Australian Government

Department of Health

MSAC Application 1380

Germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy in women with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component

Applicant Submitted Proposed Protocol

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1. Title of Application

Germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy in women with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component.

2. Purpose of application

Please indicate the rationale for the application and provide one abstract or systematic review that will provide background.

Olaparib is an orally administered, potent inhibitor of poly(adenosine diphosphate [ADP]) ribose polymerase (PARP) inhibitor that has been shown to significantly improve progression-free survival when used as maintenance therapy in women with platinum-sensitive relapsed (PSR) ovarian cancer (including fallopian tube or primary peritoneal cancer) with high-grade serous features or a high grade serous component [1,2]. Platinum sensitivity defined as complete or partial response to most recent platinum-based chemotherapy and subsequent platinum-free interval of six months or longer. Evidence to date suggests that the clinical benefit of olaparib is greatest in PSR ovarian cancer patients who are BRCA (BRCA1 or BRCA2) mutation positive regardless of whether detected in the germline or tumour[1,2]

The current application requests public funding for germline BRCA mutation testing as a co-dependent service to determine eligibility for olaparib maintenance therapy in women with PSR ovarian cancer (including fallopian tube, or primary peritoneal cancer) with high grade serous features or a high grade serous component. It is proposed that only patients who are germline BRCA mutation positive will be eligible for olaparib maintenance therapy, while those who are germline BRCA mutation negative will continue to receive standard follow-up care.

NB:

1. This application specifically focuses on germline BRCA mutation testing as the optimal method for tumour BRCA mutation testing is yet to be established.
2. This application is not intended to include germline BRCA mutation testing specifically for the purpose of determining hereditary susceptibility to BRCA-related cancers. Differences between the current and proposed uses of germline BRCA mutation testing are described in Section 4.
3. Patients with other types of invasive epithelial ovarian cancer, including those with endometrioid, mucinous and clear cell types, are excluded from this indication unless at least 10% of the tumour contains a high grade serous component.

[1] The term high grade serous features refers to a primary ovarian invasive serous carcinoma composed of cells resembling those lining the Fallopian tube with grade 2 or 3 nuclear atypia. The term 'serous component' refers to that portion of a primary ovarian invasive mixed carcinoma, comprising at least 10% of the tumour, in which the cell have high grade serous features.

3. Population and medical condition eligible for the proposed medical services

Provide a description of the medical condition (or disease) relevant to the service.

Ovarian cancer

Ovarian cancer is a rare form of cancer that arises from tissues around or within the ovary. It is often diagnosed at an advanced stage, due to the fact that clinical features tend to be vague and non-specific, and there are no proven effective tests for early detection[3]. Epithelial ovarian carcinoma accounts for over 90% of all cases of ovarian cancer, with the remainder arising from germ cell or sex cord-stromal cells. Epithelial ovarian carcinoma can be divided into high-grade serous (70%), endometrioid (10%), clear-cell (10%), mucinous (3%), and low-grade serous (<5%) subtypes[4]. Each subtype is characterised by differences in risk factors, molecular pathogenesis, patterns of spread, response to chemotherapy and prognosis[4]. Fallopian tube and primary peritoneal cancers while very rare, are clinically and morphologically similar to epithelial ovarian carcinomas, managed in a similar way, and are often included in clinical trials of ovarian cancer.

Serous subtype

High-grade serous carcinomas are the most common, and most aggressive, ovarian cancer subtype. They can be distinguished from the low-grade serous subtype by pathologists, based on differences in morphology and mitotic activity[4]. By definition high grade serous tumours have grade 2 or 3 nuclear atypia and most present at advanced stage, Almost all high-grade serous tumours harbour TP53 gene mutations.Approximately 50% have evidence of defective DNA repair by homologous recombination[5,6]and approximately 20% have amplification of CCNE1 which codes for cyclin E[7]. In contrast, low-grade serous carcinomas have grade 1 nuclear atypia and are generally indolent tumours, present in stage 1 (tumour confined to the ovary) and develop from well-established precursor lesions referred to as atypical proliferative (borderline) tumours[5]. They rarely harbour TP53 mutations and are characterised by other specific mutations, including KRAS, BRAF and ERBB2[5].

High grade serous tumours with identical morphology, molecular make - up and natural history appear to arise from the ovary, fallopian tube lining and the peritoneal lining. Given their similarity, it is thought that such tumours originate from pre-malignant intraepithelial lesions in the distal fallopian tube and then spread to the ovary or peritoneum, belong to a single category. Accordingly, they are often grouped together, particularly in clinical trials of agents that target the high grade serous subtype.

Current management of ovarian cancer

The treatment algorithm for patients with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component is discussed in detail in Section 9, but will be summarised here.

The mainstay of treatment for ovarian, fallopian tube or primary peritoneal cancer is primary cytoreductive surgery followed by intravenous platinum-based chemotherapy, which usually consists of carboplatin and paclitaxel. This approach has been shown to achieve high initial response rates. However, more than 70% of patients relapse and require re-treatment within 12 to 18 months[8].

Relapsed ovarian, fallopian tube, or primary peritoneal cancer is classified according to sensitivity to platinum-based chemotherapy. Patients who had previously achieved a partial or complete response to platinum-based chemotherapy and experienced a subsequent platinum-free interval of six months or longer are classified as having 'platinum-sensitive' ovarian cancer. [NB: In clinical trials of ovarian cancer, including the pivotal trial NCT00753545, objective response (partial or complete) are defined by the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines[9] or a cancer antigen 125 (CA-125) response according to Gynecological Cancer InterGroup Criteria[10] (GCIG). However, radiologists do not routinely report RECIST outside of the clinical trial setting. In clinical practice, evaluation of response (to treatment) is based on changes in CA-125 levels according to GCIC unless this was discordant with the patient's symptoms in which case scans would be performed (but not RECIST reported) to inform clinical determination of response.]

Upon relapse, these women are typically re-treated with platinum agents (e.g. carboplatin in combination with liposomal doxorubicin, gemcitabine, or a taxane, and carboplatin monotherapy)[11-13]. Those who progress during chemotherapy, or experience a platinum-free interval of less than six months are classified as having 'platinum-refractory' or 'platinum-resistant' ovarian cancer. These women may be considered for treatment with a non-platinum single agent (e.g. liposomal doxorubicin, a taxane, topotecan or gemcitabine)[11-13].

After re-treatment, current management of patients does not involve any specific maintenance therapy; women are simply monitored and only considered for another course of treatment if they progress and develop clinical signs or symptoms that are indicative of a subsequent relapse. Over the course of managing ovarian cancer, it may be necessary to administer several lines of therapy, as patients can experience multiple relapses. However, the duration of response to each subsequent treatment is typically, and progressively short-lived due to the onset of drug resistance and cumulative toxicities.

There remains a high unmet medical need for treatments targeted at relapsed ovarian cancer which can prolong the duration of remission, delay disease progression, maintain quality of life and extend survival. Ideally, such treatments should be able to be orally administered to avoid the need for regular infusions, and should have an acceptable tolerability profile. Olaparib is being proposed as 'active' maintenance therapy for women who have PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component after response to their last course of platinum-based chemotherapy.

BRCA mutations

BRCA1 and BRCA2 are breast and ovarian cancer susceptibility genes. The BRCA1 gene is found on chromosome 17 and BRCA2 is found on chromosome 13. BRCA1 and BRCA2 are both very large genes. BRCA1 has 24 exons that code for a 1863 amino acid protein while BRCA2 has 27 exons (26 coding) that code for a 3418 amino acid protein14. The proteins encoded by these genes are part of a multi-protein complex which repairs damaged DNA. The complex normally repairs double-strand breaks (DSBs) in the DNA by homologous recombination (HR)15.

