RATIFIED PICO

Application 1619:

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

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	**Test:** Patients diagnosed with metastatic pancreatic cancer with a good Eastern Cooperative Oncology Group (ECOG) performance status (0–1) and sufficient hepatic function (bilirubin <1.5 x ULN) who are eligible for platinum-based chemotherapy **Drug:** Patients with metastatic pancreatic cancer, ECOG performance status 0–1 and bilirubin <1.5 x ULN, who have a germline *BRCA1/2* pathogenic variant and have responded to platinum-based chemotherapy
Prior tests	Blood test for bilirubin levels to determine hepatic function
Evidentiary standard	BRACAnalysis CDx test (Myriad Genetic Laboratories) assessing genomic DNA obtained from whole blood samples
Intervention	**Test:** Germline *BRCA1/2* variant testing of a blood sample **Drug:** Maintenance therapy with olaparib following response to first-line treatment with platinum based chemotherapy
Comparator	**Test:** No test **Drug:** Watchful waiting

Outcomes	**Test:** Safety (psychological adverse events)
	         Prevalence of the biomarker
	         Clinical utility of the test
	         Concordance of the test with the evidentiary standard
	Drug: Safety including any potential risk of harm to patient
	         Clinical effectiveness:
	         Critical outcomes[a] – overall survival, objective response rate, time from randomisation to second progression, time from randomisation to first subsequent therapy or death, time from randomisation to second subsequent therapy or death, health-related quality of life
	         Important outcomes[a] – time from randomisation to study treatment discontinuation or death, progression-free survival,
	Healthcare system:
	Cost-effectiveness: cost of testing per patient treated with olaparib, incremental cost per life year gained, incremental cost per quality adjusted life year
	Net Australian Government healthcare costs

Direct assessment question	What is the safety, effectiveness, and cost-effectiveness of germline *BRCA1/2* variant testing for determining access to olaparib maintenance therapy in patients with metastatic pancreatic cancer who responded to platinum-based chemotherapy, compared with no testing and "watchful waiting"?
Linked evidence assessment questions	Is germline BRCA1/2 variant testing, as conducted by Australian pathology laboratories, concordant with the evidentiary standard used in the pivotal trial? Is there a change in management in patients in whom a germline *BRCA1/2* pathogenic variant is identified? Does olaparib maintenance therapy lead to better health outcomes in patients with metastatic pancreatic cancer and a germline *BRCA1/2* pathogenic variant compared with 'watchful waiting'? Does cascade testing of first and second degree relatives of an index case lead to better health outcomes compared with no testing?

[a]Outcomes ranked as recommended by GRADE

2 | P a g e   R a t i f i e d   P I C O – J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

PICO or PPICO rationale for therapeutic and investigative medical services only

An integrated codependent submission to MSAC/PBAC is proposed for germline *BRCA1/2* variant testing, to determine access to olaparib maintenance therapy, in patients with metastatic pancreatic cancer whose disease has not progressed following first-line platinum-based chemotherapy.

POPULATION

Please note: As per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016):

- The term 'variant' should be (and has been) used to replace the outdated term 'mutation'; and

- The term "*BRCA1/2* pathogenic variants" refers to both class 4 (likely pathogenic) and class 5 (known pathogenic) variants.

Compared to other cancer types, pancreatic cancer still has one of the lowest 5-year survival rates, increasing from 3.3% for 1986–1990 to 9.8% for 2011–2015. However, the prognosis of this cancer has not improved significantly since 1982, with the Australian age-standardised mortality rate being 9.8 per 100,000 compared to 9.7 per 100,000 in 2019 (AIHW 2019). In Australia, it is estimated that a total of 3,460 cases of pancreatic cancer will be reported in 2020, with 3,051 deaths in 2019 (AIHW 2012).

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). In 2019, it was estimated that the risk of an individual being diagnosed with pancreatic cancer by their 85th birthday was 1 in 62 (1 in 55 males and 1 in 71 females (AIHW 2019).

Cigarette smoking is strongly associated with pancreatic cancer such that up to 20–25% of cases are attributable to smoking, with a further estimated 5–10% of cases due to hereditary syndromes. High body mass index (particularly abdominal fatness), diabetes, chronic cirrhosis, pancreatitis and prior cholecystectomy are also associated with increased risk of developing pancreatic cancer. The average age at diagnosis is 70 years[1], and the median age being 71.6 years (AIHW 2019).

Ductal adenocarcinoma and its variants are exocrine tumours that usually start in the ducts of the pancreas and account for over 90% of all pancreatic cancers (Fitzgerald et al. 2008). Although acinar cells, which produce the digestive enzymes, are the most common cell types found in the pancreas (located at the end of the ducts), malignant transformation of these cells is very rare in adults and pancreatic acinar cell carcinoma accounts for only 1–2% of adult exocrine pancreatic cancers, but accounts for 15% of all paediatric pancreatic tumours (Chaudhary 2015). Pancreatic neuroendocrine neoplasms start in the islet cells and account for approximately 3% of pancreatic cancers (Cheema, Weber & Strosberg 2012).

The early stages of pancreatic cancer are asymptomatic, and this contributes to difficulties in early diagnosis of the disease. 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 et al. 2015). 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 (Huang et al. 2018). It is estimated that approximately 50% of patients present with metastatic disease (Loveday, Lipton & Thomson 2019; Tempero 2019). Treatment options for these patients are limited and dependent on the patient's health status.

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[1] Australian Pancreatic Cancer Genome Initiative. Pancreas Cancer Statistics. Available from URL: https://www.pancreaticcancer.net.au/patients-pancreatic-cancer/statistics/ [accessed 30 January 2020]

3 | P a g e   R a t i f i e d   P I C O – J U N E   2 0 2 0
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m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

The population for the proposed medical service, germline *BRCA1/2* variant testing, comprises patients with metastatic pancreatic cancer, who are fit for first-line treatment with platinum-based chemotherapy. The population recruited in the pivotal trial (Golan et al. 2018) were adult patients who had histologically or cytologically confirmed pancreatic adenocarcinoma receiving initial chemotherapy for metastatic disease and without evidence of disease progression on treatment, and a documented deleterious or suspected deleterious germline variant in *BRCA1* or *BRCA2*.

PASC confirmed the proposed population as defined. PASC noted that only those receiving or planning to receive platinum-based chemotherapy would be eligible for olaparib maintenance treatment, and thus for testing of their BRCA1/2 variant status. PASC noted local guidelines are consistent with the National Comprehensive Cancer Network (NCCN) guidelines for pancreatic cancer, which recommend all patients receive BRCA1/2 variant testing at diagnosis before first-line treatment.

Biomarker

The *BRCA1* and *BRCA2* genes encode the BRCA1 and BRCA2 proteins, which function in DNA repair, in the homologous recombination repair (HRR) pathway, which is responsible for repair of double strand DNA breaks. The lack of functional BRCA1 or BRCA2 proteins inactivates the HRR pathway, which means that double strand breaks cannot be reliably repaired. Instead, alternative more error-prone pathways are activated, such as the non-homologous end-joining pathway (NHEJ), leading to increased genomic instability. This genomic instability may lead to normal cells becoming cancerous.

The *BRCA1/2* genes are large, with 23 exons consisting of 5,592 bp encoding 1,863 amino acids for *BRCA1* and 27 exons (10,257 bp) encoding 3,418 amino acids for *BRCA2*. Sequence changes causing the loss of function in the BRCA1/2 proteins can occur anywhere within the *BRCA1/2* genes, including the exon-intron splice sites. These can be either germline or somatic in origin. More than 1,800 distinct sequence variants causing intronic changes, single nucleotide variants, and small insertions or deletions (INDELs) have been reported in *BRCA1* and 2,000 in *BRCA2* (Couch, Nathanson & Offit 2014). Large INDELs, copy number variants or other gene rearrangements also occur in both genes due to the repetitive nature of the DNA encoding these genes, but are more prevalent in *BRCA1* (14% of variants) than in *BRCA2* (2.6% of variants).

