



Australian Government

Department of Health

Application Form

Testing of blood to detect germline BRCA1 or BRCA2 gene mutations, in patients with metastatic pancreatic cancer to determine eligibility for PBS olaparib

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): Not Applicable

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

Not Applicable

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Testing of blood to detect germline BRCA1 or BRCA2 gene mutations, in patients with metastatic pancreatic cancer, to determine eligibility for PBS olaparib.

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)

Pancreatic cancer has one of the lowest 5 year survival rates with a 9.8% survival rate for the period 2011-2015. The prognosis of this cancer has not improved significantly over the past 20 years, and the incidence and mortality rates are very similar (AIHW, 2019). A total of 3307 cases of pancreatic cancer were reported in 2015, with 2911 deaths due to pancreatic cancer in 2016. It is estimated that pancreatic cancer will be the fourth most common cause of death due to cancer in 2019 (AIHW, 2019). The poor prognosis for pancreatic cancer is directly related to late diagnosis, when the disease is often locally advanced or metastatic, and surgery is not an option (AIHW 2012). Carriers of germline mutations in BRCA1/2 genes are known to have an increased risk of pancreatic cancer with up to 7% of unselected pancreatic cancer cases having a germline BRCA 1/2 mutation (Golan T, 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 testing of blood for germline BRCA 1/2 mutations, in patients with metastatic pancreatic cancer. The purpose of the test is to determine eligibility for PBS olaparib (i.e. treatment of patients whose disease does not progress following first line treatment with platinum based chemotherapy).

Germline BRCA mutation testing is currently well established in Australia. Germline BRCA 1/2 testing to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed high grade serous ovarian cancer (HGSOC) has been listed on the MBS (Item 73295) and PBS (Items 11503K; 11522K – 100 mg tablets; 11528R;11539H – 150 mg tablets; 11050N - 50 mg capsules) since 1 February 2017 (refer co-dependent MSAC/PBAC Application 1380). Germline BRCA testing is also established to screen for mutations in at risk patients with ovarian or breast cancer (MBS Item 73296) and for familial cascade testing (MBS Item 73297).

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)

Please note that there are a number of existing MBS items related to germline BRCA 1/2 testing:

- **MBS Item 73295:** Detection of germline BRCA 1/2 gene mutations in patients with platinum sensitive, relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, to determine eligibility for olaparib under the Pharmaceutical Benefits Scheme (PBS)

- **MBS Item 73296:** Characterisation of germline gene mutations including BRCA 1/2, STK11, PTEN, CDH1, PALB2 or TP53 in a patient with breast or ovarian cancer at >10% risk of having one or more of these mutations.
- **MBS Item 73297:** Characterisation of germline gene mutations in a biological relative of a patient with one or more of the gene mutations in Item 73296.

It is expected that a patient will only be tested for BRCA mutations once in their lifetime utilising the relevant MBS Item.

(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:

Not Applicable

(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):

Not Applicable

(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)

An additional population is proposed for germline BRCA 1/2 testing in patients with platinum sensitive, metastatic pancreatic cancer

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
 No

No other source of funding for germline BRCA 1/2 mutation testing other than the MBS is sought, however in this co-dependent submission, public funding for PBS access to olaparib is also being sought for patients with platinum sensitive, metastatic pancreatic cancer, with BRCA 1/2 gene mutations.

(g) If yes, please advise:

Insert description of other public funding mechanism here

7. What is the type of service:

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

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

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

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

- Pharmaceutical / Biological
- Prosthesis or device
- No

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

- Yes
- No

Olaparib is not currently reimbursed for the listing requested with this application. Olaparib is currently PBS funded for platinum sensitive relapse patients with high grade serous ovarian, fallopian tube or primary peritoneal cancer, who also have germline BRCA 1/2 gene mutations (PBS Items: 11503K; 11522K – 100 mg tablets; 11528R; 11539H – 150 mg tablets; 11050N - 50 mg capsules).

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

Insert PBS item code(s) here: Not Applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

- Yes (please provide PBAC submission item number below)
- No

Insert PBAC submission item number here: Not Applicable

A co-dependent submission to MSAC/PBAC is proposed for BRCA 1/2 mutation testing to determine PBS access to olaparib in patients with metastatic pancreatic cancer whose disease has not progressed following first-line platinum-based chemotherapy.

(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

Not Applicable

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

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

Not Applicable

(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

Not Applicable

(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

Not Applicable

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

Not Applicable

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

Single use consumables:

Multi-use consumables:

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

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

- 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: Not Applicable
Sponsor's name: Various, as follows at the time of this Application:

There is no single sponsor for germline BRCA mutation testing in Australia. At present, there are several Australian molecular pathology service providers that offer BRCA mutation testing on a commercial basis (Table 1). All Australian molecular pathology service providers that currently perform BRCA mutation testing, use in-house developed testing methods (as opposed to commercial test kits).

Local test methodology remains consistent with that previously considered by MSAC under application 1380 to reimburse BRCA mutation testing to determine eligibility for olaparib (MBS item #73295). Details of the test methodologies conducted by local service providers were summarised in the co-dependent submission for olaparib in BRCA mutation platinum sensitive high-grade serous ovarian cancer (HGSO) (submitted by AstraZeneca, October 2015). As summarised in Table 1, most laboratories use Next Generation Sequencing (NGS) based methods or Sanger sequencing.

