



Australian Government

Department of Health

Application 1507:

Germline BRCA mutation testing to determine eligibility for olaparib treatment in patients with metastatic (stage IV) HER2-negative breast cancer

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services. Please complete all questions that are applicable to the proposed service, providing relevant information only. Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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

Component	Description
Patients	<p>Test population</p> <p>Patients with metastatic (Stage IV) human epidermal growth factor receptor 2 (HER2) negative ^a breast cancer who have disease progression:</p> <ul style="list-style-type: none"> • on treatment with either a taxane or anthracycline OR • after treatment with either a taxane or anthracycline <p>AND</p> <ul style="list-style-type: none"> • are refractory to endocrine therapy ^b <p>Patients could have received a taxane or an anthracycline in the neoadjuvant or adjuvant or the metastatic setting.</p> <p>Drug population</p> <p>Those patients above who test positive for a germline BRCA 1/2 mutation (BRCA mutation) will become eligible for olaparib treatment.</p>
Prior tests	<p>Tests required to confirm diagnosis of breast cancer (i.e. biopsy)</p> <p>Tests required to confirm stage of cancer (i.e. mammogram or ultrasound, lymph node assessment, computed tomography, magnetic resonance imaging)</p> <p>Test required to confirm negative for relevant predictive biomarkers: i.e. ER status, PR status, HER2 status</p>
Intervention	<p>Test: Germline BRCA mutation testing</p> <p>Drug: Olaparib treatment for patient found to have a germline BRCA mutation.</p>
Comparator	<p>Test comparator: No testing because BRCA mutation testing is not funded by the Commonwealth for the proposed population.</p> <p>Drug comparator: single-agent standard of care chemotherapy (after first line anthracycline ± taxane chemotherapy. Capecitabine, vinorelbine and eribulin are commonly used agents.</p>

Component	Description
Outcomes	<p>Test outcomes:</p> <ul style="list-style-type: none"> • Analytical performance: sensitivity, specificity, negative predictive value, positive predictive value • Concordance with other commercially available germline BRCA 1/2 mutation platforms and assays • Re-testing rates <p>Drug outcomes</p> <ul style="list-style-type: none"> • Overall survival (OS) • Progression-free survival (PFS) • Health-related quality of life (HRQoL)

^a Either hormone receptor positive or triple negative

^b Or inappropriate for endocrine therapy

Population

The proposed population for germline BRCA 1/2 mutation (BRCA mutation) testing are patients with metastatic (Stage IV) human epidermal growth factor receptor (HER2) negative breast cancer (either hormone receptor positive or triple negative) who have disease progression on or after treatment with a taxane and an anthracycline and are also refractory to or inappropriate for treatment with endocrine therapy. Patients are eligible for germline BRCA testing if they have received an anthracycline and a taxane in either the neoadjuvant or adjuvant or the metastatic setting.

Patients with metastatic HER2-negative breast cancer who test positive for a germline BRCA mutation) and have received prior treatment with anthracycline and taxane and refractory to endocrine therapy (if hormone receptor positive) will become eligible for olaparib treatment

Background

Breast cancer is the most common cancer affecting women in Australia. In 2017, it is estimated that 17,586 women and 144 men will be diagnosed with breast cancer [1]. The risk of being diagnosed with breast cancer increases with age, with 78% of new cases of breast cancer developing in women over the age of 50 years [2]. In 2013, 5% of breast cancer cases were diagnosed in women under 40 years of age.

Breast cancer is staged using the American Joint Committee on Cancer tumour–node–metastases (TNM) staging system for breast cancer [3]. Stage IV or metastatic breast cancer is where the cancer has spread from the original (primary) tumour to distant organs or distant lymph nodes ('distant' cancer) and is detectable by classic clinical or radiographic means or histologically proven to be larger than 0.2mm [4]. Refer to Appendix A and B for further information on the staging of breast cancer.

Although treatable, metastatic breast cancer remains an incurable disease with a median overall survival of about two to three years and a five year survival of only about 25% [5].

Subtypes of breast cancer

Treatment decisions are impacted not only by receptor status/molecular subtype, but also tumour stage and grade, symptoms and patient factors. Determination of the molecular subtype is a standard part of the workup of breast cancer diagnosis as it provides valuable prognostic information and determines the treatment pathway the patient will follow. In general, the expressions of three receptors on the tumour are routinely determined in clinical practice:

- Oestrogen receptor (ER);
- Progesterone receptor (PR);
- HER2.