These variants are grouped into five classes, according to the likelihood of the variant affecting protein function. Those variants that do not affect protein function are considered to be either class 1 (known to be benign) or class 2 (likely to be benign). Variants of unknown significance (VUS) are considered to belong to class 3, with the majority eventually likely to be reclassified as either class 1 or 2. Those variants that have deleterious effects on protein function are considered to belong to class 4 (likely to be pathogenic) or class 5 (known to be pathogenic). Only patients with class 4–5 *BRCA1/2* pathogenic variants will be eligible for the proposed maintenance treatment with olaparib if they meet all other eligibility criteria.

Although the majority of pancreatic cancer cases are sporadic, up to 10% of cases have a hereditary pathogenic variant in a cancer predisposition gene, with more than half being a germline *BRCA1/2* pathogenic variant (Leung & Saif 2013; Lynch et al. 2005). Pancreatic cancer is more common among families with *BRCA2* pathogenic variants. Carriers of germline *BRCA1* pathogenic variants have an increased risk of developing pancreatic cancer of up to 5-times compared to the general population and up to 10-times for *BRCA2* pathogenic variant carriers (Loveday, Lipton & Thomson 2019). A study by Aguirre et al. (2018) found 5/71 (7%) patients with advanced pancreatic ductal adenocarcinoma had germline *BRCA1/2* pathogenic variants. Somatic *BRCA1/2* pathogenic variants have also been identified in 1–17% of metastatic pancreatic cancer patients (Aguirre et al. 2018; Bailey et al. 2016; Cho et al. 2008).

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It should be noted that, due to incomplete or low penetrance, patients with apparently sporadic pancreatic cancer and a germline *BRCA2* pathogenic variant have been identified, as have members of familial pancreatic cancer kindreds with no history of breast or ovarian cancer (Canto et al. 2013).

PASC advised that, if possible, the prevalence of the biomarker among patients with metastatic pancreatic cancer should be determined in an Australian population to inform the proportion of patients likely to receive olaparib maintenance therapy.

Greer & Whitcomb (2007) reported that the average age of onset of pancreatic cancer in patients with a germline *BRCA1/2* pathogenic variant was 65–66 years. This is only slightly younger than the average age at diagnosis of pancreatic cancer in the Australian population (reported above as age 70 years). The authors accredited the older age of onset in comparison with other genetically related cancers due to the inactivation of the wild-type *BRCA1/2* allele by loss of heterozygosity being a relatively late event in pancreatic cancer development.

The lack of a functional HRR DNA repair pathway forms the basis of platinum sensitivity in cancer patients with *BRCA1/2* pathogenic variants. Platinum-based chemotherapy generates inter-strand cross-links that inhibits DNA synthesis, and can only be adequately repaired by the HRR pathway. Consequently, cancer cells with *BRCA1/2* pathogenic variants are highly sensitive to platinum-based chemotherapy (Turner & Tutt 2012). Singh et al (2019) identified several studies that looked at the association between an inactivated HRR pathway (germline or somatic pathogenic variants in *BRCA1/2, ATM, ATR, CHEK1, FANCF* or *PALB2*) and platinum-based chemotherapy and collectively, they demonstrate the role of platinum-based chemotherapy in the treatment of patients with pancreatic cancer and pathogenic variants in a DNA repair pathway gene.

Patients with *BRCA1/2* pathogenic variants are also more sensitive to treatment with poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib. PARP enzymes are involved in the efficient repair of DNA single strand breaks, and after chromatin modification, the PARP enzyme auto-modifies itself and dissociates from the DNA so that the base-excision repair enzymes can gain access to the DNA (Michels et al. 2013). When a PARP inhibitor is bound to the active site of DNA-associated PARP enzymes, it prevents this dissociation, preventing repair of the DNA. In replicating cells, this leads to double strand breaks in the DNA when replication forks meet the PARP-DNA block. In cancer cells with non-functional BRCA1 or BRCA2 proteins, and a resultant non-functional HRR pathway, the double strand breaks cannot be reliably repaired, as discussed above. The additional genomic instability caused by PARP inhibitor-affected replication can become insupportable and result in cancer cell death (Mateo et al. 2019). Singh et al (2019) also reported that there is some evidence to indicate that pancreatic cancer patients with germline or somatic pathogenic variants in *BRCA1/2, ATM, PALB2, CHEK1/2*, or *ATR* genes respond to treatment with PARP inhibitors.

First- and second-degree relatives of a new index case

A proportion of patients with apparent sporadic pancreatic cancer will be carrying a germline *BRCA1/2* pathogenic variant (Greer & Whitcomb 2007), and members of familial pancreatic cancer kindreds with no history of breast, ovarian cancer could have a germline *BRCA2* pathogenic variant (Canto et al. 2013).

Thus, cascade testing of close family members of pancreatic cancer patients with previously unknown germline *BRCA1/2* pathogenic variants should be considered. The identification of family members carrying an inherited germline *BRCA1/2* pathogenic variant will help clinicians target tumour screening programs and develop preventive interventions with the hope of reducing the mortality of pancreatic cancer in these individuals (Klein et al. 2001).

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PASC confirmed that a cascade testing population was relevant to this application, noting the applicant's advice that there was currently limited data to support it. As also discussed under "Outcomes" below, PASC advised that the integrated codependent submission would need to provide evidence regarding the clinical utility and cost-effectiveness of this extension into predisposition testing of the cascade population. If this were supported by MSAC, it would require either a new MBS item or an amendment to existing MBS item 73297 (for cascade testing of family members of probands identified in other circumstances, but also including the genes STK11, PTEN, CDH1, PALB2, or TP53 which are not relevant to this application).

More broadly, PASC discussed whether all patients with pancreatic cancer (or at least those with a family history of pancreatic cancer, but not of breast/ovarian cancer) should be offered germline BRCA1/2 variant testing, regardless of their eligibility for platinum-based chemotherapy, for the purpose of identifying and monitoring close family members at increased risk of developing cancer in the future. PASC considered that this wider question would need to be evaluated in a separate application that would also need to consider the available evidence including the flow-on consequences for cascade testing.

Other biomarkers that inactivate the HRR pathway

The rationale for requesting testing of germline *BRCA1* and *BRCA2* genes alone was not clear from the application. It should be noted that the proposed medical service, germline *BRCA1/2* variant testing, will not identify patients with somatic *BRCA1/2* pathogenic variants, and therefore, these patients will not be eligible for maintenance therapy with olaparib after response to platinum-based chemotherapy.

The National Comprehensive Cancer Network (NCCN) guidelines[2] recommends tumour/somatic gene profiling for patients with locally advanced/metastatic pancreatic cancer who are candidates for anti-cancer therapy to identify uncommon variants in (but not limited to) the following genes: *ALK, BRAF, BRCA1/2, HER2, KRAS, NGR1, NTRK, PALB2, ROS1,* as well as the mismatch repair deficiency genes.

In *BRCA1/2* wild type tumours, there are many other genes that if inactivated can cause the same phenotypic defective DNA repair, this has been termed the 'BRCAness' phenotype; these defects include: loss of regulation/activation of DNA repair proteins, loss of RAD51-nuclear foci formation, extreme genomic instability and/or sensitivity to DNA-crosslinking agents (Turner, Tutt & Ashworth 2004). Lord & Ashworth (2016) refined the definition of 'BRCAness' as "the situation in which an HRR defect exists in a tumour in the absence of a *BRCA1/2* pathogenic variant." The assumption, in the context of clinical oncology, is that tumours with 'BRCAness' will respond to platinum-based chemotherapy and HRR-targeted therapies (such as PARP inhibitors) in the same way as tumours with *BRCA1/2* pathogenic variants (Basourakos et al. 2017).

