

MSAC Application 1716

Germline BRCA mutation test to detect BRCA1 or BRCA2 mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for PBS-listed olaparib treatment

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

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

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

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

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

Corporation name: AstraZeneca Pty Limited

ABN: 54009682311

Business trading name: AstraZeneca Pty Limited

Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

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

Yes

No

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

Yes

No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Tumour testing of breast tissue to detect BRCA1 or BRCA2 (Breast Cancer gene) mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for PBS-listed olaparib treatment.

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)

In Australia, breast cancer is the most common cancer affecting women (Breast Cancer Network Australia 2021). In 2021, it is estimated that a total of 20,030 patients (19,866 women and 164 men) will be diagnosed with breast cancer (AIHW 2021). On average, 55 Australians are diagnosed with breast cancer each day (Cancer Australia 2021). 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 (Cancer Australia 2021). 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. Patients with a BRCA1 or BRCA2 mutation are believed to have an intermediate risk of developing breast cancer (Balmana et al 2011). 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 (Antoniou et al 2003, Chen et al 2007). Unique characteristics of the BRCA mutated breast cancer patient populations can magnify the humanistic burden of disease in these individuals. Importantly, patients with germline BRCA mutated disease are typically younger than the overall breast cancer population and approximately three-quarters of breast cancer cases occur in patients aged >50 years (Dafni et al 2019).

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)

The proposed medical service is germline BRCA mutation test to detect BRCA1 and BRCA2 gene mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for adjuvant olaparib treatment. Patients with a confirmed BRCA1 or BRCA2 mutation from current MBS-listed tests (MBS Item 73302, MBS Item 73296 and MBS Item 73297) are to be excluded from the proposed medical test.

Currently, MBS item number 73301 is available for testing of tumour tissue in patients with advanced (FIGO III-IV), high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer to determine the eligibility for olaparib under the PBS. Additionally, MBS item number 73295 is available for the subsequent detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible, to determine eligibility for olaparib under the PBS. MBS item number 73296 relates to characterisation of germline variants, including BRCA1/2 genes in a patient with breast, ovarian, fallopian tube or primary peritoneal cancer; and for whom clinical and family history criteria (as assessed, by the specialist or consultant physician who requests the service, using a quantitative algorithm) place the patient at greater than 10% risk of having a pathogenic or likely pathogenic gene variation identified in the specified genes. MBS Item 73302 relates to the characterisation of germline gene variants including BRCA1/2 genes, in a patient who has had a pathogenic or likely pathogenic variant identified in either gene by tumour testing and who has not previously received a service to which items 73295, 73296 or 73297.

Germline BRCA gene mutation testing is well established in Australia especially for familial risk assessment (under MBS Item 73296 and 73297) and more recently to determine patient eligibility for olaparib in the ovarian cancer population (under MBS item 73301, 73302 and 73295).

It is estimated that 6.6% to 14.6% of breast tumours have detectable loss of function BRCA mutations (Lai et al 2022). The likelihood of a BRCA1/2 mutation found in a tumour breast tissue being somatic is approximately one third and germline is two thirds (Winter et al 2016). Patients with triple negative breast cancer (TNBC) are known to have a higher risk of tumours presenting with a BRCA mutation and it is estimated 10% of TNBC patients harbour a BRCA mutation (Wong-Brown et al 2015). Significant changes to

the local and international tumour BRCA1/2 mutation testing environment warrants reconsideration of germline testing for HER2-negative high risk early breast cancer patients with BRCA1 and BRCA2 mutations currently.

Testing for BRCA1 and BRCA2 mutations informs treatment choices and outcomes, and will ensure that targeted products such as olaparib are used for indications where patients are eligible for treatment and will get the most benefit (Tuffaha et al 2018, Tung et al 2020, Tutt et al 2021). In addition, BRCA mutation testing can help identify and address increased cancer risk in family members through surveillance or prophylactic surgery (Petruccioli et al 1993).

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)

AstraZeneca requests guidance on whether it is appropriate to request the following;

- An amendment to MBS Item 73301 to include patients with HER2-negative high risk early breast cancer. Currently, testing of tumour tissue is only available for patients with advanced (FIGO III-IV), high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer;
- An amendment to MBS Item 73295 to include patients with HER2-negative high risk early breast cancer. Currently, germline BRCA mutation testing is only available for patients with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible

Alternatively, guidance on whether new MBS item codes will be required to determine their BRCA status to be eligible to access olaparib under the PBS for patients with HER2-negative high risk early breast cancer.

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

A number of existing MBS items are relevant, including the following:

- MBS Item 73302 - Characterisation of germline gene variants including copy number variants, in BRCA1 or BRCA2 genes, in a patient who has had a pathogenic or likely pathogenic variant identified in either gene by tumour testing and who has not previously received a service to which items 73295, 73296 or 73297 applies, requested by a specialist or consultant physician
- MBS Item 73295 - Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the PBS;
- MBS Item 73296 - Characterisation of germline gene mutations including BRCA1/2, STK11, PTEN, CDH1, PALB2 or TP53 in a patient with breast or ovarian cancer at >10% risk of having one or more of these mutations
- MBS Item 73297 - Characterisation of germline gene mutations in a biological relative of a patient with one or more of the gene mutations in Item 73296

The above MBS items are routinely reimbursed in all patients with high grade serous ovarian cancer and in patients with breast cancer with a >10% risk of harbouring a mutation. This probability of heritable pathogenic mutation is included in the eviQ guidelines (eviQ guidelines, 2020) and these patients will need to meet the 10% threshold via a quantitative algorithm for access under the existing MBS item 73296 and MBS item 73302.

This application seeks funding for the detection of BRCA1 or BRCA2 gene mutations for patients with HER2-negative high risk early breast cancer to determine their eligibility to access olaparib. AstraZeneca will be guided by MSAC, PBAC and DoH to assess whether an amendment to the existing MBS items or new MBS

items will be required. Patients with a confirmed BRCA1 or BRCA2 mutation from current MBS-listed tests (MBS Item 73302, MBS Item 73296 and MBS Item 73297) are to be excluded from the proposed medical test.

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

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

An amendment is being sought to include patients with HER2-negative high risk early breast cancer to determine their eligibility to access olaparib.

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

- A new item which also seeks to allow access to the MBS for a specific health practitioner group
- 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)
- A new item for a specific single consultation item
- 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:

No other source of funding for BRCA mutation testing other than the MBS is sought, however in an upcoming co-dependent submission for PBS access to olaparib for patients with HER2-negative high risk early breast cancer is also being developed.

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):

- To be used as a screening tool in asymptomatic populations
- Assists in establishing a diagnosis in symptomatic patients
- Provides information about prognosis
- Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- 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):

PBS Item codes: 11503K, 11522K, 11528R, 11539H, 12157W, 12161C, 12169L and 12170M

(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

A PBAC submission item number is to be confirmed by the HPP system upon co-dependent PBAC application.

(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

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

- Yes
 No
 N/A

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

N/A

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

- Yes
 No

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

- Yes
 No

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

N/A

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

As per MSAC Application 1538 and 1554, the only single or multi-use consumables for in-house developed in-vitro diagnostic (IVD) assays would be kits which may be used for DNA extraction or quality assurance, or any kit for PCR amplification methods.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

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

Type of therapeutic good: In-vitro diagnostic test: In-house developed
Manufacturer's name: See Table 1 below

Sponsor's name: See Table 1 below

Currently, the following items are listed on the MBS:

- MBS Item 73302 - Characterisation of germline gene variants including copy number variants, in BRCA1 or BRCA2 genes, in a patient who has had a pathogenic or likely pathogenic variant identified in either gene by tumour testing and who has not previously received a service to which items 73295, 73296 or 73297 applies, requested by a specialist or consultant physician
- MBS Item 73295 - Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the PBS;
- MBS Item 73296 - Characterisation of germline gene mutations including BRCA1/2, STK11, PTEN, CDH1, PALB2 or TP53 in a patient with breast or ovarian cancer at >10% risk of having one or more of these mutations
- MBS Item 73297 - Characterisation of germline gene mutations in a biological relative of a patient with one or more of the gene mutations in Item 73296

The above MBS items are routinely reimbursed in all patients with high grade serous ovarian cancer and in those with breast cancer with a >10% risk of harbouring a pathogenic mutation. The probability of a heritable pathogenic mutation is included in the eviQ guidelines (eviQ guidelines, 2020) and these patients will need to meet the 10% threshold via a quantitative algorithm to access the existing MBS item number 73296.