Only patients with metastatic HER2-negative breast cancer are relevant to this application.

There are two clinical subgroups of patients with metastatic HER2-negative breast cancer:

- Hormone receptor positive, i.e. ER+ and/or PR+; and
- Hormone receptor negative (triple negative) (i.e. negative for ER, PR and HER2).

The majority of breast cancers are HER2-negative/hormone receptor positive (63%) based on histological subtypes; whereas approximately 15% are triple negative [6]. Of note, triple negative breast cancer has been associated with more aggressive disease and worse survival outcomes compared with non-triple negative breast cancer [7]. Therefore, patients with metastatic HER2 negative breast cancer have the largest unmet clinical need.

Treatments for metastatic HER2-negative breast cancer are complex and typically based upon these clinical groups. Briefly, patients with metastatic HER2-negative/hormone receptor positive breast cancer are initially recommended to be treated with endocrine therapy. Patients with metastatic HER2-negative/hormone receptor positive breast cancer who progress and become endocrine refractory and patients with metastatic triple negative breast cancer are recommended to be treated with single-agent, sequential chemotherapy (refer to clinical management algorithm for further detail) [4, 8].

BRCA mutation in breast cancer

BRCA1 and BRCA2 are tumour suppressor genes located on chromosome 17q and 13q, respectively. The BRCA genes encode factors that inhibit cell cycle growth, cell cycle control, gene transcription regulation, deoxyribonucleic acid (DNA) damage repair and apoptosis. People with a germline mutation of a BRCA gene have a higher lifetime risk of cancer, particularly breast and ovarian cancer [9]. For women with a BRCA mutation, the average risk of developing breast cancer by 70 years of age is 57-65% and 45-49% for BRCA1 and BRCA2 mutation carriers, respectively.

Patients with a BRCA1 mutation are predisposed to triple-negative breast cancer whereas BRCA2 mutation predispose patients to hormone receptor positive (specifically (ER+) breast cancer) [10]. The prevalence of germline BRCA mutations in patients with breast cancer (not selected for family history or age at onset) is low, ranging from less than 1% to 7% for BRCA1 and 1-3% for BRCA2 [11].

Mutations of the BRCA1/2 genes can occur along the full length of the coding regions and intronic sequences flanking each exon. The majority of known pathogenic mutations of BRCA1/2 are frameshifts, large deletions, rearrangements, splice-site aberrations, or nonsense changes that result in a truncated or incomplete protein. The function effect of other alterations are not known [12].

BRCA mutations are autosomal dominant, requiring only one mutated copy in the genome to be inherited [13]. A person carrying a BRCA mutation has a 50% chance of passing on the mutation to their biological children. BRCA mutations can be inherited from either the mother or father.

In normal cells, BRCA protein are involved in repairing DNA double-strand breaks by homologous recombination repair. In cells with BRCA mutations, homologous recombination repair cannot be used, therefore other more error-prone pathways are used by the cells [13].

Poly(ADP-ribose) polymerases (PARPs) are a family of proteins that repair single-strand DNA breaks. When this action is inhibited using a PARP inhibitor such as olaparib, PARP-1 and PARP-2 are unable to dissociate from the DNA, blocking the repair of the single-strand break. Unrepaired single-strand breaks stall replication forks and degrade into cytotoxic double strand-DNA breaks. Cells with a BRCA mutation cannot repair these double-strand DNA breaks using homologous recombination. This results in errors, genomic instability that results in cancer cell death. BRCA mutated cells include cells with germline and somatic BRCA mutations [14].

Clinical guidelines for BRCA testing

The applicant referenced the population recommended for BRCA mutation testing in the eviQ 'Guidelines for genetic testing for heritable mutations in the BRCA1 and BRCA2 genes'. The eviQ guidelines recommended BRCA mutation testing in patients with a greater than 10% probability of carrying a mutation based on their personal or family history. This included patients with [15]:

- a BRCA1/2 mutation probability of 10% or more based on a validated mutation prediction tool (such as BOADICEA, BRCAPRO or Manchester score);
- breast cancer diagnosed before age 40 years;
- triple-negative breast cancer (oestrogen, progesterone and HER2-negative) that is:
 - diagnosed before 50 years of age; or
 - has a family history of non-mucinous epithelial ovarian, fallopian tube or primary peritoneal cancer in a first or second degree relative;
- high-grade non-mucinous ovarian fallopian tube or primary peritoneal adenocarcinoma;
- a known BRCA mutation in a relative;
- patients from a population where a common founder mutations exists; or
- a somatic BRCA mutation detected on tumour testing.