Sanger sequencing and NGS methods have high sensitivity for the detection of single base changes and small insertions or deletions in the BRCA genes, but do not detect copy number alterations or large rearrangements (e.g. the deletion or duplication of whole exons, groups of exons or the entire gene), which can account for up to 10% of all known BRCA mutations. The most common method for detecting copy number alterations in Australia is the multiplex ligation-dependent probe amplification (MLPA) assay developed by MRC-Holland. This is a variation of the multiplex polymerase chain reaction (PCR) that permits multiple targets to be amplified with only a single primer pair.

Table 1 Australian molecular pathology service providers that offer BRCAm testing on a commercial basis

Molecular pathology service provider (State)	Method	QAP involvement
Genomics For Life (QLD)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
Pathology North (NSW)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
Pathology Queensland (QLD)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
PathWest (WA)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
Peter MacCallum Cancer Centre (VIC)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
SA Pathology (SA)	Sanger sequencing + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality assurance programs.
Genomics Diagnostics (VIC – national network)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality Assurance Programs
SONIC Genetics (NSW – National network)	NGS + MLPA	Enrolment in EMQN UQNEQAS RCPA Quality Assurance Programs

Abbreviations: EDTA, ethylenediaminetetraacetic acid; EMQN, European Molecular Genetics Quality Network; MLPA, multiplex ligation-dependent probe amplification; 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
 Not Applicable

All Australian molecular pathology service providers that currently perform BRCAm testing, use in-house developed testing methods (as opposed to commercial test kits). Under the 2010 TGA regulatory framework, BRCAm tests that are used to determine eligibility for olaparib are classified as in-house developed Class 3 in vitro diagnostic medical devices (IVDs). The TGA framework requires laboratories that deal with Class 3 IVDs to provide the TGA with a declaration of conformity that the in-house IVDs comply with the essential principles and describe the 'kinds' of IVDs manufactured.

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 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 pancreatic cancer will not be made for the Lynparza 50mg capsules.

The current indications for Lynparza tablets are as follows:

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.

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.

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

Date of submission to TGA:

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

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 to register Lynparza® (olaparib) for the treatment of pancreatic cancer is currently being prepared.

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

Proposed indication(s), if applicable: See below.

Pancreatic cancer

Lynparza is indicated as monotherapy for the:

- maintenance treatment of adult patients with germline *BRCA1* or *BRCA2* mutation and metastatic pancreatic cancer and disease that had not progressed during first-line platinum-based chemotherapy. BRCA mutation status should be determined by an experienced laboratory using a validated test method.

Proposed purpose(s), if applicable: Not Applicable

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 (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
Pivotal olaparib study					
1	Randomised, double-blind, placebo-controlled, phase 3 trial	Maintenance Olaparib for Germline <i>BRCA</i> -Mutated Metastatic Pancreatic Cancer	Evaluation of efficacy and safety of olaparib maintenance therapy in patients with germline <i>BRCA1</i> or <i>BRCA2</i> mutation and metastatic pancreatic cancer and disease that had not progressed during first-line platinum-based chemotherapy. The primary end point was progression-free survival, assessed by blinded independent central review.	https://www.nejm.org/doi/full/10.1056/NEJMoa1903387?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ et al. NEJM 2019; 381;4: 317 ClinicalTrials.gov number, NCT02184195	July 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
2	Randomised, double-blind, placebo-controlled, phase 3 trial	Geographic and ethnic heterogeneity in the BRCA1/2 pre-screening population for the randomized phase III POLO study of olaparib maintenance in metastatic pancreatic cancer (mPC)	POLO is an international, ongoing, placebocontrolled trial to determine efficacy of olaparib (tablet formulation) maintenance monotherapy in gBRCAm pts with mPC. Demographic/clinical history data were collected at enrolment from 2206 patients from 12 countries.	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01787550/full Golan T, Kindler H L, Park J O, Reni M, Mercade T M, Hammel P, Van Cutsem E, Arnord D, Hochhauser D, Locker G Y, et al. Journal of clinical oncology, 36, 15 ClinicalTrials.gov number, NCT02184195	2018
3	Randomised, double-blind, placebo-controlled, phase 3 trial	POLO: a randomized phase III trial of olaparib maintenance monotherapy in patients (pts) with metastatic pancreatic cancer (mPC) who have a germline BRCA1/2 mutation (gBRCAm)	As per the PIVOTAL trial (1)	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01765753/full Golan T, Oh D-Y, Reni M, Macarulla T M, Tortora G, Hall M J, Reinacher-Schick A C, Borg C, Hochhauser D, Walter T, et al. Journal of clinical oncology, 34 ClinicalTrials.gov number, NCT02184195	2016
Phase II Supportive study					

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
4	Multicentre Phase II study	Olaparib Monotherapy in Patients With Advanced Cancer and a Germline <i>BRCA1/2</i> Mutation	Evaluation of efficacy and safety of olaparib maintenance therapy in individuals with a germline <i>BRCA1/2</i> mutation and recurrent cancer (including pancreatic cancer with prior gemcitabine treatment). The primary efficacy end point was tumour response rate.	https://ascopubs.org/doi/full/10.1200/JCO.2014.56.2728?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed Kaufman et al 2015 J Clin Oncol 33: 244-250.	January 2015
Biomarker studies					