To date, nearly 2000 distinct mutations and sequence variations have been identified in the BRCA genes16. BRCA mutations may occur anywhere within the genes, including exon-intron splice sites. Most mutations are predicted to produce a truncated protein and thus loss of protein function16. Because complete loss of protein function is required to exert a pathogenic effect, both alleles (i.e. both the maternally and paternally inherited copies) need to be inactivated. In heterozygous BRCA mutation carriers one mutant allele is inherited in the germline. The second initially wild-type allele is invariably mutated (by a different mechanism) in the tumour (sometimes called the second hit)17. BRCA1 and BRCA2 are therefore classic tumour suppressor genes.

Of the inherited mutations, deletions are the most common and can range from whole gene deletions, deletions of one or more contiguous exons to small deletions of two or more base pairs (e.g. BRCA1 del185AG). Less frequent are point mutations including protein truncating non-sense mutations and non-truncating mis-sense mutations. Most missense mutations are of uncertain pathogenicity and are often referred to as variant of uncertain significance (VUS). These occur in up to 10% to 15% of all individuals undergoing genetic testing with full sequencing of the BRCA genes, and constitute a considerable challenge for counselling particularly in terms of cancer risk estimates and risk management. VUS represent a moving target as most are subsequently reclassified, as more information is forthcoming, as a polymorphism, or occasionally, as a deleterious mutation.

Women with germline (inherited) BRCA mutations have an increased risk of developing ovarian cancer. The lifetime risk of developing ovarian cancer is about 1% among women in the general population, compared with 59% in BRCA1 mutation carriers and 17% in BRCA2 mutation carriers[18]. In Australia, germline BRCA mutations are found in 14.1% of women with non-mucinous epithelial ovarian carcinoma, including 17.1% of those with the high-grade serous subtype[19]. An additional 6% of high-grade serous ovarian cancer patients are thought to have tumour-specific BRCA mutations in the absence of any germline variation[19]. Across all subtypes, BRCA mutations occur more frequently in patients with platinum-sensitive epithelial ovarian carcinoma (38%), compared with platinum-resistant disease (17%)[20].

Homologous recombination and rationale for olaparib

Homologous recombination

Homologous recombination (HR) is a DNA repair mechanism in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. It is most commonly used to repair harmful breaks that occur on both strands of DNA. Cells with loss of function of any of the proteins required for HR, including BRCA1 and BRCA2, are unable to repair double strand DNA breaks and are regarded as being HR-deficient[17].

The susceptibility of tumour cells to PARP inhibition is due to the inability of the cells to repair DNA by HR. High-grade serous ovarian cancer arising in women with germline BRCA mutations are known to be HR deficient. Other mechanisms that cause HR deficiency that appear to also render cancer cells susceptible to PARP inhibition are the subject of ongoing research.

Rationale for olaparib

Olaparib inhibits the activation of PARP1 and PARP2 which are essential for the repair of single-strand DNA breaks via the base excision repair pathway. Unrepaired single-strand breaks are converted into double-strand breaks during the cellular replication process. In normal cells with a functional homologous recombination repair pathway, such breaks are effectively repaired with a high degree of fidelity by the DNA repair machinery. However, cells that are unable to repair both double and single stranded DNA breaks are unable to divide and are selected for cell death[17].

PARP inhibition causes death by synthetic lethality[†] only in tumour cells where DNA repair by HR is hampered (e.g. BRCA gene mutation positive) [21]. BRCA mutation sensitise cells to PARP inhibition[22] and PARP inhibition exploits deficiencies in DNA repair pathways to preferentially kill cancer cells.

It is important to note that susceptibility to synthetic lethality by PARP inhibition requires total loss of function of BRCA1 or BRCA2, which requires both copies of the gene to be inactivated. The normal non-tumour cells of BRCA mutation carriers, have at least one functional copy of each BRCA gene and therefore produce functional BRCA proteins.

This means that only the tumour cells that have lost both copies of the BRCA gene, are sensitive to PARP inhibitors. The selectivity for BRCA mutation positive tumour cells improves the therapeutic index for olaparib over current chemotherapy agents (which unselectively target all dividing cells), and allow for sustained administration as a well-tolerated maintenance therapy.

Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.

It is proposed that public funding is provided for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy in adult patients with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component. Germline BRCA mutation positive patients who show a response (partial or complete) to their current platinum regimen will be eligible for olaparib maintenance therapy. Patients who do not respond to their current platinum regimen and those who are found to be germline BRCA mutation negative will continue to receive standard follow-up care.

Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.

[†] PARP inhibition exploits the concept of synthetic lethality in which abnormalities in independent genes or pathways are not cytotoxic if they occur individually, but cause cell death when present together. Therefore, cells that have both a functional HR repair pathway and are treated with a PARP inhibitor will not die. However, the combination of both HRR deficiency and PARP inhibition will result in cell death as both repair pathways (HRR and BER) are non-functional

Overview of efficacy of olaparib in PSR ovarian cancer (NCT00753545)

Evidence for the population that would benefit from the proposed medical service has hitherto been drawn from a multi-centre, international, randomised, double-blind, placebo-controlled Phase 2 clinical trial (NCT00753545) conducted in unselected (i.e., not discriminated on the basis of BRCA mutation status) women with PSR ovarian cancer[1,2,23]. Patients were required to have completed at least two courses of platinum-based chemotherapy, and to have had a response (partial or complete) to their most recent platinum regimen. Those who met the study eligibility criteria (N=265) were randomised, within eight weeks after completion of their last dose of platinum-based chemotherapy, to receive either olaparib maintenance therapy (400 mg b.d., capsule formulation) or placebo. The median progression-free survival (PFS) in the olaparib group was 8.4 months from the time of randomisation (on completion of platinum-based chemotherapy), versus to 4.8 months in the comparator group. This equated to a hazard ratio of 0.35 (95% confidence interval [CI] 0.25 to 0.49, p<0.001)[1,2].

The results of an initial pre-specified subgroup analysis (N=97) suggested that the subgroup of patients with germline BRCA mutation derived the greatest benefit from olaparib monotherapy. Based on this, a retrospective genotyping sub-study was performed (blinded to treatment allocation) to determine the BRCA mutation status of all consenting participants, and efficacy analyses were performed by BRCA mutation status i.e. BRCA mutation resulting from germline and/or tumour sample analysis (*a priori* planned analysis). Results of the updated subgroup analysis demonstrated that olaparib maintenance therapy was associated with a statistically significant and clinically meaningful PFS benefits in patients who were BRCA mutation positive. In the subgroup of patients with a germline BRCA mutation (determined from a blood sample, N=166), there was a 7.1 month improvement in median PFS for patients treated with olaparib compared with placebo (median 11.2 versus 4.1, p<0.001). A similar PFS benefit was observed when patients with BRCA mutations determined from tumour DNA were included in the analysis (N=196 with a median PFS of 11.2 months versus 4.3 months, p<0.0001)[2].

Ongoing Phase III studies of olaparib in ovarian cancer

There are two ongoing Phase III studies of olaparib in patients with BRCA mutation ovarian cancer (SOLO 1 and SOLO 2) with the tablet formulation.

- **SOLO 1** is a randomized Phase III trial of olaparib maintenance monotherapy (tablet formulation) compared with placebo in newly diagnosed BRCA mutated ovarian cancer patients who are in complete or partial response following first line platinum-based chemotherapy)
  http://www.clinicaltrials.gov/ct2/show/NCT01844986?term=olaparib+ovarian+cancer&rank=3&submit_fld_opt=

- **SOLO 2** is a randomized Phase III trial of olaparib maintenance monotherapy (tablet formulation) compared with placebo in patients with relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum-based chemotherapy)
  http://www.clinicaltrials.gov/ct2/show/NCT01874353?term=olaparib+ovarian+cancer&rank=2&submit_fld_opt=

Pending the outcome of SOLO 1, a submission to request listing for BRCA mutation testing to determine eligibility for olaparib maintenance therapy following first line platinum-based chemotherapy may be considered at a later date.