Populations where common founder mutations exist include people with Ashkenazi Jewish ancestry [16].

Estimates for the size of the testing population

The estimated incidence of breast cancer is based on the Australian Institute of Health and Welfare (AIHW) projected figures for 2019 [17]. Of these, the proportion of patients diagnosed with metastatic breast cancer was estimated at 7.1% based on Cancer Institute New South Wales (NSW) data [18]. In addition, it was estimated that ~2% of patients with earlier stage disease would progress to metastatic disease (Lord *et al* 2012; [19]). The estimated testing population is presented below.

Table 1: Testing population – incidence of metastatic breast cancer

	Parameter	Estimate
A	Projected new cases of breast cancer (2019)	18,066 ^a
B	Proportion metastatic at diagnosis	7.1% ^b
C	Cases progressing to metastatic disease in 2019	2.02% of cases diagnosed each year between 2015-2019 ^c
D	Total cases of metastatic breast cancer	2,823
E	Proportion HR+/HER2-negative	61% ^d
F	Proportion triple-negative	15% ^d
G	Proportion with prior treatment with anthracycline and taxane and not suitable for endocrine therapy	80% ^e
H	Patients already tested for BRCA mutations	10% ^f
I	Uptake of BRCA test in HR+/HER2-negative population	Year 1 30% Year 2 40% Year 3 50%
J	Uptake of BRCA test in triple-negative population	Year 1 60% Year 2 75% Year 3 80%
K	Eligible HR+/HER2-negative population ($D \times E \times G \times (1-H)$)	1,243
L	Eligible triple-negative population ($D \times F \times G \times (1-H)$)	307
M	Uptake in HR+/HER2-negative population ($K \times I$)	373
N	Uptake in triple-negative population ($L \times J$)	184
O	Total patients taking up BRCA test ($M + N$)	557

HER2 = human epidermal growth factor receptor 2; HR+ = hormone receptor positive; MSAC = Medical Services Authority Council; PSD = Public Summary Document

^a From application

^b Cancer Institute New South Wales data[18]

^c Based on Lord *et al* 2012. 10.1% of non-metastatic breast cancers metastasised over five years

^d Proportions from known Stage IV breast cancer from Howlader *et al* 2014 [6]

^e Assumption based on applicant's internal market research

^f Application 1411.1 MSAC PSD estimated uptake

A proportion of patients who would become eligible for olaparib would have been previously tested for BRCA mutations. Since November 2017, MBS item 73296 was added for the detection of germline BRCA mutations and five other genes for patients with breast or ovarian cancer with a > 10% risk of having a pathogenic mutation based on their clinical and family history, or based on a quantitative algorithm. Consistent with the Public Summary Document for application 1411.1, it was assumed that 10% of patients were already tested under item 73296 [20].

The application estimated that of the patients taking up BRCA mutation testing, approximately 15% would test positive and therefore be eligible for olaparib.

The application stated that the co-dependent MSAC/PBAC submission will include further detailed information to the provided estimates.

Prior test

Patients with metastatic (Stage IV) HER2-negative breast cancer would require prior testing before they can become eligible for BRCA mutation testing. These prior tests include [3, 4]:

- biopsy and imaging (mammogram, ultrasound or magnetic resonance imaging (MRI) to confirm diagnosis of breast cancer,
- molecular diagnostic studies including:
 - immunohistochemical (IHC) evaluation of ER and PR status,
 - IHC or in situ hybridisation to determine HER2 status, and,
 - IHC evaluation of proliferation marker Ki67
- staging workup which is guided by symptoms and may include clinical and ultrasound assessment of lymph nodes, computed tomography (CT), bone scan, x-rays, MRI, and fluorodeoxyglucose positron emission tomography–computed tomography, and
- tests for general health status including full blood count, liver, renal and cardiac function, alkaline phosphatase and calcium level.

Intervention

The applicant is seeking a co-dependent request for MBS listing of germline BRCA mutation testing to determine which patients with metastatic HER2-negative breast cancer who have received prior treatment with an anthracycline and a taxane in either the neo-adjuvant, adjuvant or metastatic setting and are also refractory to, or inappropriate for treatment with endocrine therapy have a germline BRCA mutation, and are therefore eligible for treatment with olaparib.