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
5	Retrospective study	Real-Time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations That Might Be Targeted With Existing Drugs or Used as Biomarkers	Identification of genomic alterations in pancreatic ductal adenocarcinomas (PDAC); Targeted genomic profile analyses of 3594 PDAC samples from an international cohort, including capture-based targeted genomic profiling of as many as 315 cancer associated genes and intron regions of 28 genes that are rearranged in cancer cells.	https://www.gastrojournal.org/article/S0016-5085(19)32505-3/fulltext?referrer=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2F Singhi AD, George B, Greenbowe JR, Chung J, Suh J, Maitra A et al. Gastroenterology 2019;156:2242–2253.	June 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
	Review	A decade of clinical development of PARP inhibitors in perspective.	Review of PARP inhibitors, including development and validation of predictive biomarkers for patient stratification mainly based on homologous recombination defects beyond BRCA1/BRCA2 mutations, identifying DNA repair deficient tumours in other cancer types such as prostate or pancreatic cancer, or by designing combination therapies with PARP inhibitors.	https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz192/5520938 Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M et al. Ann Oncol (online) doi:10.1093/annonc/mdz192	June 2019
6	Systematic review	Genomic profiling in pancreatic ductal adenocarcinoma and a pathway towards therapy individualization: A scoping review.	Systematic review of data on therapies targeting somatic and germline alterations, and their downstream pathways in PDAC	https://linkinghub.elsevier.com/retrieve/pii/S0305-7372(19)30051-9 Singh RR, Goldberg J, Varghese AM, Yu KH, Park W, O'Reilly EM Cancer Treat Rev. 2019 May;75:27-38. doi: 10.1016/j.ctrv.2019.03.003.	May 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
7	Biomarker study	Geographic and ethnic heterogeneity in the BRCA1/2 pre-screening population for the randomized phase III POLO study of olaparib maintenance in metastatic pancreatic cancer (mPC)	Analysis of germline BRCA 1/2 mutation status at randomisation pre-screening in POLO trial	https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4115 Golan T, Kindler HL, Park JO, Reni M, Macarulla T, Hammel P et al. J Clin Oncol 2018; 36(15) Suppl 1 Abstract 4115	2018
8	Molecular profiling	Comprehensive molecular profiling of patients with pancreatic adenocarcinoma: A single institution's experience.	Examination of tumours from 114 PDAC patients using NextGen sequencing, immunohistochemistry, and in-situ hybridization for DNA repair gene mutations	https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e16236 Kamgar M, Dyson G, Diab M, Tesfaye AA, Korn WM, Shields AF et al. J Clin Oncol 2018; 36(15) Suppl 1 Abstract e16236	2018
9	Review	DNA repair dysfunction in pancreatic cancer: A clinically relevant subtype for drug development.	Review describes the subgroup of patients with Pancreatic ductal adenocarcinoma with aberrant DNA repair and discusses diagnostic and therapeutic options	https://jncn.org/view/journals/jncn/15/8/article-p1063.xml Golan T, Javle M. JNCCN 2017; 15(8):1063-1069.	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
10	Retrospective analysis	Homologous recombination deficiency (HRD) in patients with pancreatic cancer (PC) and response to chemotherapy.	Retrospective analysis of 91 tumour samples from patients treated for locally advanced or metastatic pancreatic cancer in order to describe the mutation and homologous recombination deficiency status and association with treatment response/outcome.	https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.317 Shahda S, Timms K, Ibrahim A, Reid JE, Cramer HM, Radovich M et al. J Clin Oncol 2017; 35(4) Suppl 1 Abstract 317	2017
11	Diagnostic marker study	Germline mutations in seemingly sporadic pancreatic cancer.	Prevalence of germline mutations in 15 genes (including BRCA) among sporadic pancreatic cancer cases via analysis of lymphocyte DNA next generation sequencing data from 296 cases of pancreatic cancer	https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.312 Wong C, Cuggia A, Borgida A, Holter S, Hall A, Connor A et al. J Clin Oncol 2017; 35(4) Suppl 1 Abstract 312	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
12	Review	Genomic instability in pancreatic adenocarcinoma: a new step towards precision medicine and novel therapeutic approaches.	Evaluation of characteristics of genomic instability in pancreatic cancer along with clinical implications and the utility of DNA targeting agents particularly PARP inhibitors	https://www.ncbi.nlm.nih.gov/pubmed/26881472 Sahin IH, Lowery MA, Stadler ZK, Salo-Mullen E, Iacobuzio-Donahue CA, Kelsen DP et al. Expert Rev Gastroenterol Hepatol. 2016 Aug;10(8):893-905.	2016
13	Review	Changing the course of pancreatic cancer – Focus on recent translational advances	Review of Immune strategies in pancreatic cancer	https://linkinghub.elsevier.com/retrieve/pii/S0305-7372(16)00012-8 Javle M, Golan T, Maitra A. Cancer Treat Rev 2016; 44:17-25.	2016
14	Review	Familial pancreatic cancer: genetic advances.	Review of known genetic syndromes that underlie familial pancreatic cancer (including BRCA mutations), where there are opportunities for genetic counselling and testing as well as clinical monitoring of at-risk patients.	http://www.genesdev.org/cgi/pmidlookup?view=long&pmid=24395243 Rustgi AK Genes & Dev 2014;28: 1-7	2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
15	Review	Parp-inhibitors in BRCA-associated pancreatic cancer.	Authors summarise the data related to PARPi in BRCA-associated pancreatic cancer that was presented at the annual meeting of ASCO 2014.	http://www.serena.unina.it/index.php/jop/article/view/2690/2735 PARP-inhibitors in BRCA-associated pancreatic cancer. Bhalla A, Saif MW. J Pancreas 2014; 15(4):340-343.	2014
16	Diagnostic marker study	Contribution of known and novel BRCA-mediated DNA repair pathway genes to pancreatic cancer susceptibility.	Evaluation of BRCA-pathway mutation contribution to PC susceptibility in French-Canadians	Smith A, Grant R, Hall A, Alirezaie N, Holter S, Whelan T. Cancer Research. Conference: AACR Special Conference: Cancer Susceptibility and Cancer Susceptibility Syndromes 2014. United States. 74 (Supplement 23).	2014
17	Diagnostic marker study	Clinical outcomes in pancreatic adenocarcinoma (PAC) in breast cancer (BC) survivors.	Evaluation of outcomes in 30 patients with breast cancer and PAC	https://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.4152 Lowery MA, Stadler ZK, Ludwig Miller E, D'Adamo DR, Salo-Mullem E, Allen P et al.. J Clin Oncol 2010; 28(15) Suppl 1 Abstract 4152	2010