This application seeks funding for the detection of BRCA1 or BRCA2 gene mutations for patients with HER2-negative high risk early breast cancer to determine their eligibility to access olaparib. AstraZeneca will be guided by MSAC, PBAC and DoH to assess whether an amendment to the existing MBS items or new MBS items will be required. Patients with a confirmed BRCA1 or BRCA2 mutation from current MBS-listed tests (MBS Item 73302, MBS Item 73296 and MBS Item 73297) are to be excluded from the proposed medical test.

A list of Australian laboratories conducting these tests are listed in Table 1.

Table 1: Australian molecular pathology service providers that offer germline BRCA gene mutation testing on a commercial basis

Molecular pathology service provider (State)	Method	QAP involvement
Genomics for Life (QLD)	NGS	EMQN via RCPAQAP,
Pathology North (NSW)	NGS	EMQN via RCPAQAP
Peter MacCallum Cancer Centre (VIC)	NGS	EMQN via RCPAQAP
SA Pathology (SA)	NGS	EMQN via RCPAQAP
Monash Health Pathology (Vic)	NGS	EMQN via RCPAQAP
Pathwest (WA)	NGS	EMQN via RCPAQAP

Abbreviations: EDTA, ethylenediaminetetraacetic acid; EMQN, European Molecular Genetics Quality Network;; NGS, next-generation sequencing; QAP, quality assurance programme; RCPAQAP, Royal College of Pathologists of Australasia Quality Assurance Programs 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

All Australian molecular pathology service providers that currently perform BRCA mutation testing use in-house developed testing methods (as opposed to commercial test kits). Under the incoming 2022 TGA regulatory framework, BRCA mutation tests that are used to determine eligibility for olaparib are classified as in-house developed Class 3 in vitro diagnostic medical devices (IVDs). The primary use of this IVD companion diagnostic is the detection of the BRCA mutations in DNA extracted from blood. In patients with HER2-negative high risk early breast cancer, this IVD companion diagnostic intended to be used as an aid in selecting patients with germline BRCA1 or BRCA2 mutation, for treatment with Lynparza® (olaparib).

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

The in-house developed IVDs have been TGA notified but not yet been submitted to the TGA. A submission to update the IVDs to include the HER2-negative high risk early breast cancer population is currently being developed.

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

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

Please note that an application for the treatment of breast cancer will not be made for the Lynparza 50mg capsules.

The current indications for Lynparza® tablets are as follows (Lynparza® PI 2021):

Ovarian Cancer

Lynparza® is indicated as monotherapy for the:

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

Lynparza® in combination with bevacizumab is indicated for the:

- maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:
 - a deleterious or suspected deleterious BRCA mutation (germline or somatic), and/or
 - genomic instabilityHRD status should be determined by an experienced laboratory using a validated test method.

Breast Cancer

Lynparza® is indicated as monotherapy for the:

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

Adenocarcinoma of the pancreas

Lynparza® is indicated as monotherapy for the:

- maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Germline BRCA mutation (gBRCAm) status should be determined by an experienced laboratory using a validated test method.

Prostate cancer

Lynparza® is indicated as monotherapy for the:

- treatment of adult patients with BRCA-mutated (germline and/or somatic) metastatic castration-resistant prostate cancer who have progressed following prior therapy that included a new hormonal agent. BRCA mutation status should be determined by an experienced laboratory using a validated test method.

Lynparza® in combination with abiraterone and prednisone or prednisolone is indicated for the:

- treatment of adult patients with metastatic castration-resistant prostate cancer.

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

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

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

An application is being prepared for the TGA to extend the indication of Lynparza® (olaparib) as monotherapy for the:

- Adjuvant treatment of adult patients with BRCA-mutated HER2-negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy

Estimated date of submission to TGA: Q1, 2022

Proposed indication(s), if applicable: N/A

Proposed purpose(s), if applicable: N/A

The labs developing in-house IVDs will submit to TGA once they receive NATA accreditation.

PART 4 – SUMMARY OF EVIDENCE

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

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

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
	Randomised, placebo controlled, double blind Phase II trial	Study 19	Overall survival in patients with platinum sensitive, recurrent, serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo controlled double blind Phase II trial. This report includes the final overall survival results for the intent to treat and BRCA1/2 mutant subgroups as well as additional analyses in BRCA mutant subgroups	http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(16)30376-X.pdf Ledermann JA, Harter P, Gourley C, Friedlander M, <i>et al.</i> <i>Lancet Oncology</i> , 2016, 17 (November 2016): 1579-89.	November 2016
Additional diagnostic studies – Ovarian					
2.	Comparative diagnostic study		BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next generation sequencing	http://www.oncotarget.com/index.php?journal=oncotarget&page=article&op=view&path[]=6834&path[]=19269 Mafficini A, Simbolo M, Parisi A, Rusev B, <i>et al.</i> <i>Oncotarget</i> , 2016 7 (2):1076	January 2016
3.	Comparative diagnostic study		Comprehensive analysis of germline and somatic BRCA1/2 mutations in ovarian cancer population: Interim results of OVATAR prospective study	Tyulyandina A, Kekeeva T, Karaseva V, Gorbunova V, <i>et al.</i> <i>Journal of Clinical Oncology</i> , 2017 35 (15 Suppl. 1 May):Abstract e23109	May 2016
4.	Comparative diagnostic study		Cohort study of primary and recurrent ovarian cancer patients using next generation sequencing of DNA derived from blood samples and a customised Agilent gene panel for formalin-fixed paraffin-embedded (FFPE)	Hahnen E, Baumann KH, Heimbach A, Reuss A, <i>et al.</i> <i>Journal of Clinical Oncology</i> , 2016, 34 (Supplement 15 May 2016):	May 2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
5.	Comparative diagnostic study		Prevalence and clinical significance of BRCA1/2 germline and somatic mutations in Taiwanese patients with ovarian cancer	http://www.oncotarget.com/index.php?journal=oncotarget&page=article&op=view&path[]=13456&path[]=44022 Chao A, Chang T-C, Lapke N, Jung S-M, et. al. <i>Oncotarget</i> , 2016, 7 (51):85529-85541.	November 2016
6.	Comparative diagnostic study		This study aimed to identify the frequency and spectrum of germline and somatic BRCA1/2 gene mutations in a cohort of 100 women with serous ovarian cancer. Mutational analysis of BRCA1/2 genes was performed on tumour tissue (FFPE) using next generation sequencing. Germline BRCA1/2 mutation status of non-neoplastic tissue was determined using bidirectional Sanger sequencing.	Koczkowska M, Zuk M, Gorczynski A, Ratajska M, et. al. <i>Cancer Medicine</i> , 2016, 5 (7 July):1640-1646.	April 2016
7.	Comparative diagnostic study		Simultaneous detection of BRCA mutations and large genomic rearrangements in germline DNA and FFPE tumour samples. Ten ovarian cancer samples were included in this study which also reported results for a similar number of breast cancer samples. Two different next generation sequencing platforms were compared.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5308695/pdf/oncotarget-07-61845.pdf Enyedi MZ, Jaksa G, Pinter L, Sukosd F, et.al. <i>Oncotarget</i> , 2016, 7 (38):61845-61859.	August 2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
8.	Comparative diagnostic study		Germline and somatic multi-gene sequencing in patients with advanced high grade serous ovarian cancer (HGSOC). DNA extracted from matched blood and tumour samples (from FFPE) were tested using a lab developed next generation sequencing method.	https://watermark.silverchair.com/mdw392.28.pdf?toKen=AQECAHi208BE490oan9kkhW_Ercy7Dm3ZL_9Cf3qfKA485ysgAAAcgwgghEBgkqhkiG9w0BBwagggG1MIJBsQIBADCCAaoGCSqGSIb3DQEHATAeBgIghkgBZQMEAS4wEQQMctq-AmJx8VpxAGGAAgEQgIIBe0eldSzaIDmXm09ni2EVWLFH_2tIJ2FFOvo6jZgsjpC_cowGsg35w_BTEFPPuOU0n6k-p_6jzFhzbD5OAnWIOKFzlu3t3Ex_TyJQTW6bDx-COTz5PbRcnfNNyBOvEj1sXbp1hVvf5lrC-ihALi9KGevCyOc8BY6XzfnvhQa6PuBeJaSt3oHEN-X-sgX9S0BnCEq5Pd6ZCFesicmlp8v-leAV10nyibQL0Q2BjBEH6rHOAOsOUtMv0KPJnYgEZYbxIC6-R6E5tZi4BQogRwCZsyuDRdk4aTVafM1kdKHQlfqaHAptGBz1MvAXrwipb41g-lfnJetKA5xOMNFQzHFQGGZ0d7MEwFKCdS5EfdRjo3TWK5wcdY0l1t1HHT4e8Y9rgSZ56iQt_yDiLTaag176gJNv3v6wsCi_ljf0NQB_DCeio-jPD08JUIFM_x0G3dTaAutRBtbaWT-mt8ZXVH8YsOHOamSzbn59v7GlgdV1GSAM950jh754YqR8QA Stjepanovic N, Wilson M, Mandrilas V, Clarke B, et. al. <i>Annals of Oncology</i> , 2016, 27(Supplement 6):Abstract 1547P	2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
9.	Diagnostic accuracy study		This multicentre study evaluated the analytical performance of BRCA Tumor MASTR Plus Dx (Multiplicom) for diagnosis of somatic and germline BRCA mutations in formalin-fixed paraffin embedded tumour tissue derived DNA. 51 clinical and 3 reference samples were used. The clinical samples were characterised by next generation sequencing.	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e23116 Boulet G, Van Barel, Rotthier A, Goossens D, DeFavero J. <i>Journal of Clinical Oncology</i> , 2017, 35 (15 Supplement):e23116	May 2017
10.	Diagnostic accuracy study		Testing of BRCA1/2 gene mutations in FFPE samples of patients with high-grade serous ovarian cancer and the limits of its bioinformatic interpretation.	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e17060 Janikova K, Lasabova Z, Gredar M, Farkasova A, <i>et al.</i> <i>Journal of Clinical Oncology</i> , 2017, 35 (15 Supplement):e17060	May 2017
11.	Comparative diagnostic study		Next generation sequencing was used to detect deleterious mutations through all exons in 31 core homologous recombination genes. Paired whole blood and frozen tumour samples from 50 chinese women diagnosed with epithelial ovarian carcinomas were tested to identify both germline and somatic variants.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5447142/ Zhao Q, Yang J, Li L, Cao D, <i>et al.</i> <i>Journal of Gynaecologic Oncology</i> , 2017, 28 (4):e39	July 2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
12.	Comparative diagnostic study		Patients diagnosed with recurrent ovarian cancer underwent next generation sequencing of archival tumour specimens using a 65 gene panel or a 315 gene panel (Foundation Medicine). Some patients also underwent NGS of circulating free DNA from blood specimens. Genomic alterations identified from the blood based testing were compared to the archival tumour tissue.	http://mct.aacrjournals.org/content/16/10_Supplement/B29 Londono AI, Farrukh N, Smith MK, Tawfik CM, <i>et.al.</i> Molecular Cancer Therapeutics, 2017, 16 (10 Supplement 1): Abstract B29	January 2017
13.	Diagnostic accuracy study		Validation of the Devyser BRCA kit, for next generation sequencing of high risk breast/ovarian cancer susceptibility genes BRCA1 and BRCA2. The assay of 48 samples including nucleotide substitutions, small deletions/insertions and large deletions/duplications and showed 100% concordance with gold standards.	https://www.sciencedirect.com/science/article/pii/S1525157817303380 Capone GL, Putignano AL, Saavedra ST, Paganini I, <i>et.al.</i> <i>Journal of Molecular Diagnostics</i> , 2018, 20 (1):87-94.	
14.	Comparative diagnostic study		496 patient tumour samples, including 68 ovarian cancer patients with peripheral blood and archival FFPE samples were analysed to detect germline and somatic sequence variants of DNA repair genes. Enrichment of targets was carried out using the Agilent SureSelect hybrid capture baits. Next generation sequencing was carried out on Illumina platforms.	https://ac.els-cdn.com/S1525157816301787/1-s2.0-S1525157816301787-main.pdf?_tid=7264e1e2-1065-11e8-93f3-00000aacb35d&acdnat=1518489033_e391a79881ac337e09e02850e1a6d6d5 Lee W, Jo H, Yin X, Patel NM, <i>et. al.</i> <i>Journal of Molecular Diagnostics</i> , 2018, 20 (1):87-94.	January 2018

