter-assay precision of 96.2% and 96.7%, respectively when compared to the MiSeq/QSAP combination of 100% and 99.4%, respectively. All PGM/Torrent Suite inconsistencies were false-positive	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546651/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546651/</a>	Strom et al, 2015 PLoS ONE [Electronic Resource]. 10(8):e0136419.

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
			variant assignments. We began commercial testing using both platforms and in the first 521 clinical samples MiSeq/QSAP had 100% sensitivity for BRCA1/2 variants, including a 64-bp deletion and a 10-bp insertion not identified by PGM/Torrent Suite, which also suffered from a high false-positive rate. Neither the MiSeq nor PGM platform with their supplied alignment and variant calling software are appropriate for a clinical laboratory BRCA sequencing test. We have developed an NGS BRCA1/2 sequencing assay, MiSeq/QSAP, with 100% analytic sensitivity and specificity in the validation set consisting of 379 variants.		
15	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. This approach was first validated in a panel of 23 patients containing 62 unique variants that had been previously Sanger sequenced. Subsequently, 101 patients with familial breast and ovarian cancer were studied. BRCA1 and BRCA2 exon enrichment has been performed by PCR amplification using the BRCA MASTR kit (Multiplicom). In total, all 62 variants were detected resulting in a sensitivity of 100%. 71 false positives were called resulting in a specificity of 97.35%. All of them correspond to deletions located in homopolymeric stretches. The analysis of the homopolymers stretches of 6bp or longer using the BRCA HP kit (Multiplicom) increased the specificity of the detection of BRCA1 and BRCA2 mutations to 99.99%.	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4098986/pdf/BMRI2014-542541.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4098986/pdf/BMRI2014-542541.pdf</a>	Ruiz A et al, 2014. BioMed Research International. 2014:542541.
16	Study of diagnostic accuracy	Streamlined ion torrent PGM-based diagnostics: BRCA1 and BRCA2 genes as a model.	Many diagnostic laboratories are shifting from Sanger sequencing to higher throughput next-generation sequencing (NGS) platforms. Bearing in mind that the performance and quality criteria expected from NGS in diagnostic or research settings are strikingly different, we have developed an Ion Torrent's PGM-based routine diagnostic procedure for BRCA1/2 sequencing. NextGene analysis provided higher sensitivity, as four previously undetected single-nucleotide variations were found. Regarding specificity, an average of 1.5 confirmatory Sanger sequencings per patient was needed for complete BRCA1/2 screening.	<a href="https://www.nature.com/articles/ejhg2013181">https://www.nature.com/articles/ejhg2013181</a>	Tarabeux et al. 2014 Apr. European Journal of Human Genetics. 22(4):535-41.

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
17	Study of diagnostic accuracy	Molecular analysis of the breast cancer genes BRCA1 and BRCA2 using amplicon-based massive parallel pyrosequencing.	The aim of this study was to implement the massively parallel sequencing technology for diagnostic applications. We evaluated an amplicon-based method for the analysis of the BRCA1 and BRCA2 genes on the Roche 454 GS-FLX sequencer, to identify disease-causing mutations in breast and/or ovarian cancer patients. Variants were filtered on the basis of their frequency (20%) and sequencing depth (>25x). Special attention was given to sequencing accuracy in homopolymers. In the initial evaluation, all known heterozygous mutations were detected. The percentage of mutant reads ranged from 22% to 62%. For the multiplex assay, 95% sensitivity and 91% specificity were obtained.	<a href="https://www.sciencedirect.com/science/article/pii/S1525157812001833">https://www.sciencedirect.com/science/article/pii/S1525157812001833</a>	Michils et al, 2012 Nov.  Journal of Molecular Diagnostics. 14(6):623-30.
18	Randomised trial	Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation (EMBRACA).	A randomized, open-label, phase 3 trial in which patients with advanced (locally advanced and metastatic) breast cancer and a germline BRCA1/2 mutation were assigned, in a 2:1 ratio, to receive talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles). The primary end point was progression-free survival, which was assessed by blinded independent central review.	<a href="https://www.nejm.org/doi/full/10.1056/NEJMoa1802905">https://www.nejm.org/doi/full/10.1056/NEJMoa1802905</a>	Litton et al, 2018.  N Engl J Med 2018; 379:753-763
19	Randomised trial	Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial	In the EMBRACA phase III trial, talazoparib (1 mg daily, orally) demonstrated a statistically significant improvement in PFS versus physician's choice of chemotherapy (PCT; capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with HER2-negative advanced breast cancer carrying a germline BRCA1/2 mutation; we evaluated patient-reported outcomes (PROs).	<a href="https://academic.oup.com/annonc/article/29/9/1939/5074207">https://academic.oup.com/annonc/article/29/9/1939/5074207</a>	Ettl et al, 2018 September. Annals of Oncology 29: 1939–1947, 2018  doi:10.1093/annonc/mdy257  Published online 15 August 2018