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
18	Diagnostic marker study	BRCA2 mutations as a universal risk factor for pancreatic cancer has a limited role in Korean ethnic group.	Evaluation of link between BRCA2 mutation as risk factor in Korean population	https://www.ncbi.nlm.nih.gov/pubmed/18437078 Cho JH, Bang S, Park SW, Chung JB, Song SY. Pancreas 2008; 36 (4) (pp 337-340).	2008

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

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

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

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

There are no relevant studies to be published in near future.

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):

REDACTED

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):

REDACTED.

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

As discussed in Question 13 (a) there is no single sponsor for germline BRCA mutation testing in Australia. At present, there are several different Australian molecular pathology service providers that offer BRCA mutation testing on a commercial basis; please refer to Table 1.

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

Name of expert 1: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

Name of expert 2: Insert name here

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

Email address: Insert email address here

Justification of expertise: Insert a justification of expertise here

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

PART 6 – POPULATION (AND PRIOR TESTS), 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 in 2015, there were a total of 3307 cases (1,742 males and 1,565 females) of pancreatic cancer with 2911 deaths due to pancreatic cancer reported in 2016 (AIHW, 2019). It is estimated that pancreatic cancer will be the fifth most common cause of death due to cancer in 2019.

The incidence and mortality rate of pancreatic cancer increases with age and while the incidence has remained steady over the last few decades the actual number of cases has increased due to a growing and ageing population (AIHW, 2018) The median age of diagnosis is 72.8 years (AIHW, 2012). In 2019, it is estimated that the risk of an individual being diagnosed with pancreatic cancer by their 85th birthday will be 1 in 62 (1 in 55 males and 1 in 71 females) (AIHW, 2019).

Pancreatic cancer has one of the lowest 5 year cancer survival rates; in 2011-2015, the 5 year relative survival rate was 9.8% for those diagnosed with pancreatic cancer. The prognosis of this cancer has not improved significantly over the past 20 years, and the incidence and mortality rates are very similar (Cancer in Australia 2019).

In 2011, Australians lost 44,428 Disability Adjusted Life Years (DALYs) due to premature death or living with disability due to pancreatic cancer. This accounted for 5.3% of the total cancer burden, ranking pancreatic cancer the 5th greatest cause of cancer burden. This burden reflects the poor prognosis of survival for pancreatic cancer (AIHW, 2018).

The early stages of pancreatic cancer are asymptomatic, and this contributes to difficulties in diagnosis and late presentation. When symptoms occur, they generally result from a mass effect; symptoms may include back or abdominal pain, weight loss, steatorrhoea or jaundice (Ducreux M, 2015).

Tumours located in the body and the tail (20 to 25% of cases) of the pancreas are generally diagnosed at a more advanced stage than tumours located in the head (60 to 70% of cases), as these result in symptoms related to obstruction of the common bile and/or pancreatic duct (Ducreux M, 2015).

In terms of pathology, ductal adenocarcinoma and its variants account for over 90% of all pancreatic malignancies (Tempero MA, 2019). Histologically, adenocarcinoma was the most common pancreatic cancer type in 2013, representing 58% of all pancreatic cancer cases diagnosed. Australians diagnosed with this histological type had a 6.0% chance of surviving 5 years compared with their counterparts in the general population. Unspecified carcinomas and neoplasms, neuroendocrine neoplasms and other carcinomas account for the remaining histological cancer types (AIHW, 2018).

Risk factors for pancreatic cancer include tobacco use and high body mass with genetics and family history also associated with increased risk (Ducreux M, 2015). Germline mutations in BRCA1 or BRCA2, genes associated with increased risk of ovarian and breast cancers, are also known to increase the risk of pancreatic cancer. Up to 7% of unselected pancreatic cancer cases have a germline BRCA 1/2 mutation (Golan T, 2019); in some populations (e.g. Ashkenazi Jews), the prevalence of germline mutations in these genes is higher (Pilarski R, 2019). In Ashkenazi Jewish patients with pancreatic cancer, the prevalence of gBRCA mutations is 6% to 10% in unselected patients (Ferrone et al 2009; Ozelik et al 1997) and 15% in patients with a family history of the disease (Kim et al 2012). In pancreatic cancer patients with a family history of the disease, a prevalence of carrying a gBRCA2 mutation as high as 17% to 19% has been reported (Hahn et al 2003; Murphy et al 2002).