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

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
17.	Diagnostic and comparative clinical outcomes study.		Germline and somatic mutations in homologous recombination genes were detected using targeted capture (BROCA panel) and massively parallel genomic sequencing (next generation sequencing) in 390 ovarian carcinomas, including 239 high grade serous carcinomas. For all suspected loss of function variants PCR amplification and Sanger sequencing were performed both on lymphocyte derived (germline) and neoplastic DNA to confirm and classify the mutation as somatic or germline. The presence of these gene mutations predicts platinum response and survival in ovarian, fallopian tube and peritoneal carcinomas.	<p>Pennington KP, Walsh T, Harrell MI, Lee MK, et.al. <i>Clinical Cancer Research</i>, 2014, 20(3):764</p> <p>And https://ac.els-cdn.com/S0090825813009438/1-s2.0-S0090825813009438-main.pdf?_tid=8114155a-1146-11e8-aa19-0000aacb360&acdnat=1518585695_8697136926bbdb45f1192c6efe89e843</p> <p>Pennington K, Walsh T, Harrell M, Lee M <i>Gynecologic Oncology</i>, 2013, 131(1):257-58.</p> <p>And https://ac.els-cdn.com/S0090825811009814/1-s2.0-S0090825811009814-main.pdf?_tid=d5dd19d8-11f0-11e8-9f9b-0000aab0f6b&acdnat=1518658851_d764cadb5d00523acb1281dd36c70657</p> <p>Pennington K, Walsh T, Casadei S, Lee M, et.al. <i>Gynaecologic Oncology</i>, 2012, 125(Supplement 1):S5-6.</p>	<p>February 2014</p> <p>October 2013</p> <p>March 2012</p>

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

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

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

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

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

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Phase II trials – Prostate					
1.	Phase II trial	DNA-repair defects and olaparib in metastatic prostate cancer	Fifty patients with metastatic castration-resistant prostate cancer were treated with olaparib tablets at a dose of 400 mg twice a day. The primary endpoint was the response rate. Targeted next-generation sequencing, exome and transcriptome analysis, and digital polymerase-chain-reaction testing were performed on samples from mandated tumour biopsies.	https://www.nejm.org/doi/full/10.1056/NEJMoa1506859	2015
Diagnostic studies – Prostate					
2.	Diagnostic study	Germline DNA Repair Gene Mutation Landscape in Chinese Prostate Cancer Patients	Landscape of 18 germline DNA repair gene mutation in 316 Chinese patients with prostate cancer.	https://www.sciencedirect.com/science/article/abs/pii/S0302283819304531	2019
3.	Diagnostic study	Germline DNA-repair Gene Mutations and Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Receiving First-line Abiraterone and Enzalutamide	To determine whether and how germline DNA-repair gene mutations influence clinical outcomes to abiraterone or enzalutamide in patients with castration-resistant prostate cancer using germline genotyping for 50 DNA-repair genes using blood samples from 172 patients with CRPC beginning first-line systemic therapy with abiraterone or enzalutamide.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6045965/	2018