Germline BRCA mutation testing

Germline BRCA mutations are heterogeneous and can occur on the entire length of the coding regions and intronic sequences flanking each exon. As a result, testing for germline BRCA mutation involves scanning the whole coding region of each gene: 5,500 nucleotides for BRCA1 and 10,200 nucleotides for BRCA2. Over 2,000 variants of BRCA1/2 genes have been reported. These gene variants are classified into five categories according to their pathogenicity probability. These are Class 1, neutral with no clinical significance (<0.1%); Class 2, likely neutral (0.1-5%); Class 3, uncertain (5-95%); Class 4, likely pathogenic (95-99%); and Class 5, pathogenic (>99% probability). Classes 2, 3, and 4 cover likely neutral and likely pathogenic variants. These are referred to as variants of unknown significance (VUS). Germline BRCA1/2 gene variants identified during testing are classified using molecular classification databases [12]. These include National Human Genome Research Institute, Leiden Open Variation Database (LOVD), or National Genetics Reference Laboratory-Manchester (DMuDB)[15]. The PBS restriction for olaparib for the treatment of ovarian cancer require patients to have a germline class 4 or 5 BRCA1 or BRCA2 gene mutation [21].

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 variant are classified as BRCA mutation negative. As a result, the failure to identify a mutation

does not necessarily mean that the gene is normal [22, 23]. The classification of germline BRCA1/2 variants may differ between databases and the number of variants listed differ between databases [24]. The pivotal trial for olaparib (OlymiaAD) included patients with had a confirmed deleterious or suspected deleterious germline BRCA mutation[10].

Delivery

Patients eligible for BRCA testing under the proposed item will be referred to a Genetic Services or Familial Cancer Centre by a medical practitioner, usually a medical oncologist, for a pre-test consultation. This will involve the Genetic Services/Familial Cancer Centre team providing information about genetics, inheritance (family risk) and genetic testing. Patients who proceed with screening will sign a consent form. A blood sample is required to be taken from the patient to assess for germline BRCA testing. Following this, the sample is sent to pathology laboratory where BRCA testing is performed. The expected turnaround time for test results is approximately three to eight weeks.

If a pathogenic BRCA mutation is detected, a face to face post-test counselling appointment with the patient and their family is arranged to deliver the results. If the test detects a VUS or strong family history is present, a face-to- face appointment may also occur.

Germline BRCA mutations can be detected using a variety of methods. Sanger sequencing is the reference standard for detecting BRCA mutations [12]. Next-generation sequencing (NGS), which is also known as massive parallel sequencing, is commonly used in Australian practice. The application stated that the majority (90%) of laboratories are using MiSeq - NGS platform (Illumina). Other platforms in use are Ion Torrent - NGS platform (Life Technologies – Thermo Fisher) and Applied biosystems – Sanger Sequencing (Life Technologies – Thermo Fisher). In the pivotal trial for olaparib (OlymiaAD), 464 participants had their germline BRCA mutation status detected or confirmed using the BRACAnalysis (Myriad Genetics) test and five patients were tested using local testing only [10]. Genetic Technologies Ltd held the exclusive licence in Australia for BRACAnalysis [25].

Regulatory information

The application stated that all molecular pathology service providers that currently perform germline BRCA mutation testing services in Australia use in-house developed testing methods, not commercial test kits. These are classified as in-house developed Class 3 in vitro diagnostic medical devices (IVDs)[26]. Recent reforms to the TGA framework require 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 which set out the requirements relating to the safety and performance characteristics of medical devices [27].

Setting

Currently in Australia, germline BRCA mutation testing is performed by at least eight public and one private pathology laboratories in Australia. A testing centre is available in all states and territories except for the Northern Territory. All states and territories have at least one publically funded

Genetic Service centre available to patients and their families. All pathology laboratories are accredited to the Royal College of Pathologist of Australasia (RCPA) Quality Assurance Programs.

MBS listings for BRCA testing

Currently there are three BRCA mutation testing Items provided on the MBS:

- MBS item 73296 subsidises the detection of germline BRCA mutation testing (and one or more of the following genes STK11, PTEN, CDH1, PALB2, or TP53) for patients with breast or ovarian cancer whose clinical and family history criteria assessed using a quantitative algorithm, place the patient at >10% risk of having a pathogenic mutation.
- MBS item 73297 subsidises the detection of germline BRCA mutation testing (and one or more of the following genes STK11, PTEN, CDH1, PALB2, or TP53) testing for close biological relatives of individuals diagnosed with a pathogenic mutation of one of the aforementioned genes.
- MBS item 73295 subsidises the detection of germline BRCA mutations 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 eligibility for olaparib under the PBS.