The poor prognosis for pancreatic cancer is directly related to late diagnosis upon presentation, when the disease is often locally advanced or metastatic, and surgery is not an option. Chemotherapy, in the case of metastatic cancer is limited to patients with good performance status (Ducreux M, 2015).

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:

The population for the proposed medical service, germline BRCA 1/2 mutation testing, are patients with metastatic pancreatic cancer, who are fit for first-line treatment with platinum-based chemotherapy. The purpose of the test is to determine eligibility for PBS-funded treatment with olaparib.

An outline of investigations, management and referral of patients within the Australian healthcare system prior to being eligible for the proposed service is provided below.

Adults with suspected pancreatic cancer would be referred from primary to secondary care, with a specialist team that could potentially include gastroenterologists, specialist surgeons, and oncologists (Gandy RC, 2016).

Diagnostic work up for cancer staging and risk assessment would include imaging of the tumour with computed tomography (CT) for imaging of the primary lesion as well as evaluation of lymph nodes and potential sites of metastases. Magnetic resonance imaging (MRI) and endoscopic ultrasound may also be undertaken, with the latter being the preferred mode for obtaining tissue and fluid for biopsy purposes. Blood tests, which include investigations for tumour markers, such as serum tumour marker carbohydrate antigen (CA) 19-9, would also be conducted (Gandy RC, 2016).

Patients diagnosed with metastatic pancreatic cancer may require interventions to provide relief of biliary and/or duodenal obstruction, malnutrition and pain.

Treatment options for patients with metastatic pancreatic cancer are limited and dependent on the patient's status; the risks of treatment need to be balanced against the potential benefits.

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 the absence of Australian specific guidelines for the treatment of metastatic pancreatic cancer, Clinical Practice Guidelines from the European Society of Medical Oncology (Ducreux M, 2015) and the United States (US) National Comprehensive Cancer Network (Tempero MA, 2019) were used to develop the treatment algorithm; the US National Cancer Institute treatment options for Stage IV pancreatic cancer were also consulted (National Cancer Institute, 2019). For the Australian perspective, the eviQ treatment protocols for metastatic pancreatic cancer (Cancer Institute NSW, 2018) were reviewed and found to be generally consistent with the abovementioned international guidelines.

Establishing BRCA mutation status at the time of diagnosis is recommended in the NCCN clinical guidelines for the treatment of pancreatic cancer (Tempero MA, 2019).

The algorithm is based on patient ECOG status and hepatic function as these are important criteria when deciding treatment approach. Additionally, Australian specific PBS restrictions and Product Information prescribing criteria were taken into account in terms of treatment options. The PBS Authority criteria for nab-paclitaxel specify that it must be given in combination with gemcitabine and patients must have an ECOG performance status of 2 or less. Hepatic function is also included as a criteria for deciding treatment options as the Abraxane (nab-paclitaxel) Product Information (July 2019) states the following: *There are insufficient data to permit dosage recommendations for patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment. (i.e. bilirubin > 1.5 ULN).*

A summary of the treatment pathway for metastatic pancreatic cancer is provided below and provided in flowchart format in Figure 1 in the Attachment to this Form.

- For patients with performance status of 3/4, with significant morbidities and a very short life expectancy, only symptomatic treatment can be considered.
- For patients with performance status of 0 to 2 and bilirubin level below 1.5× ULN gemcitabine and nab-paclitaxel can be considered; for patents with bilirubin level higher than 1.5× ULN, monotherapy with gemcitabine could be considered
- For patients with ECOG status of 0 or 1 and bilirubin level below 1.5× ULN, FOLFIRINOX or other platinum containing regimen may be considered

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

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

1. Patient with metastatic pancreatic cancer who meets the criteria for BRCA testing is referred to Genetic Services/Familial Cancer Centre by a medical practitioner (e.g. Oncologist) for a pre-test consultation.
2. Genetic counselling with Genetic Services/Familial Cancer Centre team and patient. Genetic Services/Familial Cancer Centre team provides information about genetics, inheritance (family risk) and genetic testing. The patient decides to take a genetic test i.e. the germline BRCA mutation test. The patient will provide a signed consent form to Genetic Services who will order the BRCA test and order the collection of a blood sample to be taken. Oncology teams are currently being trained in genetic mainstreaming; the oncologist or “treating specialist” can also sign the pathology request form and arrange for the blood collection.
3. Patient’s blood sample is taken and send to a pathology laboratory where BRCA testing is performed. The turnaround for test results is around 2 to 4 weeks.
4. The results are sent to the requesting clinician. 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.
5. Based on a positive BRCA mutation result the medical practitioner will consider prescribing olaparib to patients with metastatic pancreatic cancer if they meet the PBS criteria to access treatment.

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?