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
4.	Diagnostic study	ATM deficiency promotes progression of CRPC by enhancing Warburg effect	Report on ATM mutation contributing to the CRPC progression through a metabolic rather than DNA repair mechanism, and ATM deficiency generated by CRISPR/Cas9 editing promoted CRPC cell proliferation and xenograft tumour growth.	https://www.ncbi.nlm.nih.gov/pubmed/30400006	2019
5.	Diagnostic study	Treatment Outcomes and Tumor Loss of Heterozygosity in Germline DNA Repair-deficient Prostate Cancer	To determine the clinical response of 319 mCRPC patients with germline DNA repair defects to androgen receptor-directed therapies and to establish whether biallelic DNA repair gene loss is detectable in matched circulating tumour DNA.	https://www.ncbi.nlm.nih.gov/pubmed/28259476	2017
6.	Diagnostic study	Inherited DNA-repair gene mutations in men with metastatic prostate cancer	Multicentre study that recruited 692 men with metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis. Germline DNA was isolated and used multiplex sequencing assays to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes.	https://www.nejm.org/doi/full/10.1056/NEJMoa1603144	2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
7.	Diagnostic study	Circulating tumor DNA (ctDNA) burden and actionable mutations in treatment-naive metastatic castration-resistant prostate cancer (mCRPC)	Collection of baseline cfDNA samples from 36 chemotherapy-naive mCRPC patients enrolled in an ongoing randomised phase II crossover trial of abiraterone vs enzalutamide (NCT02125357) and performed deep targeted sequencing using a custom NimbleGen SeqCap EZ Choice panel of 72 mCRPC-related genes.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01267739/full	2016
8.	Diagnostic study	Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer	Randomisation of 202 patients with treatment-naïve mCRPC to abiraterone or enzalutamide for whole exome and deep targeted 72 gene sequencing of plasma cell free DNA prior to therapy.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01610686/full	2018
9.	Diagnostic study	Abiraterone + prednisone (Abi) +/- veliparib (Vel) for patients (pts) with metastatic castration-resistant prostate cancer (CRPC): NCI 9012 updated clinical and genomics data	148 patients had metastatic disease biopsy, stratified by IHC-ETS status and randomised to Abi (Arm A) or Abi + Vel (Arm B). Primary endpoint: PSA response rate (RR >= 50% decline). Secondary endpoints: safety, objective RR (ORR), progression free survival (PFS), and molecular analysis including if DNA repair gene deficiency (DRD: BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C) predicts response.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01750310/full	2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
10.	Diagnostic study	Genomic alterations in circulating tumor DNA (ctDNA) are associated with clinical outcomes in treatment-naïve metastatic castration-resistant prostate cancer (mCRPC) patients commencing androgen receptor (AR)-targeted therapy	Deep targeted sequencing of 72 mCRPC-related genes in baseline cfDNA from 62 chemotherapy-naïve mCRPC patients enrolled in an ongoing randomised phase II trial of abiraterone vs enzalutamide (NCT02125357). Genomic alterations in cfDNA were examined for association with clinical variables including time on treatment.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01295966/full	2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
11.	Diagnostic study	Co-targeting androgen receptor (AR) and DNA repair: a randomized ETS gene fusion-stratified trial of abiraterone + prednisone (Abi) +/- the PARP1 inhibitor veliparib for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) (NCI9012)-A University of Chicago phase II consortium trial	148 eligible mCRPC pts underwent metastatic disease biopsy, were stratified by ETS status and randomised to Abi (Arm A) or Abi + Veliparib (Arm B). The primary endpoint was confirmed PSA response rate. Secondary endpoints included safety, objective RR (ORR), progression free survival (PFS), and if DNA repair gene deficiency (DRD; homozygous deletions or deleterious mutations: BRCA 1, BRCA 2, ATM, FANCA, PALB2, RAD51B, RAD51C) predicts response.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01733597/full	2016
Other studies – Prostate					
12.	Prospective report	Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition	A report on prospectively planned, serial, cfDNA analyses from patients with metastatic prostate cancer treated on an investigator-initiated phase II trial of olaparib. These analyses provide predictive, prognostic, response, and resistance data with "second hit" mutations first detectable at disease progression.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143169/	2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
13.	Case series	Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors	Identification of BRCA2 reversion mutations associated with olaparib and talazoparib resistance in prostate cancer patients.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5581695/	2017
Reviews (2018-2019) – Prostate					
14.	Review	PARP inhibitors in prostate cancer-The preclinical rationale and current clinical development	Overview of published and ongoing trials exploring PARP inhibitors in treatment of prostate cancer and discuss the underlying biology.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723995/	2019
15.	Review	Recent advances in prostate cancer research: Large-scale genomic analyses reveal novel driver mutations and DNA repair defects	Review of the recent advances in prostate cancer research, including understanding the genetic alterations that drive the disease and how specific mutations can sensitise tumours to potential therapies.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073096/	2018

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
16.	Review	A decade of clinical development of PARP inhibitors in perspective	Summary of a decade of PARP inhibitor clinical development.	https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz192/5520938	2019
17.	Review	DNA repair defects in prostate cancer: impact for screening, prognostication and treatment	Review covers the relationship between DNA repair defects and prostate cancer, highlighting the prevalence of mutations in key genes and their controversial association with clinical outcomes.	https://www.ncbi.nlm.nih.gov/pubmed/30281887	2019
18.	Review	Targeting DNA Repair Defects for Precision Medicine in Prostate Cancer	Review of the current knowledge on DNA repair defects in prostate cancer and an overview of how these alterations can be targeted towards a personalised prostate cancer management.	https://www.ncbi.nlm.nih.gov/pubmed/30919167	2019
19.	Review	DNA damage repair: An emerging strategy in metastatic prostate cancer	Review in prostate cancer discussing DNA repair abnormalities which mainly correspond to somatic or constitutional mutations of the BRCA2 and ATM genes. Therapeutic management of metastatic castration-resistant prostate cancer (mCRPC) is currently based on new hormonal therapies and taxane-type chemotherapy.	https://www.ncbi.nlm.nih.gov/pubmed/30278883	2018
Pivotal trials – Breast					

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Randomised controlled trial	OlympiA ClinicalTrials.gov Identifier: NCT02032823	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	https://clinicaltrials.gov/ct2/show/NCT02032823 https://pubmed.ncbi.nlm.nih.gov/34081848/	2021
2.	Randomised controlled trial	OlympiAD ClinicalTrials.gov Identifier: NCT02032823	This open label, randomised, controlled, multi-centre phase III study will assess the efficacy and safety of single agent olaparib vs standard of care based on physician's choice of capecitabine, vinorelbine or eribulin in metastatic breast cancer patients with gBRCA 1/2 mutations.	https://clinicaltrials.gov/ct2/show/NCT02000622 https://pubmed.ncbi.nlm.nih.gov/28578601/	2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Observational studies – Breast					
3.	Observational study	Targeted sequencing of BRCA1 and BRCA2 across a large unselected breast cancer cohort suggests that one-third of mutations are somatic	A mutation found in the BRCA1 or BRCA2 gene of a breast tumour could be either germline or somatically acquired. The prevalence of somatic BRCA1/2 mutations and the ratio between somatic and germline BRCA1/2 mutations in unselected breast cancer patients are currently unclear. However, the likelihood of a BRCA1/2 mutation found in a breast carcinoma being somatic was $\sim 1/3$ and germline $2/3$. This may have implications for treatment and genetic counselling.	https://www.sciencedirect.com/science/article/pii/S0923753419347404	2016
4	Observational Study	Landscape of homologous recombination deficiencies in solid tumours: analyses of two independent genomic datasets	Germline and somatic BRCA mutations in breast and ovarian cancers were evaluated using sequencing data from The Cancer Genome Atlas (TCGA) database. Approximately one-third of breast and ovarian cancer BRCA mutations were somatic. These showed a similar degree of bi-allelic loss and clinical outcomes to germline mutations, identifying potentially 50% more patients that may benefit from precision treatments	https://link.springer.com/article/10.1186/s12885-021-09082-y	2022
Clinical outcome studies - Breast					

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
5.	Non-randomised clinical outcome study	Comparison of BRCA versus non-BRCA germline mutations and associated somatic mutation profiles in patients with unselected breast cancer	Assess the relationship between clinicopathologic characteristics and germline mutation status and identified the somatic mutations among germline mutation carriers.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7066887/	2020
6.	Non-randomised clinical outcome study	Somatic BRCA mutation detection by circulating tumour DNA analysis in patients with metastatic breast cancer: Incidence and association with tumour genotyping results, germline BRCA mutation status, and clinical outcomes	Evaluate the presence of BRCA mutations, and the association between somatic BRCA mutations with clinical outcomes in patients with metastatic breast cancer. Somatic BRCA mutations may be detected by sensitive blood-based genotyping assays in patients who are not known BRCA carriers.	https://cancerres.aacrjournals.org/content/78/4_Supplement/PD1-13	2018