The HRR pathway may be compromised either by changes in the gene sequence or by epigenetic modification to the gene promoter. Epigenetic modification via hyper-methylation of the *BRCA1* or *FANCF* gene promoters prevents transcription of the associated gene leading to disabling of the HRR pathway. One study found that 0–31% of *BRCA1* genes and 14–30% of *FANCF* genes in sporadic tumours were hyper-methylated, depending on the tumour type (Turner, Tutt & Ashworth 2004). However, the tumour types investigated did not include pancreatic cancer. A study by Guo et al (2014) found that the promoters for 28% of *BRCA1* genes and 56% of *APC* genes were methylated in pancreatic cancer samples. Loss of a functional APC protein results in a reduced DNA damage repair response (Stefanski et al. 2019). Patients

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[2] The NCCN Pancreatic Cancer Guidelines. Available from URL:
https://www.nccn.org/professionals/physician_gls/default.aspx#site [accessed 4 February 2020]

with epigenetic changes will not be identified by germline *BRCA1/2* variant testing and will not benefit from platinum-based chemotherapy and olaparib maintenance therapy.

Pathogenic variants in many of the genes that inactivate the HRR pathway have been identified, including: *ATM, ATR, BARD1, BLM, BRIP1, CHEK1, CHEK2, ERCC4, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51C, RAD51D, RAD51L3, RAD54L, RBBP8, SLX4 XRCC2* and *XRCC3*, as well as the Fanconi anaemia complementation group (*FANC*) genes *(FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, and FANCM)* that are involved in inter-strand DNA crosslink repair in the HRR pathway. In fact, *BRCA2* and *PALB2* are also known as *FANCD1* and *FANCN*, respectively (Hofstatter et al. 2011). Pathogenic variants in the HRR pathway genes are likely to result in sensitivity to both platinum-based chemotherapy and olaparib maintenance therapy. Pathogenic variants for several of these genes have been found in pancreatic cancer (Alexandrov et al. 2013). A scoping review by Singh et al (2019) found that 14% (489/3,594) of pancreatic tumour samples had pathogenic variants in one or more genes involved in the HRR pathway; 62% of them were in genes other than *BRCA1/2*, and 44% were somatic in origin. Thus, the proposed germline *BRCA1/2* variant test would identify less than half of patients with pathogenic gene variants who may benefit from platinum-based chemotherapy and olaparib maintenance therapy.

In fact, several familial pancreatic cancer kindreds carrying pathogenic variants in either the *PALB2* (partner and localizer of BRCA2) or the *ATM* (ataxia telangiectasia mutated) genes have been identified (Jones et al. 2009; Petersen 2016; Roberts et al. 2012). Germline *PALB2* or *ATM* pathogenic variants have been identified in approximately 3–4% and 2% of familial pancreatic cancer cases, respectively (Hofstatter et al. 2011; Roberts et al. 2012).

Diagnostic work-up of patients suspected of having pancreatic cancer

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 et al. 2016).

Diagnostic work up for cancer staging and risk assessment could include:

- Imaging tests required to confirm diagnosis of metastatic pancreatic cancer, such as:
  - Computed tomography for imaging of the primary lesion as well as evaluation of lymph nodes and potential sites of metastases
  - Magnetic resonance imaging of the tumour
  - Endoscopic ultrasound may also be undertaken to obtain tissue and fluid for biopsy purposes
- Pathological cancer staging of biopsied tumour tissue
- Blood tests for tumour markers, such as serum tumour marker carbohydrate antigen 19-9
- Blood test for bilirubin levels to determine if the pancreatic tumour has affected hepatic function due to blockage of the common bile duct (bilirubin >1.5 x upper limit of normal (ULN) indicates moderate to severe hepatic impairment).

Patients diagnosed with metastatic pancreatic cancer with a good Eastern Cooperative Oncology Group (ECOG) performance status (0–1) and sufficient hepatic function (bilirubin <1.5 x ULN) would then be eligible for germline *BRCA1/2* variant testing if their planned first-line treatment was with platinum-based chemotherapy. The applicant developed assessment report (ADAR) will need to provide data on the proportion of patients with metastatic pancreatic cancer who are eligible for testing, based on these criteria.

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m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

Patients with planned first-line treatments other than platinum-based chemotherapy, higher ECOG performance status or elevated bilirubin levels would not be eligible for olaparib maintenance therapy, so testing these patients would not be in scope for this application.

Prior test

Apart from the usual imaging and pathology tests for diagnosis of metastatic pancreatic cancer, patients would require a blood test to measure bilirubin levels to determine if hepatic function is adequate for treatment with various chemotherapy options.

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

INTERVENTION

Evidentiary standard

In the POLO trial, which provided the key evidence for olaparib maintenance therapy, the presence of a *BRCA1/2* pathogenic variant was determined by central testing using the BRACAnalysis CDx test (Myriad Genetic Laboratories) (Golan et al. 2019).

The BRACAnalysis CDx® test is an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein-coding regions and intron/exon boundaries of the *BRCA1/2* genes using genomic DNA obtained from whole blood samples[3]. Single nucleotide variants and small INDELs are identified by Sanger sequencing. Variant classification is determined using the Myriad variant interpretation program. Large INDELs and duplications in *BRCA1/2* are detected in the laboratory using multiplex polymerase chain reaction (PCR).

The test

The proposed medical service is testing of a blood sample to detect germline *BRCA1/2* pathogenic variants in patients with metastatic pancreatic cancer with an ECOG performance status of 0–1 and adequate hepatic function (bilirubin >1.5 x ULN) and a management plan that includes first-line platinum-based chemotherapy. The purpose of the test is to determine eligibility for PBS-listed maintenance therapy with olaparib (i.e. treatment of patients whose disease does not progress following first-line treatment with platinum-based chemotherapy).

Testing of patients newly diagnosed with metastatic pancreatic cancer with an unknown *BRCA1/2* variant status is required as patients with apparently sporadic pancreatic cancer, and members of familial pancreatic cancer kindreds with no history of breast or ovarian cancer, can have previously unidentified germline *BRCA1/2* pathogenic variants (Canto et al. 2013).

Patients with an ECOG performance status ≥2 and bilirubin levels >1.5 x ULN, as well as all patients with a management plan that includes first-line gemcitabine plus nab-paclitaxel chemotherapy, would not be eligible for maintenance treatment with olaparib, and therefore, do not require a germline *BRCA1/2* variant test for this purpose. These patients will follow the current standard of care.

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[3] Myriad. BRACAnalysis CDx Executive Summary. Available from URL: https://myriad.com/managed-care/bracanalysis-cdx/ [accessed 27 February 2020]

8 | P a g e   R a t i f i e d   P I C O – J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

PASC confirmed the proposed intervention, noting it would not be pathologist determinable as there is also a need to know patient characteristics to determine eligibility for the test. PASC also noted the importance of pre- and post-test genetic counselling in this context.

Germline *BRCA1/2* variant testing is currently well established in Australia, and is listed on the Medicare Benefits Schedule (MBS) under the following MBS items: 73295 (to determine eligibility for olaparib maintenance therapy in patients with platinum sensitive, relapsed high-grade serous ovarian cancer) 73296 (to screen for variants in at risk patients with ovarian or breast cancer) and 73297 (for familial cascade testing for known *BRCA1/2* pathogenic variants). Some patients diagnosed with metastatic pancreatic cancer may already know their *BRCA1/2* variant status due to prior testing under one of these MBS items. These patients do not require retesting.

Only one germline *BRCA1/2* variant test (under any relevant MBS item) is required per person per lifetime.