Not Applicable

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):

As discussed in Question 13 (a) BRCA testing is well established in Australia; there are several Australian molecular pathology service providers that offer BRCA mutation testing on a commercial basis, with centres in South Australia, Western Australia, Queensland, NSW and Victoria; please refer to Table 1. Only one germline BRCA test is required for a patient 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:

Because BRCA mutation testing provides prognostic information that can have an impact on family members, testing is ordinarily preceded and followed by genetic counselling. Pre-test genetic counselling is important to ensure that individuals understand the likelihood of a BRCA mutation being identified and the risks and benefits of being tested. Post-test genetic counselling helps patients understand the practical meaning of the results including implications for family members, including risk-reducing strategies that are available if a BRCA mutation is identified (Lau C, 2011). All states/territories in Australia have at least one publicly funded Genetic Service centre available to patients and their families. With MBS funding for germline testing in patients with metastatic pancreatic cancer, coupled with increased uptake of genetic mainstreaming, the likely future scenario would be pre-test counselling and consent being obtained by the oncology team and post-test counselling for Class 3-5 being performed by Genetics/FCC.

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

Testing to identify BRCA1/2 gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

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

Not Applicable

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

Testing to identify BRCA1/2 gene mutations in patients with metastatic pancreatic 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 BRCA1/2 gene mutations should be conducted and the results interpreted and reported by suitably qualified and trained pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this diagnostic testing procedure.

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

Specify further details here

The medical service will be conducted in pathology laboratories which may be private companies or may be domiciled within private or public research institutes or hospitals. All laboratories are accredited to the

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

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

Not Applicable

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

Yes

No – please specify below

Specify further details here

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):**

Currently germline BRCA mutation testing is not funded by the Commonwealth for patients with metastatic pancreatic cancer to determine their status of the BRCA 1 and 2 gene, for olaparib eligibility.

Therefore 'no testing' is the comparator.

Currently there are no options for maintenance therapy in patients who have achieved disease control following first line treatment with platinum-based chemotherapy. The nominated comparator for olaparib monotherapy maintenance treatment following first line platinum based chemotherapy is "watchful waiting" or no active anti-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

Not Applicable as the comparator 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):**

"No germline testing" and "watchful waiting" are the nominated comparators for the germline BRCA test and olaparib respectively, in patients with no evidence of disease progression after first-line platinum based chemotherapy. As shown in Figure 1 (Attachment), patients who progress after an initial response to first-line platinum based chemotherapy, would be treated with second-line chemotherapy, including nanoliposomal irinotecan or fluoropyrimidine-based therapy containing either irinotecan (e.g. FOLFIRI, FOLFIRINOX) or oxaliplatin (e.g. XELOX, mFOLFOX6 or OFF).

- 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)

The proposed medical service (i.e. germline BRCA mutation testing) will be used instead of the comparator (no germline BRCA mutation testing).

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

The comparator (no germline BRCA mutation test) will be substituted with a germline BRCA mutation test to determine patient eligibility for treatment with olaparib. The availability of a new treatment option for metastatic pancreatic cancer could be expected to increase uptake of germline BRCA mutation testing. A patient can only access olaparib based on a positive BRCAm status and response to first line platinum based chemotherapy. Up to 100% substitution of 'no testing' with BRCA mutation testing could be assumed in the specified patient group. However, not all patients may take up testing. Reasons for patients not taking up the test could be cultural or religious beliefs (Cohen et al. 2016). Current uptake of germline BRCA mutation testing in patients with ovarian cancer is approximately 70%.

Patients without the BRCA mutation will not be eligible for maintenance therapy 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 and maintenance treatment with olaparib in patients with an eligible BRCA1/2 mutation are outlined in

Figure 2 in the Attachment to this form.

Following diagnosis of metastatic pancreatic cancer, patients who are eligible candidates for platinum based chemotherapy, i.e. ECOG status of 0 or 1 and bilirubin < 1.5 x ULN, would be offered genetic testing for germline BRCA mutation. Given the advanced cancer stage, testing at the time of diagnosis is important for decision planning and for earlier access to treatment options. Establishing BRCA mutation status at the time of diagnosis is recommended in the NCCN clinical guidelines for the treatment of pancreatic cancer (Tempero MA, 2019).

There is evidence that patients with BRCA1/BRCA2 mutations demonstrate improved responses to platinum-based therapies for pancreatic cancer (Ducreux M, 2015) and so there may be an additional benefit to the patient in establishing germline BRCA mutation status prior to deciding first line therapy for metastatic pancreatic cancer. ESMO guidelines recommend either FOLFIRINOX or gem-nab-paclitaxel in patients with good performance status. Although there are no direct head to head data to determine the relative efficacy of these two regimens, an indirect comparison suggests that FOLFIRINOX may be slightly more efficacious, but also more toxic (Ducreux M, 2015). However, patients with BRCA1/2 mutations have longer survival when treated with platinum based chemotherapy (Golan T K. Z., 2014), (Sonnenblick A, 2011) thus testing for germline BRCA mutation status at the time of diagnosis is a beneficial approach to determine the optimal choice of first line treatment

Testing at diagnosis also ensures that the 2 to 4 week turnaround time for genetic testing does not delay treatment commencement. Whilst second line treatment options following germline BRCA mutation testing remain unchanged, time to second line chemotherapy may be potentially delayed for patients with germline BRCA mutations treated with olaparib.

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 (BRCA mutation testing and olaparib as maintenance therapy) are **superior** in terms of comparative effectiveness versus the main comparator (i.e. no testing and no active maintenance treatment i.e. 'watch and wait') in patients with metastatic pancreatic cancer who have achieved disease control (absence of objective disease progression) following first-line platinum-based chemotherapy.