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
7.	Non-randomised clinical outcome study	Olaparib monotherapy as primary treatment in unselected triple negative breast cancer	Phase II PETREMAC trial, patients with primary TNBC >2 cm received olaparib for up to 10 weeks before chemotherapy. Olaparib monotherapy yielded a high response rate when administered to treatment-naive, large TNBC, with germline or somatic homologous recombination deficiency.	https://www.sciencedirect.com/science/article/pii/S0923753420431643	2020
8.	Non-randomised clinical outcome study	Comprehensive molecular comparison of BRCA1 hypermethylated and BRCA1 mutated triple negative breast cancers	BRCA1 hypermethylation and germline/somatic mutations represent separate mechanisms for gene inactivation, these alterations result in similar genomic phenotypes. TNBC patients with BRCA1 hypermethylated tumours share a similar beneficial outcome after standard of care adjuvant chemotherapy as BRCA1-null patients, suggesting that BRCA1 hypermethylation may represent a DNA based prognostic biomarker that is detectable also in low-cellularity tumour tissue specimens.	https://www.nature.com/articles/s41467-020-17537-2	2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Review - Breast					
9.	Systematic Review	A systematic review of the international prevalence of BRCA mutation in breast cancer	A systematic review was conducted, summarizing international BRCA 1 or 2 (BRCA1/2) mutation prevalence in breast cancer. Among TNBC populations, the percentage prevalence of gBRCA mutations ranged from 9.3% to 15.4%, and amongst patients with metastatic breast cancer, from 2.7% to 4.3%. Within larger studies the prevalence of BRCA mutations appeared higher for those studies that selected patients based on their family history and the presence of TNBC.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6628947/	2019

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
10	Review	Role of BRCA mutations in Cancer Treatment with Poly (ADP-ribose) Polymerase (PARP) Inhibitors	Germline or somatic BRCA deleterious mutations result in defective DSB repair by HR and patients with tumours harbouring BRCA mutations derive the greatest clinical benefit. The presence of BRCA mutations or HR-deficiency in the tumour correlated with response to platinum compounds, which is characterized by mutational and rearrangement signatures indicative of abnormalities in DNA repair that resemble those of BRCA-mutated tumours. In TNBC, the BRCAness phenotype may derive from BRCA1 promoter methylation and/or low BRCA1 mRNA or protein expression, and in some cases from BRCA mutations.	https://www.mdpi.com/2072-6694/10/12/487	2018

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

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

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

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

Professional organisations which may verify the clinical relevance of BRCA mutation testing for HER2-negative high risk early breast cancer patients to determine eligibility for olaparib treatment are:

1. The Royal College of Pathologists of Australasia (RCPA)
2. The Australian Genomic Cancer Medicine Centre (AGCMC)

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

Consumer organisations which may verify the clinical relevance of BRCA mutation testing for HER2-negative high risk early breast cancer patients to determine eligibility for olaparib treatment are:

1. Breast Cancer Network Australia (BCNA)
2. Pink Hope
3. McGrath Foundation
4. So Brave - Australia's Young Women's Breast Cancer Charity

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 BRCA gene mutation testing in Australia. There are several different Australian molecular pathology service providers that offer germline BRCA mutation testing and more recently tumour BRCA testing on a commercial basis. BRCA gene mutation testing is offered by laboratories in each of the States and Territories of Australia as part of existing ovarian or breast cancer panels.

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

REDACTED

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

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

In Australia, breast cancer is the most common cancer affecting women. In 2021, it is estimated that 19,866 women and 164 men will be diagnosed with breast cancer (Cancer Australia 2021). Early breast cancer includes both Stage I-IIIa. Although treatable, early breast cancer has a 5 year survival of 91% remains however, this varies between subtypes of breast cancer (ER+, HER2+ or TNBC) (Cancer Australia 2021). Breast cancers that do not have oestrogen receptors, progesterone receptors or HER2 are called TNBC. Because they do not respond to drugs that specifically target these hormones or HER2, they are usually treated with chemotherapy. These tumours are typically more aggressive and more common among younger women diagnosed with breast cancer (National Breast Cancer Foundation 2022).

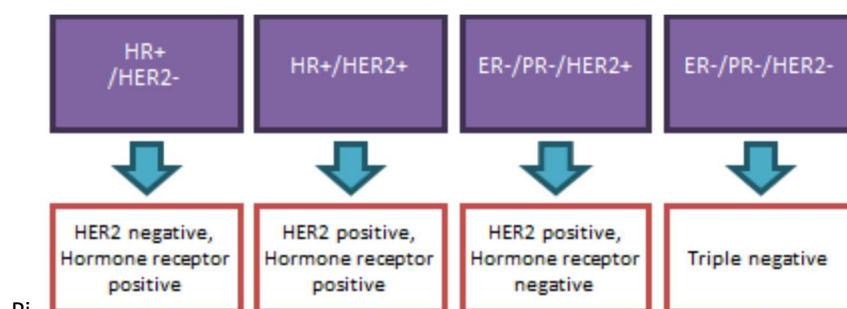
The risk of being diagnosed with breast cancer increases with age, with 61% of new cases of breast cancer developing in women aged between 50-74 (Cancer Australia 2021). A personal history of breast cancer or family history are contributing risk factors with approximately 5 to 10% of breast cancers due to a strong family history or genetic mutation; such as BRCA1 and BRCA2 (Balmana et al 2011). Patients with a BRCA1 or BRCA2 mutation are believed to have an intermediate risk of developing breast cancer (Balmana et al 2011). 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 (Antonioni et al 2003, Chen et al 2006). Unique characteristics of the BRCA mutated breast cancer patient populations can magnify the humanistic burden of disease in these individuals. Importantly, patients with germline BRCA mutated disease are typically younger than the overall breast cancer population and approximately three-quarters of breast cancer cases occur in patients aged >50 years (Dafni et al 2019).

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:

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 predictive and 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:



The majority of breast cancers are HER2-negative (80%-85%) based on histological subtypes (Morey et al 2016); whereas approximately 10% to 15% are triple negative (Chan et al 2010, Wen et al 2018, Breast Cancer Network Australia 2022) . In particular, TNBC has been associated with more aggressive disease and worse survival versus non-TNBC (National Breast Cancer Foundation, 2022). Epidemiology data show a high prevalence of BRCA1/2 mutations in TNBC patients and that these mutations are not restricted to young women or patients with a positive family history (Armstrong et al 2019, Hahnen et al 2017, Wong-Brown et al 2015). TNBC has been incorporated into BRCA1/2 genetic testing guideline recommendations from NICE and NCCN, although the guidelines vary on the age group for this cancer subtype (NICE 2019, Daly et al 2021). While the frequency of BRCA1/2 mutations is higher among patients with TNBC than in those with HR-positive breast cancer, the latter comprises a much larger proportion of the total breast cancer population. This may mean there are more patients harbouring BRCA1/2 mutations who have HR-positive breast cancer than have TNBC. As such, it is important to provide subsidised access to both HR-positive breast cancer and TNBC patient populations to ensure equitable access to olaparib for breast cancer treatment.

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 (Lau et al 2011).

In Australia, many Genetic/Familial Cancer Centres use the criteria outlined in the eviQ Guidelines (eviQ Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes, 2020), to identify suitable candidates for BRCA mutation 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 BRCA mutation 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 BRCA mutation testing in individuals with: TNBC age \leq 50; high-grade non-mucinous ovarian cancer at any age; non-mucinous ovarian cancer, any age + family history; OR known BRCA mutation in a relative.

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):

In current clinical practice, the following MBS items are routinely reimbursed in patients with ovarian cancer and related breast cancer.

MBS Item number 73302 related to characterisation of germline gene variants including copy number variants, in BRCA1 or BRCA2 genes, in a patient who has had a pathogenic or likely pathogenic variant identified in either gene by tumour testing and who has not previously received a service to which items 73295, 73296 or 73297 applies, requested by a specialist or consultant physician.

MBS Item number 73295 relates to the detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the PBS.

MBS Item number 73296 relates to characterisation of germline variants, including BRCA1/2 genes in a patient with breast, ovarian, fallopian tube or primary peritoneal cancer; and for whom clinical and family history criteria (as assessed, by the specialist or consultant physician who requests the service, using a quantitative algorithm) place the patient at greater than 10% risk of having a pathogenic or likely pathogenic gene variation identified in the specified genes.

Germline BRCA1/2 gene mutation testing (MBS Item number 73297) is also available to biological relatives of patients who have pathogenic mutations identified according to MBS Item number 73296. HER2-negative high risk early breast cancer patients and their biological relatives may qualify for germline BRCA1/2 testing under MBS Item numbers 73296 & 73297, respectively, at the time of breast cancer diagnosis. If the germline BRCA1/2 mutation status of patients is known at an earlier stage in disease management, patients with detected mutations can receive genetic counselling services and consider prophylactic surgery. This may also

significantly impact early breast cancer patients as they may develop recurrent cancer (advanced or metastatic disease) at a later stage.