Frequency of BRCA mutation testing

Germline BRCA mutations are inherited, therefore only one test is required per lifetime. Detection of a pathogenic germline BRCA1/2 mutation will have implications for family members who may also have a pathogenic BRCA mutation.

Olaparib treatment

Patients with a germline BRCA mutation will be eligible for treatment with olaparib if they have HER2- metastatic breast cancer have received prior treatment with an anthracycline and a taxane and are refractory or inappropriate for endocrine therapy (if hormone receptor positive).

Olaparib is an oral, potent inhibitor of PARP-1, PARP-2 and PARP-3 [28]. These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During this repair process, PARP auto-modifies itself and dissociates from the DNA to facilitate access for other repair enzymes. Olaparib inhibits the action of PARP-1 and PARP-2 by preventing their dissociation, trapping PARP on the DNA and blocking repair of the single-strand break. In replicating cells, this then leads to double-strand DNA breaks. In BRCA1/2 mutated cells, DNA double-strand breaks cannot be repaired by homologous recombination repair and, alternative and error prone pathways are used, resulting in genomic instability and cancer cell death. In the key OlympiAD trial of olaparib treatment in patients with HER2-metastatic breast cancer and germline BRCA1/2 mutation, olaparib increased progression-free survival compared to single-agent chemotherapy[10].

Comparator

Comparator for germline BRCA mutation testing

The applicant stated that the comparator is 'no germline BRCA mutation testing'. This was on the basis that germline BRCA mutation testing was not funded by the Commonwealth for patients with metastatic HER2-negative breast cancer. However, patients considered at high risk for BRCA mutations would be tested under MBS item 73296, as it can be performed as a part of the diagnostic workup (i.e. patients with triple negative breast cancer). The proposed MBS item relevant to this application is likely to be used by patients ineligible for item 73296 who have metastatic breast cancer that was previously treated with an anthracycline and a taxane and are refractory to or inappropriate for further endocrine therapy (if hormone receptor positive). Therefore, no germline BRCA mutation testing is an appropriate comparator.

Comparator for treatment

The application stated the comparator for olaparib treatment is single-agent chemotherapy with either capecitabine, vinorelbine and eribulin. Platinum-based regimens may also be a comparator for the proposed population. The 2017 ESMO Consensus Guidelines stated that a platinum regimen is the preferred option for patients with BRCA-associated triple negative or endocrine-resistant metastatic breast cancer previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting) if not previously administered and no suitable clinical trial is available [8].

Outcomes

Patient relevant

The applicant nominated the following outcomes

Test outcomes

Trial based (evidentiary standard) germline BRCA mutation assay analytical performance

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value

Comparative performance of germline BRCA mutation testing methods

- Concordance with other commercially available germline BRCA mutation platforms
- Concordance with other commercially available germline BRCA mutation assays
- Re-testing rates

Metastatic HER2-negative/hormone receptor positive breast cancer

The 2017 NCCN [4] and 2017 ESMO consensus guidelines[8] recommend endocrine therapy as the preferred first-line treatment option for metastatic HER2-negative/HR positive breast cancer. For post-menopausal women, initial treatment would include:

- aromatase inhibitor (including letrozole with palbociclib or ribociclib), or
- selective oestrogen receptor modulator (SERM), eg. tamoxifen, or
- selective oestrogen receptor downregulator (eg. fulvestrant).

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

The NCCN guidelines recommend trial of a new endocrine therapy following progression unless there is symptomatic visceral disease or no clinical benefit after three endocrine therapy regimens.

Chemotherapy is recommended where there is visceral crisis, immediately life-threatening disease, or concern or proof of endocrine resistance [4, 8]. The preferred single-agents recommended in the 2017 NCCN guidelines [4] were:

- Anthracyclines: doxorubicin (including peglyated liposomal formulation),
- Taxanes: paclitaxel,
- Anti-metabolites: capecitabine and gemcitabine,
- Other microtubule inhibitors: vinorelbine and eribulin.