Provide details on the expected utilisation, if the service is to be publicly funded.

As germline BRCA mutation testing is not MBS listed, there are no Medicare data available regarding its utilisation.

The expected utilisation of germline BRCA mutation testing and olaparib maintenance therapy under the proposed MBS and PBS listings will be determined based on estimates of the incidence and prevalence of PSR ovarian cancer (including fallopian tube, or primary peritoneal cancer) with high grade serous features or a high grade serous component in Australia.

Approximately 1500 new cases of ovarian cancer are diagnosed each year in Australia[24]. Epithelial ovarian carcinomas account for 90% of all ovarian cancers, and 70% of these are of the high grade serous subtype[4]. Therefore, it is estimated that around 945 (1500 x 90% x 70%) new cases of high-grade serous ovarian carcinoma are diagnosed in Australian women each year. In 2008, the median age of ovarian cancer diagnosis was ~63 years.

As primary peritoneal cancer is diagnosed at approximately one tenth the frequency of epithelial ovarian cancer, and fallopian tube cancer even less frequently[25]. In total, it is estimated that around 1040 (945 x 1.1) new cases of high grade serous ovarian, fallopian tube or primary peritoneal cancer are diagnosed in Australia each year.

Testing patterns are not well understood. However, the proportion of patients diagnosed with ovarian cancer who were <70 years in 2008 was 62%[24]. Therefore, up to 645 (1040 x 62%) of high grade serous ovarian, fallopian tube or primary peritoneal cancer patients could be eligible for gBRCA testing via the eviQ guidelines and may have potentially undergone germline BRCA testing at diagnosis (as per the eviQ guidelines). However, current compliance with eviQ guidelines is unclear and research will be conducted to determine the compliance and provided as part of the integrated submission.

Further, the 5-year prevalence of ovarian cancer was estimated to be ~ 3600 (at the end of 2008)[24]. At present, data are scant regarding the prevalence of fallopian tube and primary peritoneal cancers; prevalence of germline BRCA mutation, platinum sensitivity, disease relapse and survival among the specific subgroup of women defined above (and proposed for germline BRCA mutation testing to determine eligibility for olaparib maintenance treatment). Patterns of treatment are also not well known. Hence further research is underway to estimate the size of the testing population and expected utilisation of germline BRCA mutation testing to determine olaparib eligibility. These details will be provided in the submission. In the submission, the financial impact of assuming different estimates of the projected number of patients likely to undergo germline BRCA mutation testing and the percentage of germline BRCA mutation positive patients will be explored through detailed sensitivity analyses.

4. Intervention – proposed medical service

Provide a description of the proposed medical service.

Germline BRCA mutation testing

The proposed medical service is a diagnostic test used to identify germline BRCA mutations in women with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component. This typically involves: (i) collection of a 5 to 10 mL blood sample; (ii) extraction of genomic DNA and amplification of the 51 exons of the BRCA genes by polymerase chain reaction; (iii) sequencing of the entire coding region of the gene and splice sites at each exon –intron boundary to identify point mutations and small insertions or deletions and (iv) a multiplex ligation-dependent probe amplification (MLPA) assay that is designed to detect large gene copy number changes (e.g. the deletion or duplication of whole exons, groups of exons or the entire gene)[26]. Sequencing can be performed using either traditional Sanger sequencing techniques or next-generation sequencing methods that enable massive parallel sequencing of individual DNA fragments. Both approaches assure high sensitivity for the detection of BRCA mutations, as they provide information about the actual order of nucleotides. However next-generation sequencing is expected to be faster and less expensive.

Test results are interpreted by interrogating molecular classification databases, such as the Breast Cancer Information Core Database (BIC), the National Human Genome Research Institute, Leiden Open Variation Database (LOVD), or National Genetics Reference Laboratory-Manchester (DMuDB)[26,27]. Individuals are classified as BRCA mutation positive if they are found to have a deleterious or suspected deleterious BRCA mutation, which is likely to inactivate or alter the function of the BRCA1 or BRCA2 protein product. Those who have no mutation detected or are found to have a VUS or benign polymorphism are classified as BRCA mutation negative.

Most of the methods used for germline BRCA mutation testing in current Australian clinical practice have been developed in-house by specifically accredited molecular pathology service providers. The application for reimbursement of testing to determine eligibility for olaparib maintenance therapy in women with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high high grade serous component will include the identification of all relevant test methods and an assessment of their comparative diagnostic accuracy and analytical test performance (including sensitivity and specificity).

Current use of germline BRCA mutation testing

Germline BRCA mutation testing is currently offered to women with certain types of ovarian cancer in accordance with the eviQ '*Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes'* (**Appendix 1**). The main reason for testing in this context is to determine whether the patients and their relatives are genetically susceptible to developing (further) breast, ovarian or other BRCA-related malignancies. Knowledge of a patient's BRCA mutation status does not influence treatment decisions as there are currently no targeted therapies for BRCA mutation positive ovarian cancer. It can however, bring relief from uncertainty and allow individuals to make informed decisions about whether they are likely to benefit from targeted management strategies or preventive surgery (e.g. prophylactic mastectomy or bilateral salpingo- oophorectomy).

It is generally recommended that this type of predictive genetic testing is preceded and accompanied by genetic counselling. Pre-test genetic counselling is important for ensuring that patients are fully informed about the potential harms and benefits associated with germline BRCA mutation testing, while post-test genetic counselling is important for assisting with the interpretation of complex test results, that may have broad clinical consequences. The typical pathway for referral for germline BRCA mutation testing for inherited cancer risk assessment in Australia is shown in **Figure 1**. It can take several months for patients to receive their test results, due to access issues which may delay or limit the availability of genetic counselling and testing services.

Germline BRCA mutation testing for inherited cancer risk assessment is not currently listed on the Medicare Benefits Schedule (MBS). Therefore all tests are funded privately or through State or Territory-funded family cancer clinics.

Figure 1 Current referral pathway for germline BRCA mutation testing for inherited cancer risk assessment

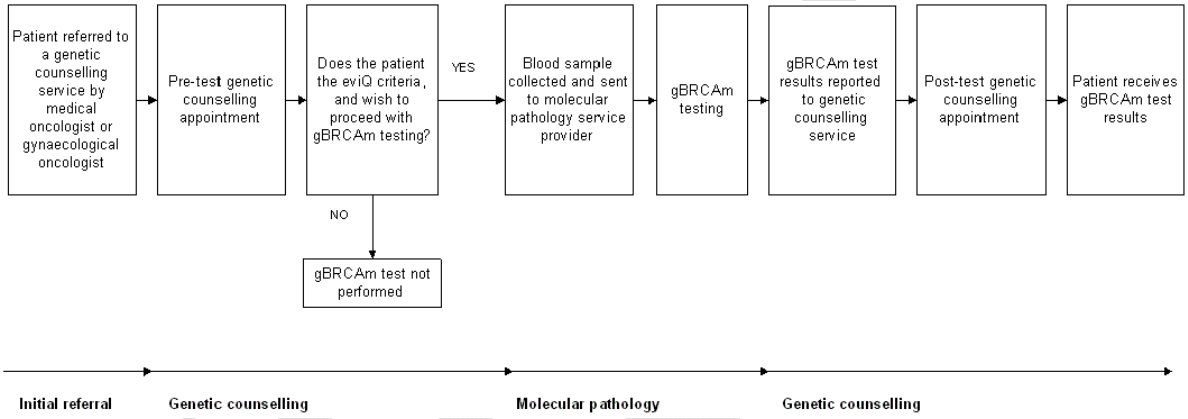


Figure 2

Abbreviations: gBRCAm, germline BRCA mutation testing

Proposed use of germline BRCA mutation testing

The current application proposes germline BRCA mutation testing as a co-dependent service which is provided to determine eligibility for olaparib maintenance therapy in women with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component. It is intended that testing of the proposed MBS population will be conducted in the context of a *subsequent* course of platinum-based chemotherapy in a patient who was established as platinum-sensitive prior to the time of relapse. This type of testing is treatment-focused and aims to identify the subgroup of patients who are most likely to obtain the greatest clinical benefit from treatment with olaparib. Test results may also have important consequences for family members. It is therefore recommended that patients who are found to carry an inactivating germline BRCA1 or BRCA2 mutation are referred for post-test genetic counselling.