There have been other significant changes to the local and international BRCA1/2 mutation testing environment to warrant reconsideration of germline testing for patients with HER2-negative high risk early breast cancer at this time.

Proposed patients for testing

The MBS items below are routinely reimbursed in patients with ovarian cancer and related breast cancer. This application seeks funding for the detection of BRCA1/2 gene mutations but for patients with HER2-negative high risk early breast cancer to be eligible to access olaparib;

- An amendment to MBS Item 73295 to include patients with HER2-negative high risk early breast cancer. Currently, germline BRCA mutation testing is only available for patients with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer for whom testing of tumour tissue is not feasible,

AstraZeneca will be guided by MSAC, PBAC and DoH to assess whether an amendment to the existing MBS items or new MBS items will be required. Patients with a confirmed BRCA1 or BRCA2 mutation from current MBS-listed tests (MBS Item 73302, MBS Item 73296 and MBS Item 73297) are to be excluded from the proposed medical test.

Germline BRCA mutation testing at diagnosis prior to initiating chemotherapy will facilitate a timely informed response to the test result. This will ensure patients eligible for olaparib treatment avoid delays that could compromise the benefit of targeted therapy.

Proposed patients for olaparib treatment

It is proposed patients with a confirmed BRCA1/2 mutation and have HER2-negative high risk early breast cancer should be eligible for olaparib treatment after \geq six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines and/or taxanes. Patients who test positive for BRCA wild-type gene mutations would receive current SoC therapy.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

1. The current key components and clinical steps involved in delivering a tumour BRCA mutation test in patients with HER2-negative high risk early breast cancer are as follows: Patient's blood sample is taken and sent to a pathology laboratory where BRCA testing is performed. DNA is extracted, purified and may be quantified using the laboratory's preferred commercially available kits. PCR amplification methods, including multiplex ligation dependent probe amplification (MLPA) may be used. Hybridisation capture baits may also be used. Libraries for sequencing are prepared and library quality may be evaluated at this step. Some gene panels (e.g. BRCA) identify all classes of mutations including single base substitutions, small insertions and deletions and large gene re-arrangements. Variants are called using comparison to reference libraries. Next-generation sequencing is performed at most Australian laboratories using the Illumina MiSeq, NextSeq or Novaseq platforms. Sequencing results are then reported to the requesting specialist or consultant physician.
2. The results are sent to the treating medical practitioner. If a mutation is detected, a face-to-face appointment with the patient is arranged to deliver the results. Individuals identified as harbouring a pathogenic mutation (Class 4 or 5) are referred to Genetics Services/Familial Cancer Centres for post-test counselling. Patients with a VUS or strong family history should also be referred for post-test counselling.
3. Based on a positive mutation for BRCA1/2, the medical practitioner will consider prescribing olaparib to the patient if they meet the PBS criteria to access treatment.

The current reference standard for BRCAm testing is Next Generation Sequencing (NGS) technology which is well established, and currently used by molecular pathology service providers for germline BRCA mutation testing in Australia.

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

Registered trademarks may be held by the various commercial kits used at the different stages of the testing process outlined in Q27 above, for example for DNA extraction, quality assurance, quantification, PCR amplification, as well as the NGS platform itself.

The drug name Lynparza® 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?

N/A

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 current reference standard for BRCA mutation testing is Next Generation Sequencing (NGS) technology which is well established, and currently used by molecular pathology service providers for germline BRCA mutation testing in Australia.

It is unlikely that a patient would require more than one germline BRCA test in their lifetime.

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:

Current germline testing for the BRCA 1/2 genes are offered to patients with high risk breast cancer or ovarian cancer.

If a patient is referred for a germline test, genetic counselling will also be required and prophylactic surgery may be considered.

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

Testing to identify BRCA gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists and/or geneticists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

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

N/A

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

Testing to identify BRCA gene mutations in patients with HER2-negative high risk early breast cancer should be based on a referral request from a specialist or consultant physician and should not be pathologist determinable.

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

Testing to identify BRCA gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained pathologists and/or geneticists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

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

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP

- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

The medical service proposed in patients with HER2-negative high risk early breast cancer 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 NATA accredited and enrolled into the RCPA QAPS. For further information please refer to the website: <https://www.rcpaqap.com.au/home-page>

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

N/A

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

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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

To present the relevant nominated comparator for the medical service of germline testing to detect BRCA1/2 gene mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for treatment with olaparib requires an understanding of the two patient populations (HR-positive and TNBC) within HER2-negative breast cancer.

In patients with HR-positive breast cancer the relevant nominated comparator for medical service of germline testing to detect BRCA1 or BRCA2 gene mutations is no test. A small group of patients with high risk HR-positive breast cancer may have a >10% risk of harbouring a mutation. This probability of heritable pathogenic mutation is included in the eviQ guidelines (eviQ guidelines, 2020) and these patients will need to meet the 10% threshold via a quantitative algorithm for access under the existing MBS item number 73296 and MBS item number 73302.

In patients with TNBC the relevant nominated comparator for medical service of germline testing to detect BRCA1 or BRCA2 gene mutations is no test. All patients with early TNBC are deemed to have tumours with high risk characteristics. This sentiment is supported by feedback from a clinician roundtable commissioned by AZ, as patients with early TNBC generally have a poor prognosis and the availability of a genetic test and subsequent targeted therapy in this patient population is welcomed by clinicians. In Australia, many Genetic/Familial Cancer Centres use the criteria outlined in the eviQ Guidelines (eviQ Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes, 2020), to identify suitable candidates for BRCA mutation testing for the purpose of familial cancer risk assessment. The eviQ guidelines currently recommend BRCA mutation 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.

The nominated comparator for adjuvant olaparib treatment in HER2-negative high risk early breast cancer is standard of care (SoC). Results from the CREATE-X trial in patients with HER2-negative high risk early breast cancer showed capecitabine as an effective treatment option for patients with TNBC (Masuda et al 2017). In another study involving capecitabine treatment in patients with early TNBC, the GEICAM-CIBOMA trial results failed to show a statistical significant increase in DFS in patients with capecitabine added on to standard chemotherapy (Lluch et al 2019). The KEYNOTE-522 trial showed pembrolizumab to be an effective

treatment involving patients with early TNBC (Schmid et al 2020). However, the BRCA mutation status of patients included in the aforementioned trials (CREATE-X trial, GEICAM-CIBOMA trial and KEYNOTE-522 trial) were unknown and as such, capecitabine and pembrolizumab are deemed inappropriate as relevant comparators due to differing patient populations.

In the monarchE trial involving patients with HR-positive early breast cancer, abemaciclib showed to be an effective treatment for patients with HR-positive early breast cancer (Harbeck et al 2021). However, similar to the CREATE-X trial, the BRCA mutation status of the included HR-positive early breast cancer patients enrolled in the monarchE trial was unknown and as such, abemaciclib is deemed inappropriate as a relevant comparator due to differing patient populations. It is to be noted, treatment with CDK4/6-inhibitors (abemaciclib, palbociclib and ribociclib) for advanced and metastatic HR-positive breast cancer are TGA approved and PBS-listed.

As outlined in the treatment pathway, presented in Figure 1 in the Attachment, prior to receiving olaparib a patient must have a confirmed BRCA1/2 gene mutation, local treatment and \geq six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines and/or taxanes. Prior platinum chemotherapy is not a limiting factor to receive olaparib for early breast cancer treatment.

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

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

In patients with HER2-negative high risk early breast cancer the relevant nominated comparator for medical service of germline testing to detect BRCA1 or BRCA2 gene mutations is no test.

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

As stated in Q38 above, the relevant nominated comparator for the medical service of germline testing to detect BRCA1/2 gene mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for treatment with olaparib requires a separation of the two patient populations (HR-positive and TNBC) within HER2-negative breast cancer.

In patients with HR-positive breast cancer the relevant nominated comparator for medical service of germline testing to detect BRCA1 or BRCA2 mutation is no test. A small group of patients with high risk HR-positive breast cancer may have a >10% risk of harbouring a mutation. This probability of heritable pathogenic mutation is included in the eviQ guidelines (eviQ guidelines, 2020) and these patients will need to meet the 10% threshold via a quantitative algorithm for access under the existing MBS item 73296 and MBS item 73302.