The key components and clinical steps involved in delivering a germline *BRCA1/2* variant test to the proposed population are as follows:

1. Patient with metastatic pancreatic cancer who meets the criteria for *BRCA1/2* variant testing receives genetic counselling from the clinician treating their cancer (e.g. oncologist), who provides information about genetics, inheritance (family risk) and genetic testing. If the patient decides to take the germline *BRCA1/2* variant test, the patient signs the blood sample request form when the blood sample is taken for the *BRCA1/2* variant test.
2. The patient's blood is sent to a pathology laboratory, where germline *BRCA1/2* variant testing is performed. The turnaround for test results is around 2 to 4 weeks.
3. The results are sent to the requesting clinician. Individuals identified as harbouring *BRCA1/2* pathogenic variants (class 4 or 5) are referred to Genetics Services/Familial Cancer Centres for post-test counselling regarding the consequences for cascade testing of family members. Patients with a VUS (class 3) or strong family history may also be referred for post-test counselling.
4. Based on a positive *BRCA1/2* variant test result (i.e. a pathogenic *BRCA1/2* class 4 or 5 variant is identified), the treating clinician will consider prescribing olaparib, if the patient meets the PBS criteria to access treatment.

There is no single sponsor for germline *BRCA1/2* variant testing in Australia. At present, there are at least eight Australian molecular pathology service providers that offer germline *BRCA1/2* variant testing on a commercial basis, with centres in New South Wales, Victoria, Queensland, South Australia and Western Australia. All Australian molecular pathology service providers use in-house developed testing methodology; this remains consistent with that previously considered by MSAC for MBS item 73295 to reimburse germline *BRCA1/2* variant testing to determine eligibility for olaparib.

Under the 2010 TGA regulatory framework, germline *BRCA1/2* variant tests 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.

Australia pathology laboratories use next generation sequencing (NGS)-based methods or Sanger sequencing, which have high sensitivity for the detection of single base changes and small insertions or deletions in the *BRCA1/2* genes. Large gene alterations, such as gene rearrangements and large insertions/deletions, which can account for up to 10% of all known *BRCA1/2* pathogenic variants, are detected using multiplex ligation-dependent probe amplification (MLPA).

9 | P a g e   R a t i f i e d   P I C O − J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

Because the results of the germline *BRCA1/2* variant test can affect family members, testing should be preceded and followed by genetic counselling. Pre-test genetic counselling is to ensure that individuals understand the likelihood of a *BRCA1/2* pathogenic variant being identified and the associated risks and benefits. Post-test genetic counselling helps patients understand the practical meaning of the results including implications for family members and the risk-reducing strategies that are available if a *BRCA1/2* pathogenic variant is identified (Lau & Suthers 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 *BRCA1/2* variant testing in patients with metastatic pancreatic cancer, the applicant predicts that the most likely future scenario would be pre-test counselling and consent being obtained by the oncology team and post-test counselling for class 3 (VUS), class 4 (likely pathogenic) and class 5 (known pathogenic) *BRCA1/2* variants being performed by genetic service providers.

Utilisation of the test

AIHW projections for pancreatic cancer using data from 1982 to 2007 estimated that 1,710 males and 1,750 women would be diagnosed with pancreatic cancer in 2020. Thus, a total of 3,460 new cases of pancreatic cancer would be diagnosed in 2020 (95% PI; 3,210 to 3,710) with approximately 50% being metastatic (Loveday, Lipton & Thomson 2019), thus the total number of patients newly diagnosed with metastatic pancreatic cancer is expected to be 1,730 in 2020.

Note: these numbers do not include any patients who were diagnosed with an earlier stage disease and progressed to metastatic disease.

As olaparib maintenance therapy will be restricted for use in patients with good performance status (ECOG 0 or 1), and germline *BRCA1/2* variant testing will occur at the time of diagnosis, only those patients with a good performance status would be tested. The application to list nab-paclitaxel on the PBS estimated that 23.5% of patients with metastatic pancreatic cancer had an ECOG performance score of 0, and 47.2% with a score of 1, based on a clinician survey (PBAC, 2014). Therefore, approximately 71% of incident patients would qualify for germline *BRCA1/2* variant testing based on their performance status. This equates to an estimated 1,223 patients in 2020.

However, an unknown proportion of these patients would have bilirubin level >1.5 x ULN, and would not be eligible for treatment with olaparib and therefore, do not need to be tested. It needs to be clarified if patients who meet all the other criteria and whose jaundice resolves bilirubin levels returning to normal after surgical implantation of a stent would be eligible for FOLFIRINOX and/or olaparib maintenance treatment.

Additionally, only those whose intended first-line treatment regimen is platinum-based chemotherapy will be eligible for olaparib maintenance therapy. Therefore, patients otherwise eligible for germline *BRCA1/2* variant testing who will not be treated with platinum-based chemotherapy do not require testing.

Testing to determine germline *BRCA1/2* gene variant status would be conducted only once per patient per lifetime. Some patients with metastatic pancreatic cancer may already know their *BRCA1/2* variant status via testing under existing MBS item codes for breast/ovarian cancer or cascade testing due to an established familial risk. Patients with poor ECOG performance status and/or high bilirubin levels would not benefit from testing, unless they have a family history of breast, ovarian or pancreatic cancer and were not eligible for testing under other MBS items.

10 | P a g e   R a t i f i e d   P I C O − J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

Additionally, not all eligible patients may take up testing. Reasons for patients not taking up the test could be cultural or religious beliefs (Cohen et al. 2016). The applicant reported that current uptake of germline *BRCA1/2* variant testing in patients with ovarian cancer is approximately 70% and suggests it will be similar for patients with pancreatic cancer.

Biomarker evidence base

The applicant identified 15 studies as providing evidence for germline *BRCA1/2* variant testing. However, seven of these studies were reviews and one provided clinical outcomes for patients who survived breast cancer prior to developing pancreatic cancer (Bhalla & Saif 2014; Golan & Javle 2017; Javle, Golan & Maitra 2016; Mateo et al. 2019; Rustgi 2014; Sahin et al. 2016; Singh et al. 2019).

The remaining eight studies (one journal article and seven conference abstracts) provided data to determine the diagnostic yield (or prevalence) of *BRCA1/2* pathogenic variants. It should be noted that conference abstracts provide low quality evidence as they provide insufficient evidence to determine the true level of bias within the study. One study did not report the germline testing method (Lowery et al. 2010). One study used Sanger sequencing and denaturing high-performance liquid chromatography to identify germline *BRCA2* pathogenic variants among Korean patients with pancreatic cancer (Cho et al. 2008). The other six studies used NGS-based testing methods to determine the diagnostic yield (or prevalence) of either germline (Golan et al. 2018; Smith et al. 2014) or somatic (Kamgar et al. 2018; Shahda et al. 2017; Singhi et al. 2019; Wong et al. 2017) *BRCA1/2* pathogenic variants.

The sensitivity and specificity of germline *BRCA1/2* variant testing was reported in MSAC assessment 1411.1, and is not expected to differ for germline *BRCA1/2* variant testing in patients with pancreatic cancer. However, evidence to show the clinical utility of the germline *BRCA1/2* variant test to determine eligibility for patients with pancreatic cancer to access olaparib maintenance therapy is still required. That is, that the test can accurately triage patients for olaparib maintenance therapy; with a greater benefit for patients with a germline *BRCA1/2* pathogenic variant from olaparib maintenance therapy compared with those without (i.e. to establish that the test is predictive of treatment effect variation).

Even though germline *BRCA1/2* variant testing is well established in the Australian diagnostic laboratory setting, the analytical concordance between NGS-based sequencing and MLPA methodologies used by Australian pathology laboratories and the evidentiary standard (based on Sanger sequencing and multiplex PCR) should be assessed.

The prevalence of the biomarker among patients with metastatic pancreatic cancer should be determined, in an Australian population if possible, in order to help inform the proportion of patients likely to receive olaparib maintenance therapy.