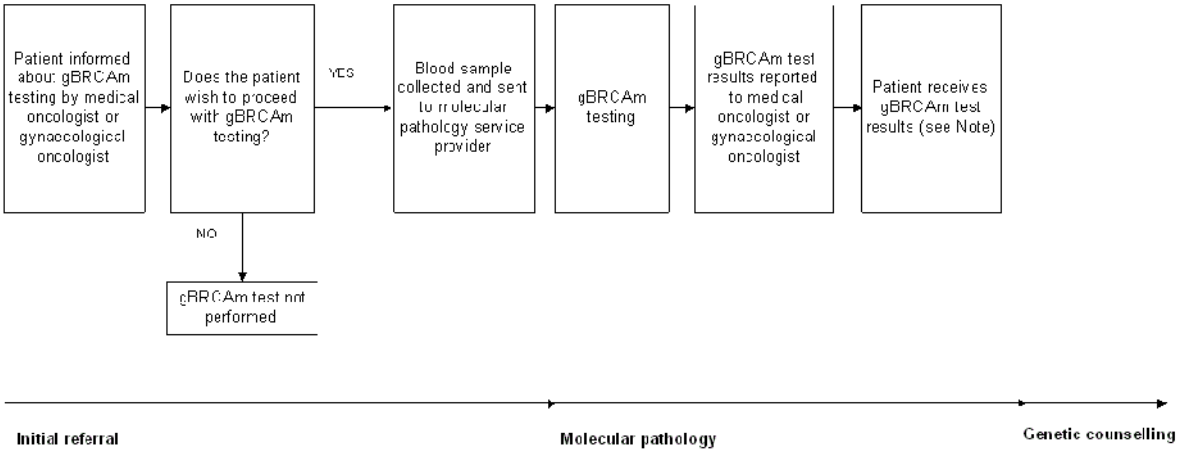
In the pivotal trial (NCT00753545), olaparib maintenance therapy was commenced within eight weeks of the last dose of platinum-based chemotherapy. Because of this, it is important to know a patient's germline BRCA mutation status as soon as possible after confirmation of

a partial or complete response to their current platinum-based regimen (if germline BRCA mutation status for patients is not already known[‡]).

It is anticipated that patients in the proposed target MBS population will be referred for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy by the managing medical or gynaecological oncologist. It is understood that urgent processing can be requested in particular cases in order to facilitate a faster turnaround time (potentially within two weeks).

The proposed referral pathway for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy is shown in **Figure 3**.

Figure 3 Proposed referral pathway for germline BRCA mutation testing to determine eligibility for olaparib



Abbreviations: gBRCAm, germline BRCA mutation testing

Note: *Patients who are found to carry an inactivating germline BRCA1 or BRCA2 mutation should be referred for post-test genetic counselling, due to the implications of the test result for other family members.*

Two scenarios are proposed in terms of the timing for germline BRCA mutation testing to determine eligibility for treatment with olaparib (if the patient's germline BRCA mutation status is not already known):

- In Scenario 1, testing is performed in patients diagnosed with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component during their current course of platinum-based chemotherapy (i.e., before a partial or complete response has been confirmed).
- In Scenario 2, testing is performed in patients diagnosed with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component who have completed and demonstrated a response (partial or complete) to their most recent platinum-based chemotherapy

[‡] Gemline BRCA mutation testing for inherited cancer risk assessment is available through family cancer clinics, in accordance with eviQ guidelines. Therefore, it is expected that BRCA mutation status for some patients would be known. Patients who have undergone a previous germline BRCA mutation test for inherited cancer risk assessment will not need to undergo a repeat test to determine eligibility for olaparib, as their germline BRCA mutation status will not have changed.

The advantage of Scenario 1 would be that it ensures that germline BRCA mutation test results are available to inform treatment decisions in a timely fashion because of the expected long turnaround time for germline BRCA mutation testing. This therefore limits delay in commencing olaparib treatment in eligible women. On the other hand, Scenario 2 is consistent with the pivotal trial (NCT00753545), and limits testing only to those patients who meet the treatment response criteria for olaparib maintenance therapy. If test results can be obtained within a short time, then Scenario 2 would be a better, more efficient and cost effective preferred option.

Tumour BRCA mutation testing

Current evidence suggests that patients with BRCA mutation positive PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component benefit from olaparib maintenance therapy regardless of whether the test is performed on a peripheral blood or a tumour sample[2]. However, the optimal method for tumour BRCA mutation testing is yet to be established. Tumour BRCA mutation testing will be subject to the same analytical challenges associated with EGFR, KRAS and BRAF somatic mutation testing in patients with other forms of cancer (e.g. lower quality DNA and the presence of formalin-induced artefacts). Current BRCA sequencing methods are being redeveloped to ensure accurate and robust results from tumour samples. For example, the Centre for Translational Pathology at the University of Melbourne has developed and validated a next generational sequencing panel for BRCA testing on tumour samples and is evaluating the acceptability, feasibility and accuracy of this method in both formalin fixed archival tissues obtained at diagnosis and on fresh tissues collected at relapse. The advantage of testing the patient's tumour over testing a blood sample, is the ability to detect somatic mutations and epigenetic changes in the *BRCA* genes as well as other genes involved in HR. There is some evidence that patients with tumours that harbour these changes may also benefit from olaparib. Since this is still in a research setting, the current application is focused on germline BRCA mutation testing. The feasibility and cost-effectiveness of tumour BRCA mutation testing to determine eligibility for olaparib may be considered at a later date.

If the service is for investigative purposes, describe the technical specification of the health technology and any reference or "evidentiary" standard that has been established.

The current reference standard for germline BRCA mutation testing in women with ovarian cancer is direct sequencing with MLPA to detect large gene copy number changes (as described above). The eviQ guidelines note that methods which combine direct sequence analysis with MLPA provide the highest sensitivity currently available[27].

Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.

It is understood that Myriad Genetics Inc in Utah USA, hold the patents for BRCA1 and BRCA2. Genetic Technologies Inc in Melbourne hold the license for use of the BRACAnalysis™ test developed by Myriad Genetics Inc. This was used to determine the germline BRCA mutation status of participants of the NCT00753545 randomised controlled trial described in Section 3.

Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.

The proposed medical service is an in-vitro diagnostic test which will be performed in pathology laboratories that hold National Association of Testing Authorities (NATA) accreditation for germline mutation testing by DNA sequencing for medical use. There are presently at least seven public laboratories (Familial Cancer Service Westmead, Hunter Area Pathology Service, Molecular Pathology Peter MacCallum Cancer Centre, Molecular Pathology (at Flinders Medical Centre) SA Pathology, SEALS molecular and cytogenetics South Eastern Area Laboratory Service, Molecular Genetics Laboratory (Haematology) pathology Queensland, PathWest Western Australia) and one private laboratory (Genetic Technologies) that offer germline BRCA mutation testing in Australia.

Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).

As is the current requirement, germline BRCA mutation testing will be performed only by diagnostic pathology laboratories that have been accredited by NATA for the detection of germline mutations for medical use. Each accredited laboratory will be required to comply with standards established by the NPAAC, and demonstrate satisfactory performance in an external quality assurance program. A specific quality assurance program for Familial Breast Cancer, which includes germline BRCA mutation testing is offered by the European Molecular Genetics Quality Network (EMQN) through the Royal College of Pathologists of Australasia (RCPA) and the Human Genetics Society of Australasia (HGSA) Quality Assurance Program.