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
20	Phase 2 study	Final results of a phase 2 study of talazoparib following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO).	ABRAZO is a 2-cohort, 2-stage phase 2 study of TALA (1 mg/d) following platinum-based therapy (Cohort 1 [C1]) or ≥ 3 platinum-free cytotoxic-based regimens (Cohort 2 [C2]) in pts with locally advanced or metastatic breast cancer (MBC) and gBRCA1/2 mutation. From May 2014 to Feb 2016, 84 pts were enrolled (C1, n = 49; C2, n = 35). At data cutoff (1 Sep 2016), 9 pts continued on treatment. Both cohorts proceeded to stage 2 before enrollment closed. Median age was 50 (range, 31–75) years; 58% of pts had an ECOG PS of 0. TNBC/HR+ incidence in C1 and C2 was 59%/41% and 17%/83%, respectively. Median number of prior cytotoxic regimens administered for advanced disease was 2 in C1 and 4 in C2. ORR by IRF for BRCA1/BRCA2 was 24%/34%, and ORR by IRF for TNBC/HR+ was 26%/29%. Common all grade AEs: anemia (52%), fatigue (45%), nausea (42%), diarrhea (33%), thrombocytopenia (33%), and neutropenia (27%). Grade ≥ 3 AEs: anemia (35%), thrombocytopenia (19%), and neutropenia (15%). Nonhematological AEs grade ≥ 3 did not occur. AEs related to TALA led to drug discontinuation in 3 pts (4%); 4 AEs resulted in death, none related to TALA.	<a href="http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.1007#affiliationsContainer">http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.1007#affiliationsContainer</a>	Turner et al, 2017. NCT02034916.  DOI: 10.1200/JCO.2017.35.15_suppl.1007 Journal of Clinical Oncology 35, no. 15_suppl (May 20 2017) 1007-1007.

\* 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.

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

	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.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					

\* 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

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

The Royal College of Pathologist of Australasia

A statement of clinical relevance from RCPA for the proposed medical service is attached to this application.

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

Not applicable

- 21. 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).

A statement of clinical relevance from BCNA for the proposed medical service is attached to this application.

- 22. 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 *BRCA*m testing in Australia.

- 23. 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**

Email address: **REDACTED**

Justification of expertise: EMBRACA investigator and leading recruiter, KOL in TNBC / BRCA breast cancer

Name of expert 2: **REDACTED**

Phone number: **REDACTED**

Email address: **REDACTED**

Justification of expertise: One of Australia's leading breast cancer research expert with a special interest in TNBC

*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**

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

Breast cancer was the second most commonly diagnosed cancer in Australia in 2014. It is estimated that it will be the most commonly diagnosed cancer in 2018 among both persons and females.<sup>7</sup>

The number of new cases of breast cancer diagnosed increased from 5,372 in 1982 (61 males and 5,311 females) to 16,753 in 2014. Over the same period, the age-standardised incidence rate increased from 44 cases per 100,000 persons (1.2 for males and 81 for females) in 1982 to 65 cases per 100,000 persons in 2014. In 2018, it is estimated that 18,235 new cases of breast cancer will be diagnosed in Australia (148 males and 18,087 females).<sup>7</sup>

In 2016, breast cancer was the fourth leading cause of cancer death in Australia. The number of deaths from breast cancer increased from 1,435 (19 males and 1,416 females) in 1968 to 3,004 in 2016. Over the same period, the age-standardised mortality rate decreased from 17 deaths per 100,000 persons (0.5 for males and 30 for females) in 1968 to 11 deaths per 100,000 persons in 2016. In 2018, it is estimated that the number of deaths from breast cancer will increase to 3,157 deaths (28 males and 3,128 females).