The 2017 NCCN guidelines also listed several combination chemotherapy regimens for metastatic disease. None of the regimens listed included a combination of both an anthracycline and taxane. Consequently, for patients diagnosed with hormone receptor positive metastatic breast and who have not received prior chemotherapy, olaparib is likely to be a fourth or later line treatment following at least one line of endocrine therapy, a taxane and an anthracycline. Conversely, olaparib may be a first-line treatment for metastatic hormone receptor positive breast cancer if an anthracycline and a taxane were used for adjuvant or neoadjuvant treatment and the cancer was considered endocrine resistant due to rapid disease progression on adjuvant endocrine therapy.

Metastatic triple negative breast cancer

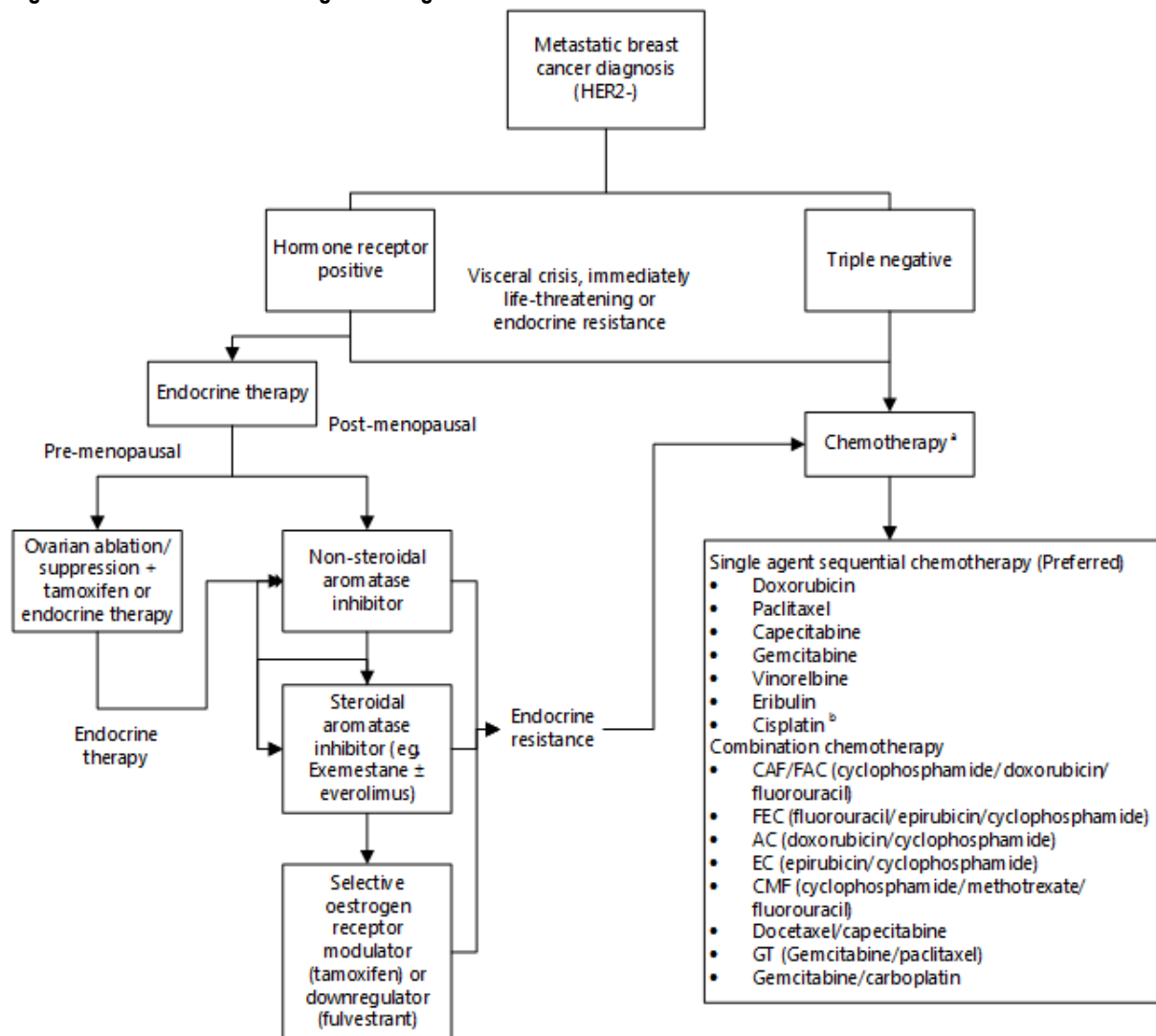
The treatment algorithm for metastatic triple-negative breast cancer was less clear. The 2015 ESMO guidelines for breast cancer state that chemotherapy is recommend for the vast majority of triple-negative breast cancers[3]. The 2017 ESMO guidelines considered platinum-based regimen to be the preferred option for BRCA associated triple negative metastatic breast cancer previously treated with an anthracycline (with or without a taxane) [8]. No specific chemotherapy regimens were recommended for triple-negative metastatic breast cancer in the NCCN guidelines (refer to metastatic hormone receptor positive breast cancer) [4].