Each laboratory will be supervised by a molecular or genetic pathologist and managed by a senior scientist with a PhD, FFSc (RCPA) or FHGSA and at least 10 years experience in genetics.

Currently each public laboratory is closely affiliated with a familial cancer genetics and genetic counselling service. Private laboratories employ their own genetic counsellors to ensure compliance with the ethical requirements.

Strict privacy and confidentiality provisions will be in place in each laboratory to prevent the inadvertent release of sensitive medical information about the patient and her relatives.

One germline BRCA test is performed per patient in her lifetime.

Access to germline BRCA mutation testing for patients in regional or remote areas would be facilitated by the collection of a blood sample at a local specimen collection or treatment centre and transportation to an accredited pathology for testing.

5. Co-dependent information (if not a co-dependent application go to Section 6)

Please provide detail of the co-dependent nature of this service as applicable

Germline BRCA mutation testing is required before treatment with olaparib, as it enables the identification of the subgroup of patients who are most likely to respond to maintenance therapy. The rationale and mechanism of action for olaparib is described in Section 2. At present, there are no other targeted maintenance therapies available for patients in the proposed PBS population i.e. patients diagnosed with PSR ovarian cancer (including fallopian tube or primary peritoneal) with high grade serous features or a high grade serous component who are known to carry an inactivating germline BRCA1or BRCA2 mutation, and are in response (complete response or partial response) following the subsequent course of platinum-based chemotherapy (note that olaparib maintenance therapy should commence within eight weeks of the last dose of the subsequent course of platinum-based chemotherapy).

Therefore the comparator for germline BRCA mutation testing to determine eligibility for treatment with olaparib is 'no testing', and the comparator for olaparib maintenance therapy is 'standard follow-up care (i.e. watch and wait)'. It is intended that MBS listing of the germline BRCA mutation test and PBS listing of olaparib for eligible patients will occur simultaneously.

6. Comparator – clinical claim for the proposed medical service

Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.

The current application proposes MBS listing of germline BRCA mutation testing as a co-dependent service to determine eligibility for olaparib maintenance therapy in women with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component. As discussed in Section 4, the main reason for performing a germline BRCA mutation test in this context is to identify the subgroup of patients who are most likely to respond to treatment with olaparib. This will change clinical management and the way in which ovarian cancer is treated. It will also be provided in a different clinical setting, compared to the current use of germline BRCA mutation testing to ascertain an individual's inherited risk of developing cancer. The comparator for the germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy in women with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component is the current scenario in which there is no public funding for germline BRCA mutation testing. The overall comparator for the proposed co-dependent technologies is therefore defined as '*no testing with standard follow-up care (i.e. watch and wait)*'.

7. Expected health outcomes relating to the medical service

Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).

The overall clinical claim is that germline BRCA mutation testing followed by olaparib maintenance therapy is superior in terms of comparative effectiveness, with acceptable safety, versus the comparator situation (no testing with the standard follow-up care i.e. 'watch and wait') in patients with germline BRCA mutation positive, PSR ovarian cancer

(including fallopian tube,or primary peritoneal cancer) with high grade serous features or a serous component. Reimbursement of the proposed co-dependent technologies is expected to result in improvements in several patient-relevant health outcomes, including overall survival, progression-free survival, objective response, disease-related symptoms and health-related quality of life.

The identification of a germline BRCA mutation to determine eligibility for treatment with olaparib may also benefit family members via the identification of a familial mutation that places one in two of the patient's female blood relatives at heightened risk of breast and ovarian cancer. Family members may choose to undergo genetic counselling and subsequent testing to identify whether they have also inherited the pathogenic BRCA mutation originally identified in the proband. This can enable them to determine whether they are likely to benefit from targeted management strategies or preventive surgery to manage their inherited cancer risk.

Describe any potential risks to the patient.

The direct medical risks, or harms, of germline BRCA mutation testing are minimal as it is a physically safe procedure. However, knowledge of test results can have important clinical and psychological consequences for patients and their families.

The risk of obtaining a false positive or false negative test result is low, as germline BRCA mutation testing is already performed at a very high level of quality in Australian NATA accredited laboratories. It is common practice to require two blood samples to be collected from the patient and processed on separate days, to minimise the risk of sample mix-ups or errors of interpretation. This helps to reduce uncertainty around the accuracy of test results.

In the context of testing to ascertain an individual's inherited risk of developing cancer, a false negative result could lead to false reassurance, while a false positive result could lead to unnecessary psychological stress and/or medical procedures (e.g. monitoring or preventative surgery). In the context of testing to determine eligibility for treatment olaparib, however, a false negative result could lead to denial of a potentially effective and life extending treatment, while a false positive result could lead to treatment with a lower likelihood of clinical benefit.

The proposed MSAC application will comprehensively assess the potential benefits, harms and costs of germline BRCA testing for the proposed indication, taking into account the accuracy of testing, the size and profile of the target population and underlying prevalence of germline BRCA mutations in the target population. Furthermore, sensitivity analyses will explore the impact of variations to key input data.

The overall safety and tolerability profiles for olaparib are appropriate for long-term maintenance therapy. The most frequently reported adverse events in BRCA mutation positive patients who received olaparib in the pivotal trial (NCT00753545) were nausea, fatigue, vomiting, diarrhoea, and anaemia. These are generally low grade (CTCAE grade 1 or 2) and do not require dose modification or lead to discontinuation of study treatment.

Specify the type of economic evaluation.

The economic evaluation of the proposed co-dependent technologies will be conducted as a cost-effectiveness/ cost-utility analysis.

8. Fee for the proposed medical service

Explain the type of funding proposed for this service.

The current application requests the creation of a new MBS item number for germline BRCA mutation testing as a co-dependent service performed to determine eligibility for olaparib maintenance therapy in women with PSR ovarian cancer (including fallopian tube or primary peritoneal cancer) with high grade serous features or a high grade serous component. Public funding for olaparib will be requested through a submission to the Pharmaceutical Benefits Advisory Committee (PBAC).

Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.

The technology and expertise required for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy is identical to that used in current practice for testing to assess familial cancer risk.

The main capital costs relate to the purchase and maintenance of DNA sequencing instruments. Most laboratories use the ABI3730xl or the Illumina MiSeq next generation sequencer, which cost approximately AUD $350,000 and $150,000, respectively. All laboratories currently performing *BRCA* testing will already have this equipment installed so there should be no additional capital expenditure required.

Provide details of the proposed fee.

The proposed MBS fee for germline BRCA mutation testing in the proposed patient population will be determined based on the time and expertise required to perform the service, and will be in line with the MBS fee for 'similar' services. A final proposed fee will be provided in the submission based on a cost survey of the laboratories providing germline BRCA mutation testing in Australia.

It is expected that the unit cost for germline BRCA mutation testing will decrease with economies of scale and as new technologies (e.g. NGS) become more widely available. As such, the final proposed fee for germline BRCA mutation testing is likely to be lower than the current fees being charged by pathology laboratories.

The proposed item descriptor is:

A mutation test for inactivating germline BRCA1 or BRCA2 mutations, in a patient diagnosed with platinum sensitive relapsed ovarian carcinoma (including fallopian tube or primary peritoneal carcinoma) with high grade serous features or a high grade serous component to determine whether the eligibility criteria for maintenance treatment with olaparib under the Pharmaceutical Benefits Scheme have been met.

Note: This test will ordinarily be requested by a medical oncologist or gynaecological oncologist. Patients who are found to carry an inactivating germline BRCA1 or BRCA2 mutation should be referred for post-test genetic counselling, due to the implications of the test result for other family members.