In 2010–2014, individuals diagnosed with breast cancer had a 91% chance (84% for males and 91% for females) of surviving for 5 years compared to their counterparts in the general Australian population. Between 1985–1989 and 2010–2014, 5-year relative survival from breast cancer improved from 73% to 91%.<sup>7</sup>

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

Breast cancer is a biologically diverse and genetically heterogeneous disease.<sup>16</sup> Breast cancer susceptibility (BRCA) genes 1 and 2 (BRCA1 and BRCA2) are key components in the repair pathway for deoxyribonucleic acid (DNA) double strand breaks, and women who carry a fault in BRCA1 or BRCA2 have a high lifetime risk of breast cancer, estimated to be in the range of 30-60%. Men who carry a fault in BRCA1 or BRCA2 may be at some increased risk of prostate cancer and male breast cancer. A person with a cancer-predisposing gene fault has a 50% chance of passing on the faulty gene to any child (male or female).<sup>14</sup> Such mutations may be inherited (germline) or arise de novo (somatic) as a result of combinatorial genetic and environmental factors.<sup>3</sup> Specific subgroups of individuals have been identified as having a higher proportion of individuals who carry a BRCA, including those who have been diagnosed with triple negative breast cancer (TNBC) and those from different ethnic groups, including Black populations and those of Ashkenazi Jewish heritage.<sup>4-6</sup>

Well-known prognostic and predictive factors for breast cancer include hormone receptors and human epidermal growth factor receptor-2 (HER2) expression.<sup>19,20</sup> Estrogen receptor (ER)-negative, progesterone receptor (PgR)-negative, HER2-negative tumours, known as TNBC, are associated with a poor prognosis. Metastatic TNBC has the worst prognosis of all breast cancer subtypes, with a median progression-free survival (PFS) of 3 to 5 months and a median overall survival of <12 months with currently available therapies.<sup>20,21</sup>

The identification of such BRCA carriers through genetic testing, offers the opportunity to increase monitoring and surveillance for breast and other cancers, in addition to offering such individuals prophylactic, risk reducing interventions.

In Australia, the eviQ 'Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes', are most commonly used to identify suitable candidates for BRCAm testing for the purpose of familial cancer risk assessment. 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  $\leq$  50; high-grade non-mucinous ovarian cancer age  $\leq$  70; non-mucinous ovarian cancer, any age + family history; OR known BRCA mutation in a relative.<sup>13</sup>

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

Locally advanced or metastatic HER2-negative/hormone receptor positive breast cancer

As in previous advanced breast cancer guidelines, the 2018 NCCN<sup>10</sup> and 2018 ESMO consensus guidelines<sup>9</sup> recommend endocrine therapy as the preferred treatment for advanced (locally advanced or metastatic) HER2-negative/HR positive breast cancer in the majority of cases, excluding only those with visceral crisis or concern or proof for endocrine resistance.

For pre-menopausal women, this would include a SERM or ovarian ablation/suppression and endocrine therapy as per post-menopausal women.

The ESMO guidelines recommend that the choice among different available agents as well as their sequence largely depends on which agents were previously administered and the response obtained, due to the link with endocrine resistance. Hence, previous exposure, and not only line of treatment, should guide the recommendations. Available options include aromatase inhibitor (AI), tamoxifen, fulvestrant, AI/fulvestrant + CDK 4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and oestradiol, as well as repetition of previously used agents, may be used.

The NCCN guidelines<sup>10</sup> recommend an additional line of endocrine therapy following progression unless there is symptomatic visceral disease or no clinical benefit after three endocrine therapy regimens.

Chemotherapy is recommended where there is visceral crisis, immediate need for rapid disease control, or endocrine resistance.<sup>9,10</sup> The preferred single-agents recommended in the 2018 NCCN guidelines (Version 2.2018) were:

- Anthracyclines: doxorubicin (including peglyated liposomal formulation),
- Taxanes: paclitaxel,
- Anti-metabolites: capecitabine and gemcitabine,
- Other microtubule inhibitors: vinorelbine and eribulin and a;
- PARP inhibitor as an option for patients with HER2-negative tumours and germline BRCA-1/2 mutation

The 2018 NCCN guidelines state that sequential single agents are preferred however also listed several combination chemotherapy regimens for locally advanced or metastatic disease with the caveat that they may be used in select patients with high tumour burden, rapidly progressing disease or visceral crisis.

In patients diagnosed with hormone receptor positive locally advanced or metastatic breast cancer, and who have not received prior chemotherapy, a PARP inhibitor is likely to be fourth or later line treatment following at least one line of endocrine therapy, a taxane and an anthracycline. In patients previously treated (adjuvant and/or metastatic setting) with an anthracycline and a taxane, single agent capecitabine, eribulin or vinorelbine are preferred choices and/or earlier-line treatment with a PARP inhibitor.<sup>9</sup>

### Locally advanced or metastatic triple negative breast cancer

The 2018 ESMO guidelines state that a platinum regimen is the preferred option for patients with BRCA-associated advanced (locally advanced or metastatic) TNBC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), consistent with the 2017 guidelines. Chemotherapy was also recommended as an option however, no specific chemotherapy regimens were specified in the NCCN guidelines (Version 2.2018).