Endocrine therapy is also recommended in the 2017 NCCN guidelines for patients with hormone receptor-negative disease localised to the bone or soft tissue only or with asymptomatic visceral disease [4].

For patients diagnosed with metastatic triple-negative breast and who have not received prior chemotherapy, olaparib is likely to be a third or later line treatment following a taxane and an anthracycline. Conversely, olaparib may be a first-line treatment for metastatic triple-negative breast cancer if an anthracycline and a taxane were used for adjuvant or neoadjuvant treatment.

Figure 1 presents the current treatment algorithm for metastatic HER2-negative breast cancer.

Figure 1: Current Clinical Management Algorithm



Source: NCCN Invasive breast cancer guidelines (2.2017)[4] and ESMO 2017 Consensus Guidelines for Advanced Breast Cancer[8]

ESMO = European Society for Medical Oncology; HER-2 = human epidermal growth factor receptor 2; NCCN= National Comprehensive Cancer Network

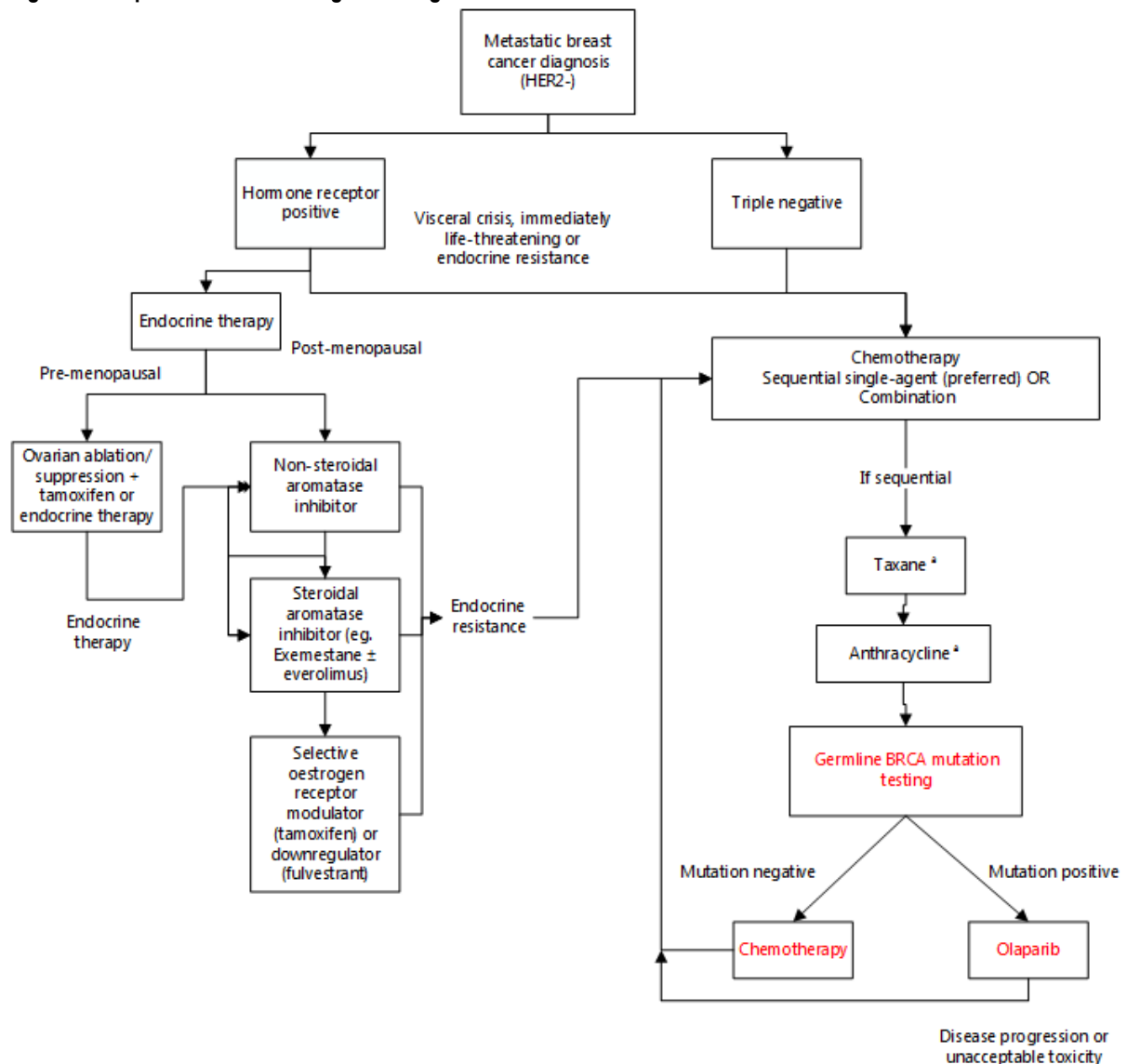
^a Some patients will have received chemotherapy for adjuvant or neoadjuvant treatment. Taxanes may be re-used if there has been at least one year of disease-free survival. Anthracyclines may be re-used if cumulative dose has not been achieved and there has been at least one year of disease-free survival [8].