9. Clinical Management Algorithm - clinical place for the proposed intervention

Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.

Current clinical management algorithm for women with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high-grade serous features or a high grade serous component

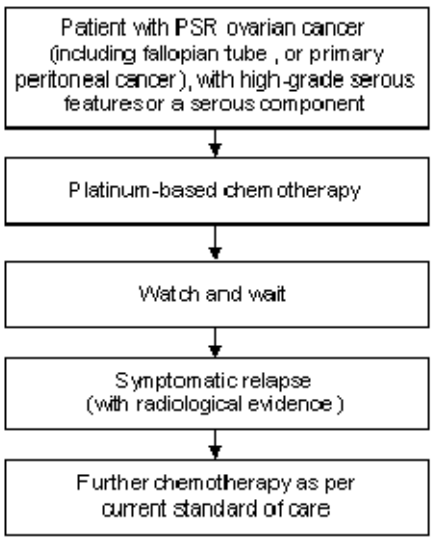
In the current clinical management algorithm for women with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component (**Figure 4**), patients are re-treated with platinum agents i.e. patients receive a subsequent course of platinum-based chemotherapy (e.g. carboplatin in combination with liposomal doxorubicin, gemcitabine, or a taxane, and carboplatin monotherapy), then receive standard follow-up care until the next relapse.

Standard follow-up care is based on a 'watch and wait' strategy, whereupon the treating gynaecological or medical oncologist provides general supportive care, manages treatment-related side effects, and screens for clinical and investigative features of relapse[28]. The frequency of follow-up consultations is individually determined. One commonly reported programme involves follow-up at 3-monthly intervals for the first two years, then 4-6 monthly intervals for the next three years, with annual visits thereafter[28]. The basic format of a follow-up consultation includes updating the patient's history, assessing psychosocial and supportive care needs, and undertaking a physical pelvic examination. Serum CA125 levels may be monitored to assist with the early detection of relapse, but there is no evidence to suggest that this results in survival benefit. Routine radiological imaging is not recommended, but a magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography (PET) scan should be performed to confirm the presence of relapsed ovarian cancer if a patient develops symptoms or clinical signs (e.g. rapidly rising CA125 levels) that indicate recurrent disease [28].

As discussed in Section 4, a subset of patients may be referred for germline BRCA mutation testing to determine their inherited cancer risk, in accordance with the eviQ guidelines (**Appendix 1**), but this does not change the way in which ovarian cancer is treated.

Differences between the current and proposed uses of germline BRCA mutation testing in ovarian cancer patients are described in Section 4.

Figure 4 Current clinical management algorithm



* Germline BRCA mutation testing to assess the inherited risk of developing cancer is available through family cancer clinics, in accordance with the eviQ guidelines (Appendix 1)

Abbreviations: PSR, platinum-sensitive relapsed.

Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.

Proposed clinical management algorithm for women with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component

Scenario 1: Germline BRCA mutation testing to determine eligibility for olaparib during the subsequent course of chemotherapy (i.e. before a partial or complete response has been confirmed)

The proposed clinical management algorithm for women with PSR ovarian, fallopian tube, or primary peritoneal cancer (

Figure 5) is similar to the current algorithm, in that patients are retreated with platinum agents i.e. patients receive a subsequent course of platinum-based chemotherapy. These patients, however, become eligible for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy, during the subsequent course of platinum-based chemotherapy (if their germline BRCA mutation status is not already known).

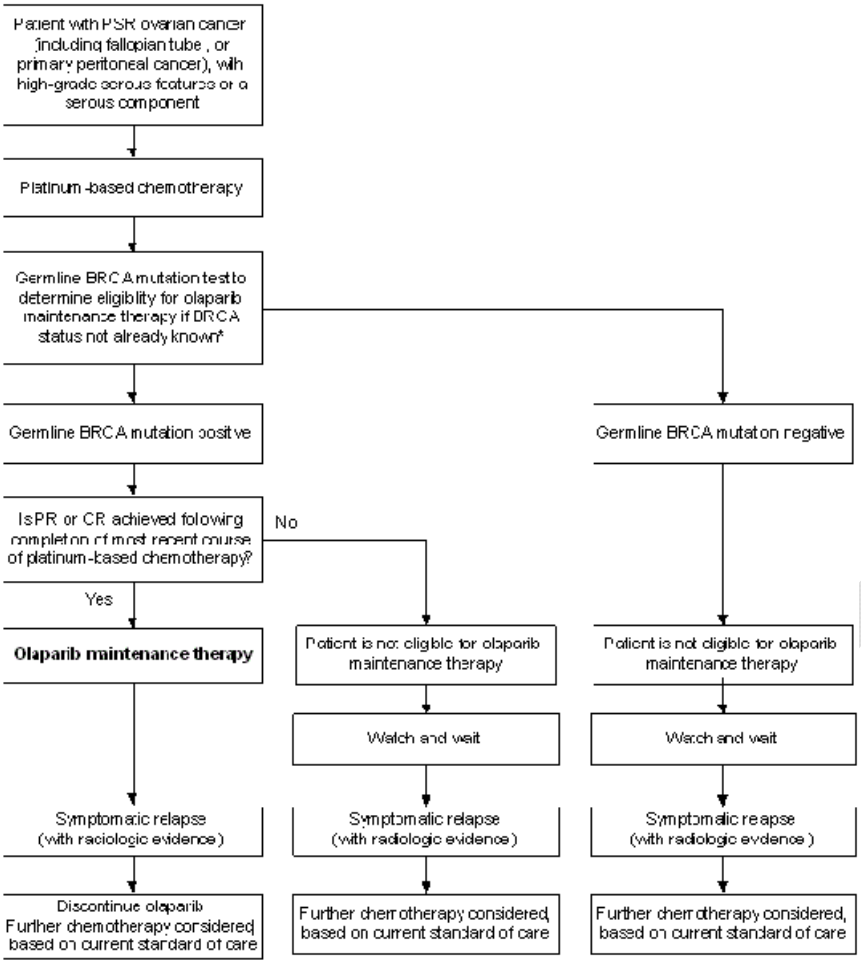
Germline BRCA mutation positive patients who achieve a partial or complete response to the subsequent course of platinum-based chemotherapy will be eligible for olaparib maintenance therapy (which should commence within eight weeks of the last dose of platinum-based chemotherapy). Those who fail to respond to the subsequent course of platinum-based chemotherapy and/or patients who are found to be germline BRCA mutation negative will continue to receive standard follow-up care (as per the current algorithm).

Scenario 2: Germline BRCA mutation testing to determine eligibility for olaparib following completion and a response (partial and complete) to the subsequent course of platinum-based chemotherapy

Scenario 2 **(**

Figure 6) is similar to proposed algorithm presented in Scenario 1, apart from the proposed timing of germline BRCA mutation testing. In this scenario, patients with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component are retreated with platinum based chemotherapy i.e. patients receive a subsequent course of platinum-based chemotherapy, and only those who achieve a partial or complete response are eligible for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy (if their germline BRCA mutation status is not already known).