In the pivotal randomised, placebo-controlled, double-blind, phase 3 study, POLO, the efficacy of olaparib as maintenance therapy in patients who had a germline *BRCA1* or *BRCA2* mutation and metastatic pancreatic cancer was evaluated. Trial entry required patients to have had a minimum of 16 weeks first-line platinum-based chemotherapy with no evidence of disease progression. Patients were randomised in a 3:2 ratio, to receive maintenance olaparib tablets (300 mg twice daily) or placebo (Golan T, 2019).

Of the 3315 patients screened for trial entry, 247 (7.5%) had a germline BRCA mutation and a total of 154 patients were assigned to either intervention (92 olaparib; 62 placebo).

The median progression-free survival was significantly longer in the olaparib group than in the placebo group (7.4 months vs. 3.8 months; hazard ratio for disease progression or death, 0.53; 95% confidence interval [CI], 0.35 to 0.82; P = 0.004), and from 6 months onward, the percentage of patients who were alive and free from disease progression in the olaparib arm was twice that of the placebo group. A planned interim analysis of overall survival that took place at a data maturity of 46% showed no evidence of a difference in overall survival between the groups (median, 18.9 months in the olaparib group and 18.1 months in the placebo group; hazard ratio for death, 0.91; 95% CI, 0.56 to 1.46; P = 0.68).

There was no clinically meaningful change from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire global health related quality-of-life score in either trial group and no significant difference in the overall change from baseline between the groups (between-group difference, - 2.47 points; 95% CI, - 7.27 to 2.33).

Adverse events leading to discontinuation of trial agent occurred in 5% of the patients who received olaparib and in 2% of the patients who received placebo; adverse events were usually managed by dose interruption or reduction.

Olaparib represents a significantly improved treatment option for patients with metastatic pancreatic cancer, a cancer with one of the lowest 5-year survival rates. For eligible patients, olaparib is an alternative option to the watch and wait scenario following first round platinum-based chemotherapy; olaparib offers patients and medical specialists a targeted treatment for biomarker defined metastatic pancreatic cancer and offers clinically meaningful efficacy outcomes, acceptable safety and toxicity profile and with the ease of oral administration.

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:

Trial based (evidentiary standard) analytical performance:

Clinical utility of test:

Prognostic effect of BRCA1/2 mutation in patients with platinum-sensitive metastatic pancreatic cancer.

Treatment effect modification of olaparib in patients with platinum-sensitive metastatic pancreatic cancer.

Drug related outcomes

Primary Endpoint:

Progression-free survival (PFS)

Secondary Endpoints:

Overall survival (OS)

Time from randomisation to second progression (PFS2)

Time from randomisation to first subsequent therapy or death (TFST)

Time from randomisation to second subsequent therapy or death (TSST)

Time from randomisation to study treatment discontinuation or death (TDT)

Objective Response Rate (ORR)

Health-related quality of life (HRQoL)

Safety

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

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Since gBRCAm testing will happen once per lifetime for patients, an incident approach to estimating the proposed population has been used.

The incidence of pancreatic cancer is estimated from the AIHW Cancer incidence projections, Australia 2011-2020 (AIHW, 2012). This approach has previously been used and was accepted by PBAC and DUSC in their evaluation of nab-paclitaxel for the treatment of metastatic pancreatic cancer (PBAC, 2014) (DUSC, 2017).

AIHW modelled projections for pancreatic cancer in males on all data from 1982 to 2007. Age standardised rate of pancreatic cancer was estimated to be 11.3 cases diagnosed per 100,000 males in 2020. Equating to 1,710 cases.

Unlike males, rates of pancreatic cancer in females had increased steadily from 1982 to 2007 at about 0.5 cases per 100,000 females per year. Extrapolation of age-specific trends from 1982 onwards suggested that age-standardised rates would continue to increase slowly to about 9.8 new cases diagnosed per 100,000 females in 2020, equating to approximately 1,750 new cases.

Based in the AIHW predictions, it is estimated that **3,460 new cases of metastatic pancreatic cancer would be diagnosed in 2020** (95% PI; 3,210 to 3,710).

It is assumed that approximately 50% of new incident cases will be metastatic (stage IV). The PBAC submission for nab-paclitaxel presented a range of sources to estimate the staging of pancreatic data. Most of the sources estimated the proportion of patients with stage four disease to be approximately 50%.

Estimated number of patients diagnosed with metastatic pancreatic cancer is 1,730 in 2020.

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

Testing to determine germline BRCA1/2 gene mutation status would be conducted only once per patient per lifetime. Some patients with metastatic pancreatic cancer may already know their gBRCAm status via testing under existing MBS item codes for breast/ovarian cancer or cascade testing due to an established familial risk.

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

Testing to determine germline BRCA1/2 gene mutation status would be conducted only once per patient per lifetime

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 metastatic pancreatic cancer (which is estimated in Question 46 to be 1,730 in 2020).

Establishing BRCAm status at the time of diagnosis is recommended in the NCCN clinical guidelines for the treatment of pancreatic cancer (Tempero MA, 2019).

Since the co-dependent therapeutic drug, olaparib, is intended for use in patients with good performance status (ECOG 0 or 1), it is assumed that gBRCA testing could be offered at the time of diagnosis, to patients with good performance status. The application to list nab-paclitaxel on the PBS included an estimate of performance status in patients with metastatic pancreatic cancer, based on a clinician survey. They estimated that 23.5% of patients present with an ECOG score of 0, and 47.2% with ECOG score of 1 (PBAC, 2014).