^b The 2017 ESMO Consensus Guidelines stated that a platinum regimen is the preferred option for patients with BRCA-associated triple negative or endocrine-resistant metastatic breast cancer previously treated with an anthracycline with or without a taxane [8].

Proposed clinical management algorithm for identified population

Figure 2 presents the proposed clinical management algorithm.

Figure 2: Proposed Clinical Management Algorithm



Source: NCCN Invasive breast cancer guidelines (2.2017)[4] and ESMO 2017 Consensus Guidelines for Advanced Breast Cancer[8]

ESMO = European Society for Medical Oncology; HER-2 = human epidermal growth factor receptor 2; NCCN= National Comprehensive Cancer Network

^a Some patients will have received chemotherapy for adjuvant or neoadjuvant treatment. Taxanes may be re-used if there has been at least one year of disease-free survival. Anthracyclines may be re-used if cumulative dose has not been achieved and there has been at least one year of disease-free survival [8].

Proposed economic evaluation

The overall clinical claim is for superiority. The applicant claimed that the proposed co-dependent technology (germline BRCA mutation testing and olaparib treatment) is superior in terms of comparative effectiveness versus the main comparator (no testing and single agent chemotherapy) in patients with metastatic HER2-negative breast cancer (either hormone receptor positive or triple negative) who have a BRCA mutation and received prior treatment with anthracycline and taxane and also refractory to, or inappropriate for treatment with endocrine therapy.

Proposed item descriptor

The proposed item descriptor is provided below.

Category – 6 – PATHOLOGY SERVICES
Detection of germline BRCA 1 or BRCA 2 mutation, in a patient with human epidermal growth factor-2 (HER2) negative metastatic breast cancer who have received prior chemotherapy with anthracycline and a taxane in either the adjuvant or metastatic setting. Hormone receptor positive patient must be refractory or inappropriate for treatment with endocrine therapy. Request for medical service is by a specialist or consultant physician to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime Fee: \$1,200

The application sought either a new item number or an amendment of Item 73295 to include the proposed testing population. The creation of a new item will allow monitoring of utilisation for the proposed population.

Appendices

Appendix A: TNM Classification of breast cancer (abridged)

Parameter	Description
T	Primary tumour
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤ 20 mm or less in greatest dimension
T2	Tumour > 20 mm but ≤50 mm in greatest dimension
T3	Tumour > 50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).
N	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinical detected ^a ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s); or in clinically detected ^a ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s).
M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Source: NCCN Invasive breast cancer guidelines (2017)[4]

NCCN = National Comprehensive Cancer Network; TNM = tumour node metastases

^aClinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration

Appendix B: TNM staging groups for breast cancer (abridged)

Stage	Tumour	Node	Metastases
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1 ^a	M0
	T1	N1 ^a	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
Stage IIB	T2	N2	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Source: NCCN Invasive breast cancer guidelines (2017)[4]

NCCN = National Comprehensive Cancer Network; TNM = tumour node metastases

^aT0 and T1 tumours with nodal micrometastases only are classified Stage IB.

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