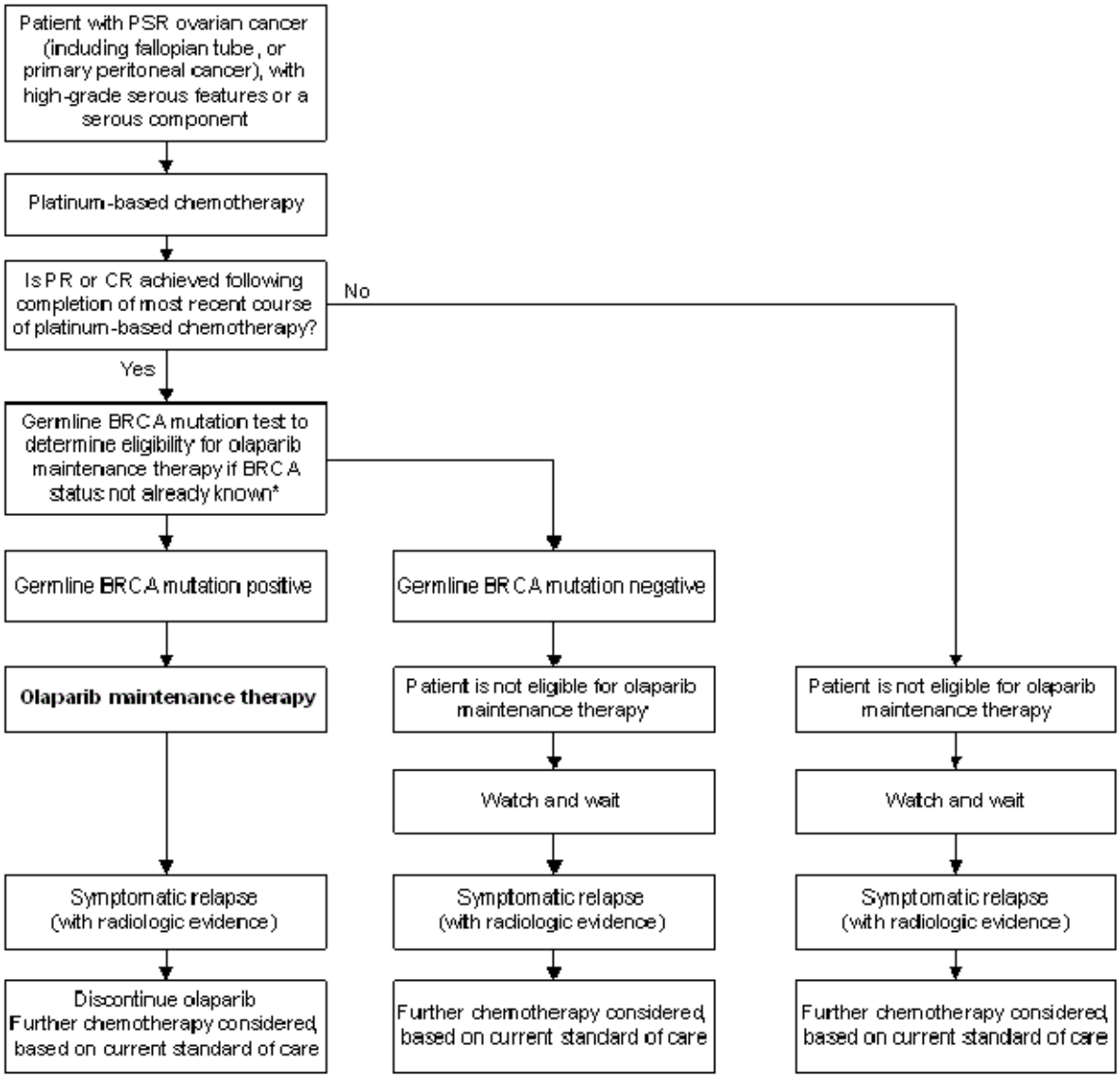
Figure 5 Proposed clinical management algorithm, with germline BRCA mutation testing to determine eligibility for olaparib performed during the subsequent course of platinum-based chemotherapy (Scenario 1)



* Germline BRCA mutation testing to assess the inherited risk of developing cancer is available through family cancer clinics, in accordance with the evidence guidelines (Appendix 1)

Abbreviations: CR, complete response; PR, partial response; PSR, platinum-sensitive relapsed.

Figure 6 Proposed clinical management algorithm, with germline BRCA mutation testing to determine eligibility for olaparib following completion and a response (partial or complete) to the subsequent course of platinum-based chemotherapy (Scenario 2)



* Germline BRCA mutation testing to assess the inherited risk of developing cancer is available through family cancer clinics, in accordance with eviQ guidelines (Appendix 1).

Abbreviations: CR, complete response; PR, partial response; PSR, platinum-sensitive relapsed.

Please note that Figures 3, 4 and 5 are presented for the purpose of illustrating the clinical algorithms associated with the various assessments outlined in this proposed protocol and are not intended to reflect the economic models required in the final assessment.

10. Regulatory Information

Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.

The proposed medical service involves the use of an in-vitro diagnostic test to detect germline BRCA mutations in a subgroup of ovarian cancer patients, to identify individuals who may benefit from olaparib maintenance therapy. Such tests are classified as Class 3 in vitro diagnostic medical devices (IVDs) under the 2010 Therapeutic Goods Administration (TGA) regulatory framework. At present, it is unclear from publically available information whether any applications have been lodged by manufacturers of commercial or in-house BRCA mutation tests.

Laboratories that deal with Class 3 IVDs are required to be accredited by NATA. As part of the accreditation process, NATA evaluates test repeatability and inter-lab reliability.

11. Decision analytic

Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC.

Table 1 provides a summary of the PICO framework that will be used to define the questions for public funding, select the evidence that will be used to assess the safety and effectiveness of the proposed co-dependent technologies, and provide the evidence-based inputs for the economic evaluation.

Table 1 Summary of PICO to define research question

Criteria	Description
Population	Patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal cancer) with high-grade serous features or a high grade serous component who have completed and demonstrated a response (partial or complete) following the subsequent course of platinum-based chemotherapy* (see 'Proposed use of germline BRCA mutation testing' under Section 4). * If germline BRCA mutation testing results can be obtained within a short time It is intended that testing of the proposed MBS population will be conducted in the context of a subsequent course of platinum-based chemotherapy in a patient who is established as platinum-sensitive prior to the time of relapse. Note: Two scenarios have been proposed in the protocol with respect to timing of germline BRCA mutation testing to determine elgibility for treatment with Olaparib: (1) testing to be performed during the subsequent course of chemotherapy or (2) testing to be performed after completion and demonstration of a response (partial or complete response) to the subsequent course of chemotherapy
Intervention	Germline BRCA mutation testing, followed by olaparib maintenance therapy in patients who are BRCA mutation positive patients
Test reference standard	Direct sequencing with MLPA to detect large gene copy number alterations
Comparator for the proposed co-dependent technologies	No testing with standard follow-up care (watch and wait)

Criteria	Description
Outcomes	Patient-relevant health outcomes: • Overall survival • Time to progression (progression-free survival) • Objective response • Disease-related symptoms • Health-related quality of life • Avoidance of chemotherapy toxicity associated with future cycles (by treating patients with olaparib in place of further chemotherapy cycles) Safety outcomes: • Adverse events associated with olaparib maintenance therapy (e.g. nausea, fatigue, vomiting, diarrhoea and anaemia) Test-related outcomes: • Diagnostic accuracy • Other potential benefits and harms Familial outcomes • Impact of identification or exclusion of an inactivating germline BRCA1 or BRCA2 mutation in family members including further genetic testing in family members, on both QoL and health outcomes

12. Healthcare resources

Using tables 2 and 3, provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.

The evaluation of the proposed co-dependent technologies will include assessments of changes in health-care utilisation and costs as detailed in Table 2

The introduction of public funding for germline BRCA mutation testing to determine eligibility for olaparib maintenance therapy will increase the number of patients with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component who are aware of their germline BRCA mutation status. This, in turn, will increase the demand for non-MBS germline BRCA mutation testing and genetic counselling services among the relatives of known germline BRCA mutation carriers. However, it is not expected that these services would be reflected in the economic analysis.

13. Questions for public funding

Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- *Which health / medical professionals provide the service*
- *Are there training and qualification requirements*
- *Are there accreditation requirements*

Is germline BRCA mutation testing in women with PSR ovarian cancer (including fallopian tube,or primary peritoneal cancer) with high grade serous features or a high grade serous component, followed by olaparib maintenance therapy in patients who are BRCA mutation positive, safe, effective and cost-effective compared to no testing with standard follow-up care (i.e. watch and wait)?