Therefore, we estimate that 71% of incident patients would qualify for gBRCA testing if it was offered after performance status was established. This equates to 1,223 patients in 2020.

However, it is unlikely that all eligible patients will take up testing due to cultural or religious beliefs.

There may be an additional benefit to the patient in establishing gBRCAm status prior to deciding first line therapy for metastatic pancreatic cancer. ESMO guidelines recommend either FOLFIRINOX or gem-nab-paclitaxel in patients with good performance status. Although there are no direct head to head data to determine the relative efficacy of these two regimens, an indirect comparison suggests that FOLFIRINOX may be slightly more efficacious, but also more toxic (Ducreux M, 2015). However, patients with BRCA1/2 mutations have longer survival when treated with platinum based chemotherapy (Golan T K. Z., 2014), (Sonnenblick A, 2011) thus testing for gBRCAm at the time of diagnosis may be a useful approach to determine the optimal choice of first line treatment.

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

It is not anticipated that there would be any supply or demand issues as the overall number of patients requiring testing to detect BRCA1/2 gene mutations is manageable even if the number of laboratories conducting testing does not increase. Risk of leakage is expected to be low given the specific details of the proposed item descriptor.

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

Some patients diagnosed with metastatic pancreatic cancer may already know their BRCA1/2 mutational status due to prior testing under the existing MBS items codes 73296 or 73297.

PART 8 – COST INFORMATION

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

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

It is anticipated that the cost will be the same for metastatic pancreatic cancer patients. Only one test is required per lifetime.

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

Testing turnaround time from when the blood sample is collected to test result is between 2 to 4 weeks.

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.

Category 6 - PATHOLOGY SERVICES
Proposed item descriptor: Detection of germline BRCA1 or BRCA2 gene mutation, in a patient with metastatic pancreatic cancer requested by a specialist or consultant physician to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime Fee: \$1200.00 Benefit: 75% = \$900.00 85% = \$1020.00

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Attachment

Figure 1 Current clinical algorithm for metastatic pancreatic cancer

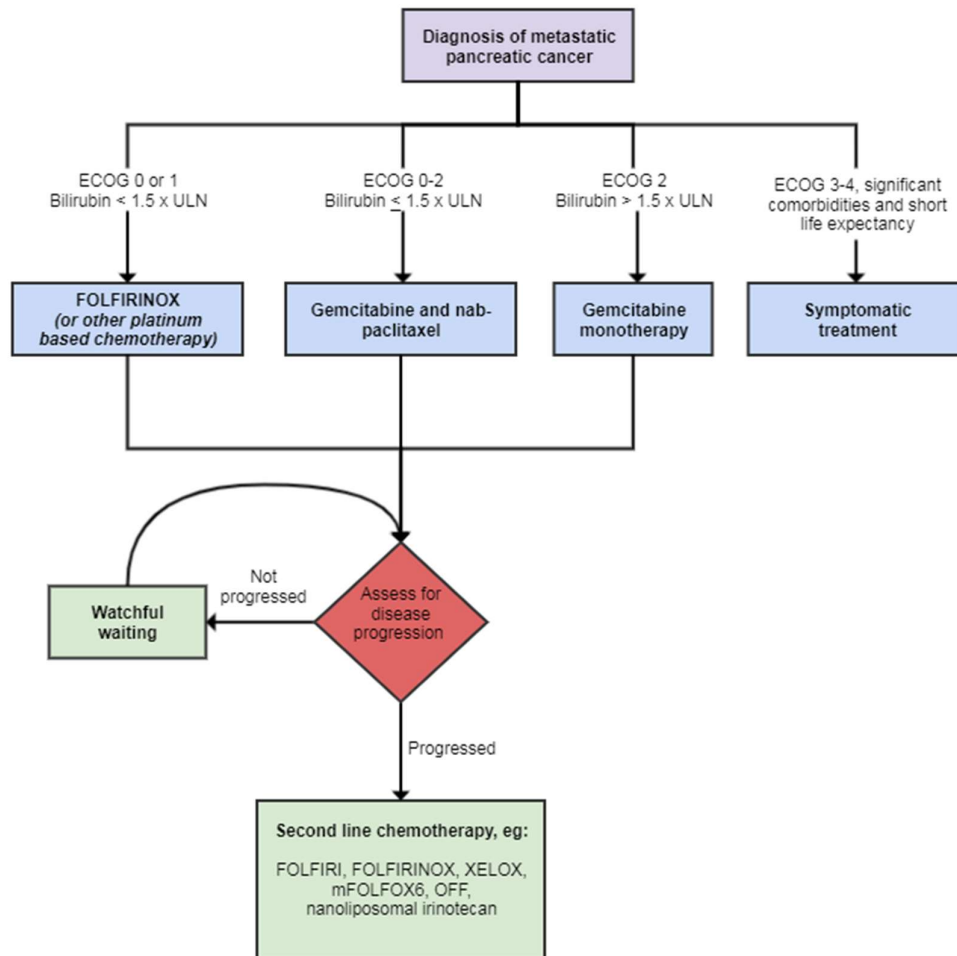


Figure 2 Clinical algorithm following introduction of germline BRCA mutation testing