The drug

The pharmaceutical product Lynparza® (olaparib) is a PARP enzyme inhibitor. PARP enzymes are involved in the efficient repair of DNA single strand breaks. As described above, when olaparib binds to DNA-associated PARP, preventing disassociation, it leads to double strand breaks in the DNA during replication. These double strand breaks are normally repaired via the HRR pathway. However, if the HRR pathway is defective (due to pathogenic variants in *BRCA1/2* or a related gene), the cell cannot effectively repair the double strand breaks, leading to increased genomic instability and eventually cell death (Mateo et al. 2019).

An application to register Lynparza® (olaparib) on the ARTG for the treatment of pancreatic cancer as outlined below, was being prepared at the date this application was initiated:

- Maintenance treatment of adult patients with germline *BRCA1* or *BRCA2* variant and metastatic pancreatic cancer (and disease) that had not progressed during first-line platinum-based chemotherapy. *BRCA1/2* variant status should be determined by an experienced laboratory, using a validated test method.

Lynparza® is currently registered on the ARTG for the following indications:

- Maintenance treatment of adult patients with advanced *BRCA*-variant (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. *BRCA1/2* variant 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.
- 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 *BRCA1/2* variant status should be determined by an experienced laboratory using a validated test method.

Olaparib is currently PBS-listed for platinum sensitive relapse patients with high grade serous ovarian, fallopian tube or primary peritoneal cancer, who also have a germline class 4 or 5 *BRCA1* or *BRCA2* gene variant (PBS Items: 11503K; 11522K – 100 mg tablets; 11528R;11539H – 150 mg tablets; 11050N - 50 mg capsules). Olaparib is not currently reimbursed for patients with metastatic pancreatic cancer.

Rationale for codependency

Both platinum-based chemotherapy and olaparib maintenance therapy introduce double strand breaks in the DNA that can only be adequately repaired by the HRR pathway, and rely on a deficiency in the pathway to kill cancer cells. Thus, nearly all patients who respond to first-line platinum-based chemotherapy are likely to have tumours with a defective DNA repair pathway. This suggests that these patients are also likely to benefit from olaparib maintenance therapy.

There is some evidence to support this biological rationale in patients with platinum-sensitive recurrent serous ovarian, fallopian tube or primary serous peritoneal cancer (especially with respect to time to subsequent first treatment), but the response (especially with respect to overall survival) in those with *BRCA1/2* pathogenic variants was greater (Ledermann, J et al. 2014; Ledermann, JA et al. 2016). However, there is no evidence to support this in patients with metastatic pancreatic cancer who have responded to platinum-based chemotherapy.

Resistance to platinum-based chemotherapy and olaparib

Reversion *BRCA1/2* sequence changes that reinstate their function in DNA repair can occur in the setting of either germline or somatic *BRCA1/2* pathogenic variants, both prior to and during treatment with either platinum-based chemotherapy or PARP inhibitor maintenance. In fact, Norquist et al (2011) found that post-platinum therapy, 28% of recurrent ovarian carcinomas had secondary *BRCA1/2* sequence changes. Such changes have been shown to result in acquired resistance to both treatments in breast cancer

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m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

(Afghahi et al. 2017; Barber et al. 2013; Cruz et al. 2018), ovarian cancer (Barber et al. 2013; Lin et al. 2019; Sakai et al. 2008; Swisher et al. 2008), and prostate cancer (Carneiro et al. 2018).

Variants in other DNA repair genes that can restore the functionality of the HRR pathway in repairing double-strand breaks, even in the presence of inactive BRCA1/2 proteins have also been identified. When BRCA1 is deficient, the repair of double-strand breaks is prevented by 53BP1, RIF1 and the REV7–SHLD1–SHLD2–SHLD3 (shieldin) complex, and loss of any of these factors results in tumour cells becoming resistant to PARP inhibitors (Mirman et al. 2018; Xu et al. 2015). Conversely, increased expression of RAD51 is thought to be another mechanism of platinum-based chemotherapy and PARP inhibitor resistance in some tumours with *BRCA1/2* pathogenic variants (Cruz et al. 2018). Resistance to platinum-based chemotherapy also occurs via increased expression of genes involved in other DNA repair pathways, such as the nucleotide excision repair (NER) pathway, especially the excision repair cross-complementation group 1 (*ERCC1*) gene in this pathway (Basourakos et al. 2017).

It would be expected that these resistance mechanisms would be ubiquitous for all types of solid tumours, including pancreatic cancer, given the pivotal role of effective DNA repair for the survival of all cells. Thus, patients who do not respond to platinum-based chemotherapy, due to restoration of DNA repair pathways, are unlikely to benefit from olaparib maintenance therapy even in the presence of a *BRCA1/2* pathogenic variant.

However, resistance to platinum-based chemotherapy can also occur via other mechanisms that should not interfere with (or reduce) the subsequent response to olaparib (Basourakos et al. 2017; Chen & Chang 2019). The effectiveness of platinum-based chemotherapy can be reduced by less intracellular drug accumulation either by decreased drug influx or by increased drug efflux. A number of membrane transporters facilitate the influx of platinum-based agents into cancer cells and one that has been associated with therapeutic results is the copper transport protein 1. Cytosolic inactivation/metabolism of platinum-based agents is another mechanism of platinum resistance; for example, the platinum-based agent is conjugated with glutathione, and neutralised through exportation of the glutathione-conjugated molecules.

Patients whose metastatic tumours have acquired resistance to olaparib, due to reactivation of the HRR pathway, and are treated with olaparib maintenance therapy would suffer from treatment side effects without gaining any benefit. A discussion on the prevalence rate of resistance variants after platinum-based chemotherapy, and during olaparib maintenance therapy, should be included. A discussion on the likely health outcomes for patients with a false positive *BRCA1/2* variant test result receiving olaparib maintenance therapy should also be included.

Therapeutic evidence base

Three publications (one journal article and two conference abstracts) were identified that reported on the POLO trial, a phase III randomised, double-blind, placebo-controlled trial (ClinicalTrials.gov number NCT02184195). This trial randomised patients who had a germline *BRCA1/2* pathogenic variant and metastatic pancreatic cancer that had not progressed during first-line platinum-based chemotherapy, in a 3:2 ratio, to receive maintenance olaparib (300 mg twice daily) or placebo (Golan et al. 2019; Golan et al. 2018; Golan et al. 2016).

Another study, reported on olaparib treatment of pancreatic cancer patients with a germline *BRCA1/2* pathogenic variant and prior gemcitabine treatment (Kaufman et al. 2015). Although it should be noted that olaparib was used as a therapy in this study and the primary efficacy end point was tumour response rate, the dose of olaparib administered (400 mg twice per day) was 25% higher than in the POLO trial.

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m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

Additional supporting evidence for the use of other PARP inhibitors, niraparib (Kasi et al. 2019), rucaparib (Shroff et al. 2018), and veliparib (Lowery et al. 2018), as a second- or later-line treatment for patients with metastatic pancreatic cancer, and a germline or somatic *BRCA1/2* pathogenic variant, were identified in the scoping review by Singh et al (2019).

COMPARATOR

The test

Currently, germline *BRCA1/2* variant testing is not funded by the MBS for patients with metastatic pancreatic cancer to determine their *BRCA1/2* variant status for eligibility to treatment with olaparib.

Therefore 'no testing' is the comparator.

PASC confirmed the comparator for the test.

PASC advised that, although germline BRCA1/2 variant testing is well established in Australia, the analytical concordance between methods using next-generation sequencing or MLPA, and the evidentiary standard (Sanger sequencing and multiplex PCR) should be assessed.

The drug

Currently there are no options for maintenance therapy in patients who have achieved disease control following first-line treatment for metastatic pancreatic cancer. Therefore, the nominated comparator for olaparib maintenance treatment following response to first line platinum-based chemotherapy is "watchful waiting" or no continuing active anti-cancer treatment.