In patients with TNBC the relevant nominated comparator for medical service of germline testing to detect BRCA1 or BRCA2 mutation is no test. All patients with early TNBC are deemed to have tumours with high risk characteristics. This sentiment is supported by feedback from a clinician roundtable commissioned by AZ, as patients with early TNBC generally have a poor prognosis and the availability of a genetic test and subsequent targeted therapy in this patient population is welcomed by clinicians. In Australia, many Genetic/Familial Cancer Centres use the criteria outlined in the eviQ Guidelines (eviQ Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes, 2020), to identify suitable candidates for BRCA mutation testing for the purpose of familial cancer risk assessment. The eviQ guidelines currently recommend BRCA mutation 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.

Consequently, the treatment pathway provided at Q26 describes the current clinical management for patients with HER2-negative high risk early breast cancer.

Changes to the treatment pathway after introduction of germline BRCA mutation testing are described in answer to Q42. A patient with HER2-negative high risk early breast cancer who has been identified to have a BRCA1/2 gene mutation is eligible to access treatment with olaparib if all other PBS criteria are met.

Olaparib is a potent oral human polyadenosine 5'diphosphoribose polymerisation (PARP) inhibitor (PARP-1, -2 and -3) whose anti-tumour effects are dependent on an underlying defect in a cancer cell's DNA damage response (DDR) mechanisms, rather than a direct interaction with a mutated gene or protein (McCabe et al 2006), to preferentially kill cancer cells with these deficiencies compared to normal cells. These defects in DDR mechanisms arise from mutations that cause homologous recombination deficiency, of which BRCA mutations are only one subtype. Olaparib traps PARP at the sites of single-strand DNA damage and prevents their repair (Murai et al 2012). During replication, the single-strand breaks where PARP is trapped are converted to double-strand DNA breaks, which are normally repaired by a high fidelity process known as HRR (Lord et al 2016, Pommier et al 2016). Tumours with homologous recombination deficiency, such as patients with TNBC with BRCA1, BRCA2, ATM or other HRR gene mutations, cannot accurately repair the DNA damage, which may become lethal to tumour cells as it accumulates (Lord et al 2016). In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available platinum, anthracycline or taxane-based chemotherapy regimens.

Tumours with homologous recombination deficiency are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Hay et al 2009, Rottenberg et al 2008) and in the clinic (Fong et al 2009, Tutt et al 2010). Clinical studies suggest that single agent olaparib is effective in HER2-negative high risk early breast cancer patients, particularly those with a BRCA1 or BRCA2 gene mutation (Tutt et al 2021, Robson et al 2017).

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

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

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

As stated in Q38 above, the relevant nominated comparator for the medical service of germline BRCA mutation testing to detect BRCA1/2 gene mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for treatment with olaparib requires an understanding of the two patient populations (HR-positive and TNBC) within HER2-negative breast cancer.

In patients with HR-positive breast cancer the relevant nominated comparator for medical service of germline BRCA mutation testing is no test. Similarly, in patients with TNBC, the relevant nominated comparator for medical service of germline BRCA mutation testing is no test.

It could be assumed that up to 100% substitution of no testing (the comparator) with testing for BRCA mutations will occur for patients with HR-positive breast cancer and for patients with TNBC, to determine patient eligibility for treatment with olaparib. Germline BRCA1/2 gene mutation testing (MBS Item number 73297) is also available to biological relatives of patients who have pathogenic mutations identified according to MBS Item number 73296.

The availability of a new treatment option (a PARP-inhibitor) will increase uptake of germline BRCA mutation testing. However, it is unlikely that all eligible patients will take up testing due to personal patient reasons.

A patient with HER2-negative high risk early breast cancer can only access olaparib treatment based on a confirmed BRCA1/2 gene mutation. Patients without the BRCA1/2 gene mutation will not be eligible for olaparib treatment and will follow current standard of care.

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):

Changes to the current clinical management pathway following introduction of germline BRCA mutation testing in patients with HER2-negative high risk early breast cancer are outlined in Figure 1 in the Attachment to this form.

Germline BRCA mutation testing at diagnosis prior to initiating chemotherapy will facilitate a timely informed response to the test result and also protect tissue integrity which would be impacted by chemotherapy. This will ensure patients eligible for olaparib treatment avoid delays that could compromise the benefit of targeted therapy.

It is proposed patients with a confirmed BRCA1/2 mutation and have HER2-negative high risk early breast cancer should be eligible for olaparib treatment after \geq six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines and/or taxanes. Patients who test positive for BRCA wild-type gene mutations would receive current SoC treatment.

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 olaparib therapy) are superior in terms of comparative effectiveness versus the main comparator (no testing and current standard of care) in patients with HER2-negative high risk early breast cancer is based on the phase III OlympiA trial (Tutt et al 2021).

The OlympiA trial compared the efficacy of the PARP inhibitor, olaparib, in patients with HER2-negative high risk early breast cancer with BRCA1 or BRCA2 germline pathogenic or likely pathogenic variants and high risk clinicopathological factors who had received local treatment and \geq six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines and/or taxanes (Tutt et al 2021).

In the overall trial population (approximately 20% were HR-positive patients and 80% were TNBC), treatment with olaparib was administered for up to 12 months and the results showed that there was a statistically significant and clinically meaningful 42% reduction in the risk of invasive disease recurrence or death in the olaparib arm compared with the placebo arm (HR 0.58; 99.5% CI: 0.46-0.74, $P < 0.001$). In a subgroup analysis of TNBC patients only, a statistically significant and clinically meaningful 44% reduction in the risk of invasive disease recurrence or death in the olaparib arm compared with the placebo arm (HR 0.56; 95% CI: 0.43-0.73). Similarly, in a subgroup analysis of HR-positive patients only, a non-significant but numerical reduction of 30% (HR 0.70; 95% CI: 0.38-1.27) in the risk of invasive disease recurrence or death in the olaparib arm compared with the placebo arm. The results show a positive trend in benefit for olaparib versus placebo in the HR-positive subgroup population, however the lack of statistical significance can be attributed to the smaller included patient population and limited number of events (Tutt et al 2021).

Although insufficient deaths had occurred for a conclusive result, interim overall survival results showed a 32% numerical reduction in the risk of death (HR 0.68, 99% CI: 0.44, 1.05, $p = 0.02$). However, likely due to the length of follow-up and limited number of events this was insufficient to reach statistical significance at the time of this interim OS analysis. Results from further interim OS analyses are to be presented in the near future and are likely expected to show statistical significant benefit (Tutt et al 2021).

Germline BRCA gene mutation testing is well established in Australia especially for familial risk assessment (under MBS Item 73297) and more recently to determine patient eligibility for olaparib in the ovarian cancer population (under MBS item 73301).

It is estimated that 6.6% to 14.6% of breast tumours have detectable loss of function BRCA mutations (Lai et al 2022). The likelihood of a BRCA1/2 mutation found in a tumour breast tissue being somatic is approximately one third and germline is two thirds (Winter et al 2016). Patients with triple negative breast cancer (TNBC) are known to have a higher risk of tumours presenting with a BRCA mutation and it is estimated 10% of TNBC patients harbour a BRCA mutation (Wong-Brown et al 2015). Significant changes to the local and international germline BRCA mutation testing environment warrants reconsideration of germline BRCA mutation test for HER2-negative high risk early breast cancer patients with BRCA1/2 mutations at this time.

Testing for BRCA1/2 mutations informs treatment choices and outcomes, and will ensure that targeted products such as olaparib are used for indications where patients are eligible for treatment and will get the most benefit (Tuffaha et al 2018, Tung et al 2020, Tutt et al 2021). In addition, BRCA mutation testing can help identify and address increased cancer risk in family members through surveillance or prophylactic surgery (Petruccioli et al 1993).

The proposed medical service is germline BRCA mutation test to detect BRCA1/2 gene mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for adjuvant olaparib treatment in early breast cancer. Patients with a confirmed BRCA1 or BRCA2 mutation from current MBS-listed tests (MBS Item 73302, MBS Item 73296 and MBS Item 73297) are to be excluded from the proposed medical test.