Table 2: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Equivalent to current practice										
Resources provided to deliver proposed intervention										
Germline BRCA mutation testing	MBS	Pathology services	To be provided in submission	To be provided in submission						
Blood sample collection	MBS Hospitals Other (eg, RDNS)	General practice Hospitals Pathology services Home blood collection services (eg, RDNS)	To be provided in submission	To be provided in submission						
Resources provided in association with proposed intervention										
Medical or gynaecological oncology	MBS Hospitals	Hospitals Private clinics	To be provided in submission	To be provided in submission	Items 132 and 133					
Olaparib	PBS	Hospitals	To be provided in	To be provided in						

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
		Private clinics	submission	submission						
General practice	MBS	General practice	To be provided in submission	To be provided in submission	Items 3, 4, 20, 23, 24, 35, 36					
Investigations for patient monitoring (radiology and pathology)	MBS	Hospitals Radiology services Pathology services	To be provided in submission	To be provided in submission						
Resources provided to deliver comparator										
No germline BRCA mutation testing										
Resources provided in association with comparator (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
Medical or gynaecological oncology	MBS Hospitals	Hospitals Private clinics	To be provided in submission	To be provided in submission						
Drugs avoided because of the use of olaparib	PBS	Hospitals Private clinics	To be provided in submission	To be provided in submission						

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
General practice	MBS	General practice	To be provided in submission	To be provided in submission						
Investigations for patient monitoring (radiology and pathology)	MBS	Hospitals Radiology services Pathology services	To be provided in submission	To be provided in submission						
Resources used to manage patients successfully treated with the proposed intervention										
See above										
Resources used to manage patients who are unsuccessfully treated with the proposed intervention										
See above										
Resources used to manage patients successfully treated with comparator 1										
See above										
Resources used to manage patients who are unsuccessfully treated with comparator 1										
See above										

* Include costs relating to both the standard and extended safety net.

References

1. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *New England Journal of Medicine.* 2012;366(15):1382-1392.
2. Ledermann JA, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm). *Journal of Clinical Oncology.* 2013;31(suppl; abstr 5505).
3. Jordan SJ, Francis JE, Nelson AE, Zorbas HM, Luxford KA, Webb PM. Pathways to the diagnosis of epithelial ovarian cancer in Australia. *Medical Journal of Australia.* 2010;193(6):326-330.
4. Prat J. New insights into ovarian cancer pathology. *Annals of Oncology.* 2012;23(Suppl 10):x111-x117.
5. Kurman RJ. Origin and molecular pathogenesis of ovarian high-grade serous carcinoma. *Annals of Oncology.* 2013;24:x16-x21.
6. Vang R, Shih I, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: Pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. *Advances in Anatomic Pathology.* 2009;16(5):267-282.
7. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474(7353):609-615.
8. Romero I, Bast RC. Minireview: Human ovarian cancer: Biology, current management, and paths to personalizing therapy. *Endocrinology.* 2012;153(4):1593-1602.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *Journal of the National Cancer Institute.* 2000;92(3):205-216.
10. Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *International Journal of Gynecological Cancer.* 2011;21(2):419-423.
11. The Australian Cancer Network and National Breast Cancer Centre. *Clinical practice guidelines for the management of women with epithelial ovarian cancer* 2004; https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp98.pdf.
12. Greater Metropolitan Clinical Taskforce. *Best Clinical Practice - Gynaecological Cancer Guidelines 2009* 2009; http://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0010/154549/go_clinical_guidelines.pdf.
13. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2013;24(Suppl. 6):vi24-vi32.
14. Hondow HL, Fox SB, Mitchell G, et al. A high-throughput protocol for mutation scanning of the BRCA1 and BRCA2 genes. *BMC Cancer.* 2011;11:265.
15. Lau C, Suthers G. BRCA testing for familial breast cancer. *Australian Prescriber.* 2011;34(2):49-51.
16. National Cancer Institute. *Genetics of Breast and Ovarian Cancer (PDQ®)* 2014; http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page2.
17. Toss A, Cortesi L. Molecular mechanisms of PARP inhibitors in BRCA-related ovarian cancer. *Journal of Cancer Science & Therapy.* 2013;5(409-416).
18. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst.* 2013;105(11):812-822.
19. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. *Journal of Clinical Oncology.* 2012;30(21):2654-2663.

20. Dann RB, DeLoia JA, Timms KM, et al. BRCA1/2 mutations and expression: response to platinum chemotherapy in patients with advanced stage epithelial ovarian cancer. *Gynaecologic Oncology.* 2012;125(5):677-682.
21. Guha M. PARP inhibitors stumble in breast cancer. *Nature Biotechnology.* 2011;29(5):373-374.
22. McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. *Cancer Research.* 2006;66(16):8109-8115.
23. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *The Lancet Oncology.* 2014;15(8):852-861.
24. Gynaecological cancers in Australia an overview. *Cancer series number 70* 2012; http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737422901. Accessed 15 September 2014, 2014.
25. Jordan SJ, Green AC, Whiteman DC, et al. Serous ovarian, fallopian tube and primary peritoneal cancers: A comparative epidemiological analysis. *International Journal of Cancer.* 2008;122(7):1598-1603.
26. Calistri D, Zampiga V, Zoli W. Characterization of molecular alterations of BRCA1/2: Analysis and interpretation guidelines. *Current Women's Health Reviews.* 2012;8(1):4-11.
27. eviQ Cancer Treatments Online. *Genetic Testing for Heritable Mutations in the BRCA1 and BRCA2 Genes* 2014; https://www.eviq.org.au/Protocol/tabid/66/categoryid/440/id/620/Genetic%20Testing%20for%20Heritable%20Mutations%20in%20the%20BRCA1%20and%20BRCA2%20Genes.aspx.
28. Cancer Australia. *Follow-up of women with epithelial ovarian cancer* 2012; http://canceraustralia.gov.au/publications-resources/cancer-australia-publications/follow-women-epithelial-ovarian-cancer.

Appendix 1: EviQ guidelines on genetic testing for heritable mutations in the BRCA1 and BRCA2 genes

Germline BRCA1/BRCA2 testing should be considered in individuals

- using a mutation prediction score:
    - with breast and/or ovarian cancer whose personal or family history of cancer predicts a combined mutation carrier probability of >10% according to either BOADICEA, BRCAPRO or pathology adjusted Manchester score (combined score of 16 or greater)
    - who are obligate carriers, where the family history meets the above criteria

- who fall into specific categories:
    - with a triple negative breast cancer < age 40 yrs
    - **with an isolated high grade (Grades 2 & 3) invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer < age 70 yrs**
    - **with invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer at any age and a family history* of breast or ovarian cancer**
    - with a personal and/or family history* of breast and/or ovarian cancer, from a population where a common founder mutation exists
    - where a known pathogenic mutation has been identified in a relative

Genetic testing should be considered on the basis of the pre-test probability of identifying a heritable mutation, the false negative rate of the test, the patient's choice and available resources and technology.

Where feasible genetic testing should first be offered to individuals in the family with the highest probability of a mutation.

**The definition of family history used in the AOCS study was "(a) a first degree relative diagnosed with breast cancer at an age younger than 60 years; (b) a first degree relative diagnosed with ovarian cancer at any age; (c) a combination of two of more first degree relatives with breast or ovarian cancer; or (d) a male first degree relative diagnosed with breast cancer at any age."*

Source: Genetic testing for heritable mutations in the BRCA1 and BRCA2 genes 2014 V.3, eviQ Cancer Treatments Online, Cancer Institute NSW, accessed 28 February 2014, https://www.eviq.org.au/Protocol/tabid/66/categoryid/440/id/620/Genetic+Testing+for+Heritable+Mutations+in+the+BRCA1+and+BRCA2+Genes.aspx