OUTCOMES

Test-related outcomes

- Safety – physical and psychological
- Prevalence of the biomarker in the testing population
- Predictive validity of the *BRCA1/2* variant test for predicting response to treatment with olaparib
- Clinical utility of the germline *BRCA1/2* variant test
- Concordance between NGS-based germline *BRCA1/2* variant testing and the evidentiary standard

Drug-related outcomes

Clinical effectiveness

Critical outcomes (GRADE):

- Overall survival (OS)
- Objective response rate (ORR)
- 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)
- Health-related quality of life (HRQoL)

Important outcomes (GRADE):

- Time from randomisation to study treatment discontinuation or death (TDT)
- Progression-free survival (PFS)

Safety

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

Healthcare system outcomes

- Cost-effectiveness: Cost of testing per patient treated with olaparib, incremental cost per life year gained, incremental cost per quality adjusted life year
- Net Australian Government healthcare costs

PASC confirmed the proposed outcomes.

PASC advised that the assessment should investigate whether, and, if so, how prolongation of progression free survival (PFS) is associated with improvement in quality of life.

As also discussed under "Population" above, PASC advised that it would be necessary for the integrated codependent submission to provide evidence to inform MSAC on how the estimated extent of health outcome benefit (clinical utility) and cost-effectiveness consequences would compare for an index case with pancreatic cancer (as proposed) rather than breast or ovarian cancer (as already funded). This additional information is needed to enable MSAC to judge whether to support the extra funding for this other consequence of the requested testing.

Current and proposed clinical management algorithms

Current clinical management algorithm for identified population

In the absence of Australian specific guidelines for the treatment of metastatic pancreatic cancer, the clinical management algorithm was developed according to current EviQ treatment protocols[4] and the 2019 National Compressive Cancer Network (NCCN) guidelines[5]. The EviQ protocols take into account Australian specific PBS restrictions and Product Information criteria. Three first-line treatment options for metastatic pancreatic cancer were endorsed by EViQ and/or NCCN:

- **FOLFIRINOX (modified) (fluorouracil, leucovorin, irinotecan and oxaliplatin)**
  Indications: EviQ: patients with ECOG performance status 0 to 1
  　　　　　　NCCN: also patients with *BRCA1/2* pathogenic variants
  Exclusions: EviQ: patients with biliary stents or elevated bilirubin, or aged >75 years.

- **Gemcitabine and nab-paclitaxel**
  Indications: EviQ: as first-line treatment
  　　　　　　NCCN: for patients with ECOG performance status 0 to 1
  Exclusions: EviQ: patients with biliary stents or elevated bilirubin, or aged >75 years
  　　　　　　PBS indication does not exclude those with stents and normal bilirubin levels

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[4] Cancer Institute of NSW, EviQ Pancreas and biliary medical oncology. Available from URL: https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary [accessed 12 February 2020]

[5] The NCCN Pancreatic Cancer Guidelines. Available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx#site [accessed 4 February 2020]

- **Gemcitabine**
  Indications: NCCN: patients with poor ECOG performance status (>2)

The main factors determining selection of the first-line chemotherapy regimen are patient performance status, hepatic function, treatment intent and patient choice based on side effect and adverse-event profile (Loveday, Lipton & Thomson 2019). The proportion of patients with ECOG performance status 0-1 and bilirubin <1.5 x ULN would get platinum-based chemotherapy vs gemcitabine plus nab-paclitaxel is unknown.

For patients with an ECOG performance status of 3 or 4, with significant morbidities and a very short life expectancy, only symptomatic treatment can be considered.

If the patient responds to first-line treatment, patients are monitored for disease recurrence (watchful waiting). On disease progression or recurrence, the recommended second-line treatment options are dependent on the first-line treatment choice.

After first-line treatment with platinum-based chemotherapy (most likely with FOLFIRINOX), options for patients with ECOG performance status 0–1 is restricted to:

- **Nanoliposomal irinotecan, fluorouracil and leucovorin**
  Indications: EviQ: after previous treatment failure with gemcitabine-based therapy
  NCCN: also after fluoropyrimidine-based therapy failure if not had irinotecan before
  Cautions: EviQ: patients with albumin less than 30 g/L were not included in the trial.

The NCCN guidelines also recommend treatment with gemcitabine plus nab-paclitaxel after fluoropyrimidine-based therapy failure. However, the PBS restrictions for nab-paclitaxel indicate that it can only be used in patients who have had no previous PBS-subsidised therapy, suggesting patients who had platinum-based chemotherapy that was not subsidised via the PBS (e.g. via a clinical trial) would be eligible for treatment with gemcitabine plus nab-paclitaxel on progression. The EviQ protocols also restricts the use of gemcitabine plus nab-paclitaxel to first-line therapy only. Thus, this option has not been included in the clinical management algorithms as a second-line therapy option.

After first-line treatment with gemcitabine-based therapy:

- **FOLFIRINOX (modified) (fluorouracil, leucovorin, irinotecan and oxaliplatin)**
  Indications: EviQ: line of treatment not specified
  NCCN: after previous treatment failure with gemcitabine-based therapy
  Exclusions: EviQ: patients with biliary stents or elevated bilirubin, or aged >75 years.

- **FOLFIRI (modified) (fluorouracil, leucovorin and irinotecan)**
  Indications: EviQ: after previous treatment failure with gemcitabine-based therapy

- **Nanoliposomal irinotecan, fluorouracil and leucovorin**
  Indications: EviQ: after previous treatment failure with gemcitabine-based therapy
  NCCN: after previous treatment failure with gemcitabine-based therapy
  Cautions: EviQ: patients with albumin less than 30 g/L were not included in the trial.

- **OFF (oxaliplatin, fluorouracil and leucovorin)**
  Indications: EviQ: after previous treatment failure with gemcitabine
  NCCN: after previous treatment failure with gemcitabine-based therapy
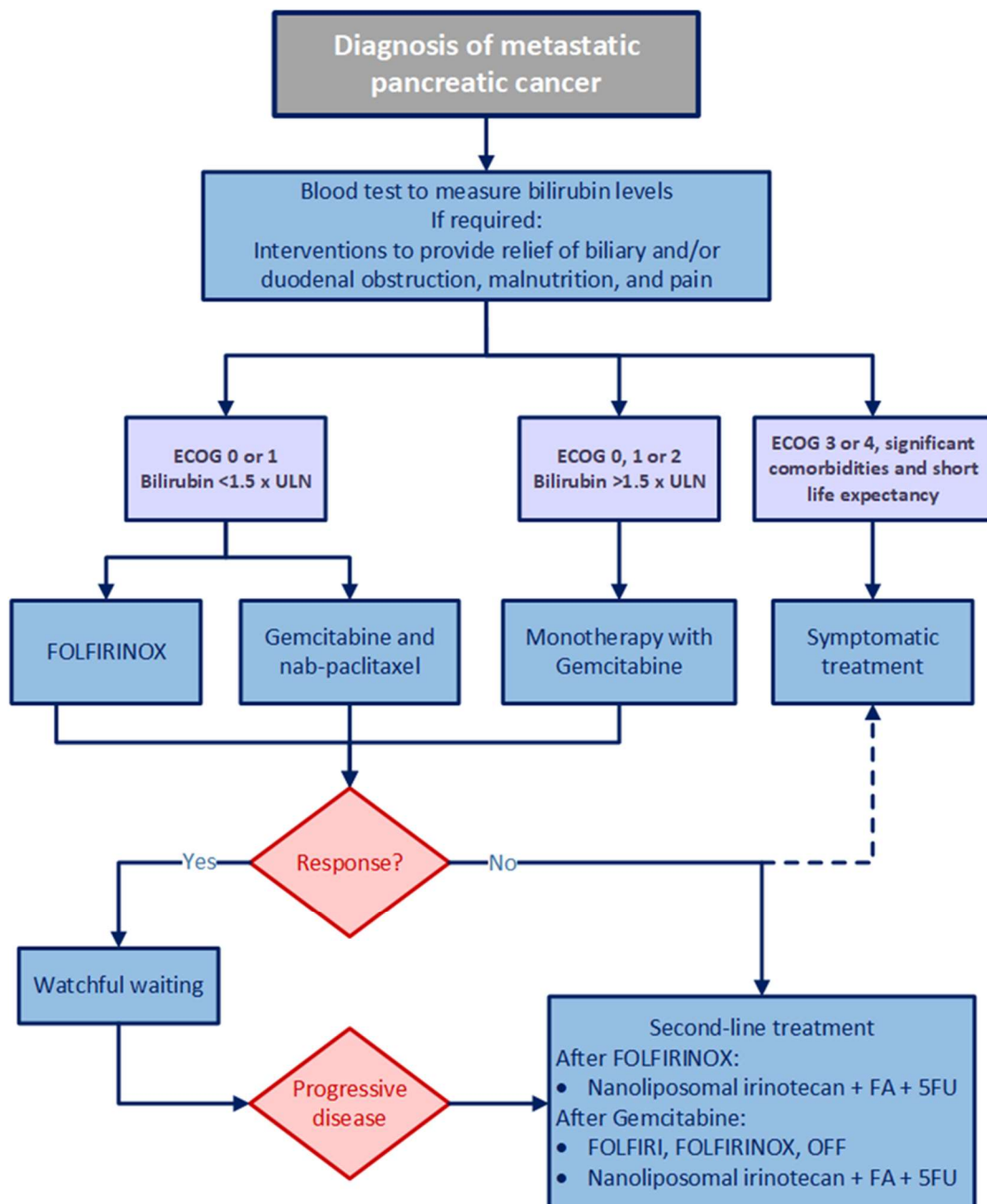
Figure 1 Current clinical management algorithm for metastatic pancreatic cancer