In addition, the ESMO 2018 guidelines state that a PARPi (olaparib or talazoparib) is also a reasonable treatment option for patients with BRCA-associated advanced (locally advanced or metastatic) TNBC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL and a favourable toxicity profile.<sup>9</sup>

Current treatment algorithm attached

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

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

Currently, BRCA testing is generally limited to “high risk” patients (young, family history of breast or ovarian cancer, TNBC) in line with the EVIQ guidelines<sup>13</sup>.

The process of genetic testing in a family begins by testing an individual with cancer (usually with a high risk family history) and searching their BRCA1 and BRCA2 genes for a causative mutation. If a mutation is found, then other adult at-risk genetic relatives can be offered predictive genetic testing for this family-specific mutation. Relatives who have inherited the family mutation are confirmed to be at higher risk of cancer, whereas relatives who have not will usually remain at the background risk for breast and ovarian cancer (depending on the cancer history on the other side of the family).<sup>14</sup>

Testing is usually performed on a routine blood sample (EDTA) and involves screening the full sequence of the genes *BRCA1* and *BRCA2* along with an additional test for copy number variations

Any specialist or consultant physician (in public or private practice) can order genetic testing for breast cancer for “high risk” patients under certain criteria, covered by the Medicare Benefits Schedule (MBS) item numbers 73296 and 73297. Testing is usually performed on a routine blood sample (EDTA) and involves screening the full sequence of the genes *BRCA1* and *BRCA2* along with an additional test for copy number variations

The clinician who orders the test must be able to interpret the results and communicate the implications of the results, to the patient and their genetic relatives. In addition, professional genetic counselling usually precedes and accompanies the test.<sup>14</sup>

When the chance of detecting a mutation is less than 10%, self-funded BRCA1 and BRCA2 testing is available in public or private genetic services.<sup>14</sup>

#### **28. 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.

Talazoparib (TALZENNA®) is a registered trademark.

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

Yes, inclusion of germline BRCA mutation testing on the MBS to determine eligibility for access to talazoparib treatment on the Pharmaceutical Benefits Scheme (PBS) would present a new approach towards the management of locally advanced or metastatic HER2-negative breast cancer patients (hormone receptor positive or triple negative).

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

The BRCA test can be requested by specialists or consultant physicians (familial cancer clinics, public or private practice) or clinical geneticists if it is considered appropriate and should be accompanied by pre- and post-test genetic counselling. These services are available across Australia, and can be accessed by referral from a general practitioner. The blood sample will be sent to an accredited laboratory that specialises in genetic testing.

BRCA testing is well established in Australia. It is performed by many public and private pathology laboratories in Australia.

**31. 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 additional healthcare resources or other medical services need to be delivered at the same time as germline BRCA mutation testing.

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

Any specialist or consultant physician (in public or private practice) can request the BRCA test for a patient if it is considered appropriate and should be accompanied by pre- and post-test genetic counselling. The blood sample will be sent to a laboratory that specialises in genetic testing.

The clinician who orders the test interprets the results and communicates the implications of the results to the patient and their genetic relatives.

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

Not applicable

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

Refer to Question 30 and 32

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

All laboratories that perform BRCA testing are accredited to the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs.

**36. (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

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

Not applicable

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

- Yes
- No – please specify below

**PART 6c – INFORMATION ABOUT THE COMPARATOR(S)**

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

The nominated comparator is no germline BRCA mutation testing. The proposed population for the BRCA test are patients who are ineligible for MBS item number 73296 i.e. not “high risk” patients. The proposed patient population have locally advanced (Stage III) or metastatic (Stage IV) HER2-negative breast cancer and have previously been treated with an anthracycline and a taxane and are refractory to or inappropriate for further endocrine therapy.

- 39. 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

- 40. 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 germline BRCA mutation testing.

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

Yes  
 No

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

As discussed in Question 38, the current MBS item 73296 is not expected to be substituted. The proposed population for BRCA testing are patients who are ineligible for MBS item number 73296 i.e. not “high risk” patients.

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

Please find attached proposed treatment algorithm which presents how the current management pathway is expected to change as a consequence of introducing BRCA mutation testing in locally advanced or metastatic HER2-negative breast cancer patients who are ineligible for MBS item number 73296.

**PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME**

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

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

**44. Please advise if the overall clinical claim is for:**

- Superiority  
 Non-inferiority

**45. 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:**

In the EMBRACA trial, safety was assessed according to adverse events, use of concomitant medications, and clinically relevant changes in laboratory values. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

**Clinical Effectiveness Outcomes:**

Test Outcomes:

1. Sensitivity
2. Specificity
3. Re-testing rates

Drug Outcomes (EMBRACA):

*Primary outcomes*

1. Progression free survival (PFS), as determined by blinded independent central review (according to RECIST)

*Secondary outcomes*

1. Overall Survival (OS)
2. Objective response rate
3. Clinical benefit rate at 24 weeks (defined as the rate of complete response, partial response, or stable disease at 24 weeks or more)
4. Duration of response

*Patient reported outcomes*

Health related quality of life (according to European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C30]) and the breast cancer-specific QLQ-BR23 at baseline, the beginning of each treatment cycle, and the end of treatment as supportive pre-specified exploratory endpoints.

## PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

The estimated incidence of breast cancer was calculated using the actual number of new cases in 2014 (AIHW) and extrapolated to 2020 using the AIHW Cancer incidence projections (2011-2020). Of these, the proportion of patients with locally advanced disease (Stage III) and metastatic disease (Stage IV) was estimated to be 12% and 5%, respectively based on estimates from Cancer Australia.<sup>11</sup> In addition, it was estimated that ~2% of patients with earlier stage disease would progress to metastatic disease (Lord *et al* 2012).

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

*BRCA* testing would be delivered only once to a patient to determine eligibility for talazoparib treatment. One lifetime germline *BRCA* mutation test is required per patient.

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

One lifetime germline *BRCA* mutation test is required per patient.

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

Parameter	Estimate	Reference
Projected new cases of breast cancer (2020)	18881	AIHW
Proportion locally advanced (stage III A, III B or IIIC) at diagnosis	12%	Cancer Australia
Proportion metastatic at diagnosis (stage IV) at diagnosis	5%	Cancer Australia
Cases progressing to metastatic disease in 2020	2.02% of cases diagnosed each year between 2016-2020	Lord 2012
Number of locally advanced (stage III A, III B or IIIC) patients	2266	
Number of metastatic (stage IV) patients	944	
Total cases of locally advanced or metastatic breast cancer	3591	
Proportion HR+/HER2-negative (average Stage III and stage IV )	61.7%	Howlander 2014
Proportion triple-negative (average Stage III and stage IV )	16%	Howlander 2014
Proportion with prior treatment with anthracycline and taxane and not suitable for endocrine therapy	80%	PICO confirmation (App.1507)
Patients already tested for BRCA mutations	10%	As above
Uptake of BRCA test in HR+/HER2-negative population	30%	As above
Uptake of BRCA test in triple-negative population	60%	As above
Eligible locally advanced or metastatic HR+/HER2-negative population	1594	
Eligible locally advanced or metastatic triple negative breast population	403	
Uptake in HR+/HER2-negative population	478	
Uptake in BRCA test in triple-negative population	242	
<b>Total patients taking up BRCA test</b>	<b>720</b>	

### 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:

Of the patients taking up the proposed *BRCA* mutation testing, approximately 13-21% would test positive and therefore be eligible for talazoparib. This assumption is based on the prevalence of germline *BRCA* mutation in the advanced HR+/HER2-negative population of 4.3%<sup>12</sup> and the prevalence of germline *BRCA* mutation in the TNBC population (all stages) of 9.3%.<sup>22</sup>

## 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 cost of the germline BRCA mutation test for MBS item 73295 is \$1200 per test. It is anticipated that the cost will be the same for the proposed medical service. Only one test is required per lifetime.

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

Results will typically take a minimum of 8 weeks to become available, but turnaround times will vary between labs.

**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 application seeks an amendment to MBS Item 73295 to include human epidermal growth factor-2 (HER2) negative locally advanced or metastatic breast cancer patients and to determine eligibility for talazoparib.

Category 6 – PATHOLOGY SERVICES
Proposed item descriptor: Detection of germline BRCA 1 or BRCA 2 mutation, in a patient with human epidermal growth factor-2 (HER2) negative locally advanced or metastatic breast cancer who have received prior chemotherapy with a taxane and/or anthracycline in either the neoadjuvant, adjuvant, locally advanced, 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 talazoparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.  Maximum one test per lifetime Fee: \$1,200