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: Safety and tolerability of olaparib treatment assessed by adverse events and collection of clinical chemistry/haematology parameters

Clinical Effectiveness Outcomes:

Test outcomes

Trial based (evidentiary standard) analytical performance:

Sensitivity, Specificity, Positive predictive value, Negative predictive value

Clinical utility of test:

Prognostic effect of BRCA1 or BRCA2 genetic mutation in HER2-negative high risk early breast cancer

Other test-related considerations:

Re-biopsy rates

Test turnaround time

Estimated number of patients being tested

Cost of testing per patient

Drug outcomes

Invasive Disease Free Survival (IDFS)

Distant Disease Free Survival (DDFS)

Overall Survival (OS)

Clinical Outcomes Assessment/Quality of Life (QLQ-C30 and FACIT-Fatigue)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

In Australia, breast cancer is the most common cancer affecting women. In 2021, it is estimated an incidence of 20,030 patients (19,866 women and 164 men) will be diagnosed with breast cancer (AIHW 2021). 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. Patients with a BRCA1 or BRCA2 mutation are believed to have an intermediate risk of developing breast cancer (Balmana et al 2011). 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 (Antoniu et al 2003, Chen et al 2007). The majority of breast cancers are HER2-negative (80%-85%) based on histological subtypes (Morey et al 2016); whereas approximately 10% to 15% are triple negative (Chan et al 2010, Wen et al 2018, Breast Cancer Network Australia 2022). In particular, TNBC has been associated with more aggressive disease and worse survival versus non-TNBC (National Breast Cancer Foundation 2022). Epidemiology data show a high prevalence of BRCA1/2 mutations in TNBC patients and that these mutations are not restricted to young women or patients with a positive family history (Armstrong et al 2019, Hahnen et al 2017). While the frequency of BRCA1/2 mutations is higher among patients with TNBC than in those with HR-positive breast cancer, the latter comprises a much larger proportion of the total breast cancer population. This may mean there are more patients harbouring BRCA1/2 mutations who have HR-positive breast cancer than have TNBC. As such, it is important to provide subsidised access to the to both HR-positive breast cancer and TNBC patient population to ensure equitable access to olaparib for breast cancer treatment.

For the year 2021, it is estimated:

20,030 patients will be diagnosed with breast cancer (using the estimates from AIHW);

17,987 patients will be diagnosed with early stage breast cancer (Stage I to III from AIHW); and

12,393 patients will be diagnosed with HR-positive breast cancer (Estimate 69% of breast cancer patients are HR-positive from Onitilo et al 2009)

2,698 patients will be diagnosed with triple negative breast cancer (Estimate 15% of breast cancer patients are triple negative from Breast Cancer Network Australia 2021)

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

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

Germline BRCA mutation test to determine BRCA1/2 gene mutation status would be conducted only once per patient in most cases. Some patients with early HER2-negative high risk early breast cancer may already know their germline BRCA gene mutation status via testing under existing MBS item codes for breast cancer or cascade testing due to an established familial risk.

The proposed medical service is germline BRCA mutation test to detect BRCA1/2 gene mutations in patients with HER2-negative high risk early breast cancer to determine eligibility for adjuvant olaparib treatment in early breast cancer. Patients with a confirmed BRCA1 or BRCA2 mutation from current MBS-listed tests (MBS Item 73302, MBS Item 73296 and MBS Item 73297) are to be excluded from the proposed medical test.

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

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

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

The number of patients utilising the proposed medical service is dependent on the number of patients diagnosed with HER2-negative high risk early breast cancer (which is estimated in Question 46).

If the BRCA test is administered at the time of diagnosis of HER2-negative high risk early breast cancer, then up to 15,091 newly diagnosed patients could be eligible for the test in 2021. However, it is unlikely that all eligible patients would take up testing as they may test positive to a germline BRCA1/2 mutation.

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

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

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

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

PART 8 – COST INFORMATION

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

The current MBS fee for detection of germline BRCA1 or BRCA2 mutations according to Item 73302, Item 73295 or Item 73296 is \$1,200.00.

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

Germline BRCA mutation testing turnaround time from when the blood sample is collected to test result is between 3 to 8 weeks. This includes time for the request and time to transport the blood sample to a specialist laboratory, if needed (7-10 days). Testing in the laboratory may require several hours of activity to perform plus run time for automated processes depending on instrumentation and procedures being followed and could take up to 4 weeks. Reporting results to the requesting specialist or consultant physician takes a further 1-2 days.

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.

As mentioned in in Q6 AstraZeneca seeks guidance on whether an amendment to the existing MBS Item numbers or if new MBS Item codes are required for eligibility of olaparib in patients HER2-negative high risk early breast cancer.

Amendment to current MBS Item numbers

Category 6 – Pathology Services	
MBS item number 73295	Group P7 - Genetics
<p>Detection of germline BRCA1 or BRCA2 pathogenic or likely pathogenic gene variants, in a patient with advanced (FIGO III-IV) high-grade serous or high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer or HER2-negative high risk breast cancer for whom testing of tumour tissue is not feasible, requested by a specialist or consultant physician, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS)</p>	
<p>Fee: \$1,200.00 Benefit: 75% = \$900.00 85% = \$1,112.10</p>	

ATTACHMENT

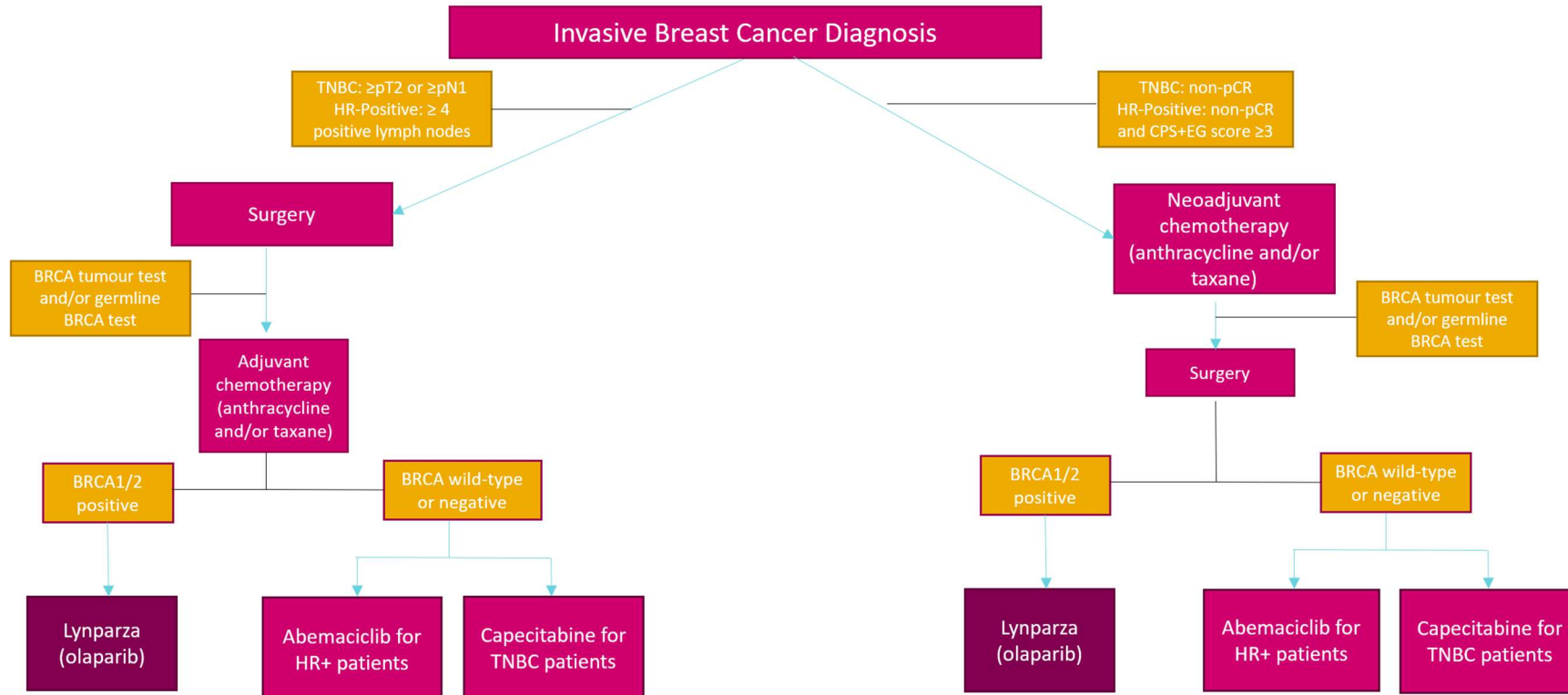


Figure 1: Proposed clinical management treatment pathway for patients diagnosed with HER2-negative breast cancer
 Abbreviations: HR, hormone receptor; TNBC, triple negative breast cancer; pCR, pathologic complete response; BRCA, BReast CAncer gene;

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