The current clinical management algorithm was based on treatments for metastatic pancreatic cancer that are supported by EviQ (Cancer Institute of NSW) for the Australian context and the NCCN Pancreatic Cancer Guidelines (available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx#site)

5FU = fluorouracil; ECOG = Eastern Cooperative Oncology Group performance status; FA = folinic acid; FOLFIRI = combination of chemotherapy drugs FA, 5FU and irinotecan; FOLFIRINOX = combination of chemotherapy drugs FA, 5FU, irinotecan and oxaplatin; OFF = combination of chemotherapy drugs oxaplatin, FA and 5FU; ULN = upper limit of normal.

Proposed clinical management algorithm for identified population

Establishing germline *BRCA1/2* variant status at the time of diagnosis of all pancreatic cancer patients and possibly a somatic gene variant profile in those with metastatic disease is recommended in the NCCN clinical guidelines for the treatment of pancreatic cancer[6].

In the proposed clinical management algorithm, the first-line treatment choice will be driven mainly by ECOG performance status and bilirubin levels. Those patients diagnosed with metastatic pancreatic cancer

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[6] The NCCN Pancreatic Cancer Guidelines. Available from URL:
https://www.nccn.org/professionals/physician_gls/default.aspx#site [accessed 4 February 2020]

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m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

who are considered suitable for platinum-based chemotherapy (i.e. ECOG performance status of 0–1 and bilirubin < 1.5 x ULN) would be offered germline *BRCA1/2* variant testing. Given the advanced cancer stage, testing at the time of diagnosis is important for decision planning and for earlier access to olaparib maintenance therapy. It is expected that up to 30% of patients suitable for platinum-based chemotherapy will refuse the germline *BRCA1/2* variant test. Those patients eligible for platinum-based chemotherapy according to ECOG performance status and bilirubin levels but have planned treatment with gemcitabine and nab-paclitaxel chemotherapy instead (by either clinician or patient choice), will not be offered a germline *BRCA1/2* variant test. These patients would not be eligible for olaparib maintenance therapy so testing is not required.

It should be noted that if required, by either the clinician or the patient, the choice of first-line treatment can still be revised after testing. However, only those receiving platinum-based chemotherapy will be eligible for olaparib maintenance treatment, regardless of their *BRCA1/2* variant status.

Patients with a germline *BRCA1/2* class 3–5 variant will be offered genetic counselling. Those with class 4–5 pathogenic variants may have first or second degree relatives that require cascade testing to determine their *BRCA1/2* status and associated risk of developing *BRCA*-associated cancers. Families with inherited risk of pancreatic cancer (but no breast or ovarian cancer history) with *BRCA1/2* pathogenic variants have been identified in the literature (Greer & Whitcomb 2007; Klein et al. 2001) identifying at-risk family members is important for early detection of pancreatic cancer in these individuals.

PASC confirmed that that the proposed clinical management algorithm should include cascade testing of first- and second-degree relatives.

Patients with germline *BRCA1/2* pathogenic variants (class 4–5) and no evidence of disease progression after first-line platinum-based chemotherapy would be offered olaparib maintenance therapy. All other patients who respond to first-line treatment will have "watchful waiting" until disease progression as per current clinical practice. Second-line therapy choices are the same as for the current algorithm for all patients, regardless of *BRCA1/2* variant status.
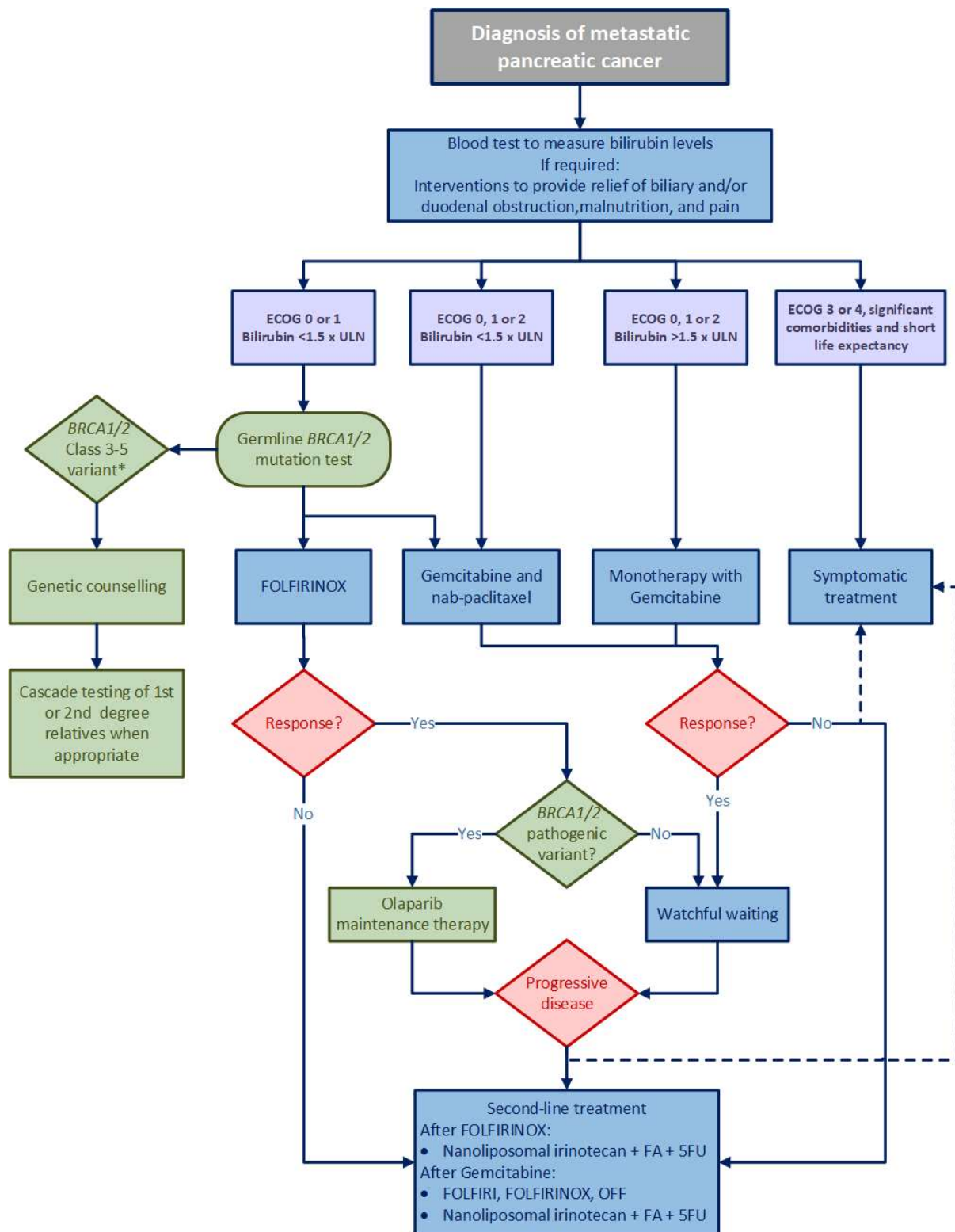
18 | P a g e   R a t i f i e d   P I C O – J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

Figure 2 Clinical management algorithm following introduction of germline *BRCA1/2* variant testing

*Pathogenic variant refers to either a class 5 pathogenic variant or a class 4 likely to be pathogenic variant.

The proposed clinical management algorithm was based on the current clinical management algorithm with the addition of germline *BRCA1/2* variant testing.

5FU = fluorouracil; BRCA1/2 = breast cancer genes 1 and 2; ECOG = Eastern Cooperative Oncology Group performance status; FA = folinic acid; FOLFIRI = combination of chemotherapy drugs FA, 5FU and irinotecan; FOLFIRINOX = combination of chemotherapy drugs FA, 5FU, irinotecan and oxaliplatin; OFF = combination of chemotherapy drugs oxaliplatin, FA and 5FU; ULN = upper limit of normal.

Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (germline *BRCA1/2* variant 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) in metastatic pancreatic cancer patients who have not progressed following first-line platinum-based chemotherapy. However, it is likely to have inferior safety due to any adverse events arising from olaparib therapy.

The appropriate type of economic evaluation to be included in the assessment report would be either a cost-effectiveness analysis or a cost-utility analysis.

PASC confirmed the proposed economic evaluation, and advised that the consequences of cascade testing should be included into an economic evaluation as appropriate.

Proposed MBS item descriptor and MBS fee

There are a number of existing MBS items related to germline *BRCA1/2* variant testing (Table 1).

Please note: While these items currently contain the terms 'mutation' and 'mutations', [variant] and [variants] have been inserted, for the purpose of demonstrating correct, updated terminology use.

Table 1   Current MBS item descriptors for germline *BRCA1/2* variant testing

	Category 6 - PATHOLOGY SERVICES
MBS item 73295	Group P7 - Genetics
Detection of germline *BRCA1* or *BRCA2* gene mutations *[variants],* in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime	
MBS Fee: $1,200 Benefit: 75% = $900 85% = $1,115.30	
	Category 6 - PATHOLOGY SERVICES
MBS item 73296	Group P7 – Genetics
Characterisation of germline gene mutations *[variants],* requested by a specialist or consultant physician, including copy number variation in *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11, PTEN, CDH1, PALB2,* or *TP53* in a patient with breast or ovarian cancer 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 >10% risk of having a pathogenic mutation *[variant]* identified in one or more of the genes specified above.	
MBS Fee: $1,200 Benefit: 75% = $900 85% = $1,115.30	
	Category 6 - PATHOLOGY SERVICES
MBS item 73297	Group P7 – Genetics
Characterisation of germline gene mutations *[variants],* requested by a specialist or consultant physician, including copy number variation in *BRCA1* and *BRCA2* genes and one or more of the following genes *STK11, PTEN, CDH1, PALB2,* or *TP53* in a patient who is a biological relative of a patient who has had a pathogenic mutation *[variant]* identified in one or more of the genes specified above, and has not previously received a service under item 73296.	
MBS Fee: $400 Benefit: 75% = $300 85% = $340	

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m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

The proposed MBS item descriptor for germline *BRCA1/2* variant testing, in patients with metastatic pancreatic cancer, with a good performance status (ECOG 0–1) and adequate hepatic function (bilirubin levels <1.5 x ULN), who are eligible for platinum-based chemotherapy, is shown in Table 2.

Table 2   Proposed MBS item descriptor

	Category 6 - PATHOLOGY SERVICES
Proposed item descriptor:	Group P7 - Genetics
Detection of germline BRCA1 or BRCA2 gene variant, in a patient with metastatic pancreatic cancer, an ECOG performance status of 0–1 and bilirubin levels <1.5 x ULN who is eligible for platinum-based chemotherapy, requested by a specialist or consultant physician to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime **MBS Fee: $1,200 Benefit: 75% = $900 85% = $1,115.30**	

However, the proposed wording did not explicitly limit testing to patients with an ECOG performance status of 0–1 and bilirubin levels <1.5 x ULN. Thus, leakage may occur for the purpose of identifying patients with inherited disease. *PASC confirmed the proposed MBS item descriptor (with the inclusion of the ECOG and hepatic function markers to confirm eligibility for platinum-based chemotherapy to be consistent with the defined population and the proposed clinical management algorithm) and fee. The MBS item descriptor was updated accordingly.* Germline *BRCA1/2* variant testing should be conducted in specialist laboratories holding the appropriate accreditation and registration for this testing procedure and participate in the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs. Testing should be conducted and the results interpreted and reported by suitably qualified and trained molecular pathologists.

Testing to identify *BRCA1/2* gene variants in patients with metastatic pancreatic cancer should be based on a request from a specialist or consultant physician and should not be pathologist determinable. It is expected that a patient will only be tested for germline *BRCA1/2* variants once in their lifetime utilising only one of the relevant MBS items.

Consideration should be given to the consequences for close relatives of pancreatic cancer patients with previously unknown germline *BRCA1/2* pathogenic variants, including whether cascade *BRCA1/2* variant testing could occur using MBS item 73297.

Consultation feedback

- Avner Foundation, established in 2008, is a national charity dedicated to pancreatic cancer.

  Patients with metastatic pancreatic cancer have very few treatment options and trials using this regime have shown an increase in progression free survival.

- From The Centre for Community-Driven Research, a non-profit organisation implementing community engagement to support treatments decisions and services available to Australians.

  This submission is in support of the listing of germline BRCA1/2 variant testing for a patient with metastatic pancreatic cancer to determine eligibility to be treated with targeted treatments

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- Royal College of Pathologists of Australia

  The College generally is supportive of MSAC application for germline BRCA1/2 variant testing for pancreatic cancer. The use of this test is consistent with the updated National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology and American Society of Clinical Oncology (ASCO) 2018 Recommendations.

PASC noted the consultation feedback received supported the application.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR (applicant-developed assessment report) in the form of an integrated codependent submission.

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(Please note: Where publication titles include 'mutation', 'mutations' or 'mutational', these have been retained, noting the current correct terms are 'variant' or 'variants')

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27 | P a g e   R a t i f i e d   P I C O – J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b

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28 | P a g e   R a t i f i e d   P I C O − J U N E   2 0 2 0
A p p l i c a t i o n   1 6 1 9 :   G e r m l i n e   *B R C A 1 / 2*   v a r i a n t   t e s t i n g   i n   p a t i e n t s   w i t h
m e t a s t a t i c   p a n c r e a t i c   c a n c e r   t o   d e t e r m i n e   e l i g i b i l i t y   f o r   o l a p a r i b