1507 Ratified by PASC Chair (25 January 2018)

8 December 2017 PICO Advisory Sub-Committee Meeting

PASC Outcome

Application Number: 1507

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

The purpose of Application 1507 is to seek listing on the Medicare Benefits Schedule for germline (not tumour) *BRCA* mutation (gBRCAm) testing as a codependent service to help determine eligibility for olaparib, in patients with metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

PASC noted the proposal is for either a new item or an amendment to existing item 73295 (for gBRCAm testing to determine eligibility for olaparib maintenance therapy in women with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer).

PASC considered that the following points from MSAC Public Summary Document (PSD) for Application 1380 (resulting in the listing of MBS item 73295) were relevant to this application (1507):

- *MSAC noted the claim of codependence between BRCA testing and olaparib relied on acceptance that BRCA testing predicted important variation in effectiveness of olaparib, distinguishable from prognostic value of BRCA.*
- *MSAC considered the claim of clinical utility to be biologically plausible.*
- *MSAC noted in a pivotal trial (Study 19) that BRCA status was not established prior to randomisation, but interaction testing for BRCA status within each treatment group was statistically significant. This suggested gBRCAm was predictive of better PFS response to olaparib.*
- *Pre-test genetic counselling was not considered mandatory, as BRCA testing was being used for diagnostic purposes and would be arranged by a specialist for the benefit of the individual patient.*
- *MSAC recommended that patients in whom a heritable BRCA mutation was identified should be referred for post-test genetic counselling.*
- *MSAC noted that identification of BRCAm has further implications for a patient's family, but considered this consequence of testing was outside the application's scope.*
- *MSAC noted the economic model is driven by olaparib, rather than BRCA testing.*
  - *Sensitivity analyses which varied the prevalence of BRCAm within the patient population, or varied the sensitivity and specificity of BRCA testing, had little impact upon cost-effectiveness.*
  - *Similarly, reducing the number of BRCA tests carried out by 31%, to account for women who already know their BRCA status from previous testing, did not influence cost-effectiveness.*

PASC also considered that the recent listing of MBS items 73296 (gBRCAm testing in a patient with breast or ovarian cancer with prior >10% risk of pathogenic mutation: rebate $1,200) and 73297 (testing in a relative of a patient with a pathogenic mutation identified: rebate $400) were relevant to this application (1507). PASC anticipated that these items may have increasing impact over time, in terms of the number of women who have already had BRCA1/2 testing before the question arises as to whether they are eligible for olaparib.

Population

PASC noted that the pivotal trial for this application is the Olympiad AD trial.[1]

PASC confirmed that the population is patients with metastatic HER2-negative breast cancer (irrespective of whether estrogen receptor positive (ER+) or progesterone receptor positive (PR+) or triple negative):

- On or after treatment with either a taxane or anthracycline (provided in the neoadjuvant, adjuvant or metastatic setting), AND
- If hormone receptor (HR) positive, who are refractory to endocrine therapy or for whom endocrine therapy is inappropriate.

PASC noted that the aim is to test eligible patients with breast cancer when they are first diagnosed with metastatic disease. PASC noted that the advantage of testing early is to determine subsequent treatment options after the initiation of first-line therapy for metastatic disease. PASC also noted that the current turnaround time for test results is up to eight weeks and suggested that two to four weeks would be more acceptable.

Intervention

PASC confirmed that the intervention is germline *BRCA* mutation testing (once per lifetime) to determine eligibility for olaparib treatment for patients found to have a germline *BRCA* mutation.

PASC noted that prior tests include:

- Biopsy and imaging (mammogram, ultrasound or magnetic resonance imaging (MRI) to confirm diagnosis of breast cancer
- Molecular diagnostic studies including:
  - Immunohistochemistry (IHC) evaluation of ER/PR status,
  - IHC or in situ hybridisation to determine HER2 status
  - IHC evaluation of proliferation marker Ki67
- Staging workup which is guided by symptoms and may include clinical and ultrasound assessment of lymph nodes, CT, bone scan, x-rays, MRI, PET
- Tests for general health status (including full blood count, liver, renal and cardiac function, alkaline phosphatase and calcium level).

Comparators

PASC confirmed that the test comparator is no testing.

PASC considered that patients at higher prior risk for BRCAm may have already been tested under 73296, performed as a part of the diagnostic workup (being BRCA1m is associated with higher risk of triple negative breast cancer), and so the proposed item is likely to be used only by those patients ineligible for item 73296. PASC therefore recommended varying the proportion of patients who will have had prior testing in the sensitivity analyses, noting this proportion will increase over time.

[1] Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. New England Journal of Medicine. 2017;377(6):523-33.

PASC noted that the nominated comparator for olaparib is single-agent standard of care chemotherapy after first-line anthracycline ± taxane chemotherapy. Capecitabine, vinorelbine and eribulin are commonly used agents.

Outcomes

PASC confirmed the following test outcomes**:**

- Analytical performance: sensitivity, specificity, negative predictive value, positive predictive value
- Concordance across commercially available gBRCA1/2m platforms and assays
- Re-testing rates

PASC noted the following health outcomes

- Overall survival
- Progression-free survival (according to RECIST criteria)
- PFS2/death (potential outcome)
- Health-related quality of life (HRQoL)
- Toxicity/treatment-related adverse events (potential outcome)

Clinical management algorithms

PASC requested changing the clinical practice algorithms to reflect the eligible population for testing as confirmed above, ie the eligibility criteria of the Olympiad AD trial. For example, the algorithm should reflect the possibility that the taxane or anthracycline therapy could have been received in the adjuvant or neoadjuvant setting rather than necessarily in the metastatic setting.

PASC also requested changing the proposed clinical management algorithm to reflect the earlier time of gBRCAm testing of patients with metastatic breast cancer to be alongside when first-line chemotherapy or endocrine therapy is initiated in this setting.

PASC also suggested adding a footnote to the algorithms stating that the hormone therapy options may change in the future to reflect the uptake of CDK inhibitors for the treatment of hormone positive, HER2-negative metastatic breast cancer.

MBS item

PASC supported the following proposed descriptor:

Category 6 – Pathology Services
Detection of germline *BRCA1* or *BRCA2* gene mutations, in a patient with human epidermal growth factor 2 (HER2) negative metastatic breast cancer who has received prior chemotherapy with anthracycline or a taxane (unless contraindicated) in either the adjuvant or metastatic setting and, if hormone receptor positive, has also received at least one line of endocrine therapy (unless clinically inappropriate), requested by a specialist or consultant physician, to determine whether eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Maximum one test per lifetime

PASC noted that ‘specialist’ in this setting is intended to be a medical oncologist.

MBS fee

PASC noted that the fee proposed is $1,200, the same as the BRCA1/2 test MBS item 73295, recently listed on the MBS. PASC also noted consultation feedback from RCPA that testing for BRCA1/2 only should be cheaper than the related gene panel test MBS item 73296 (currently also on the MBS at $1,200) due to the fact that it is interpretively less complex.

Economic evaluation

PASC noted the utilisation estimates differ between the Application Form and the Draft PICO Confirmation. The applicant confirmed the estimates in the original application did not account for the proportion with metastatic disease. The applicant indicated the codependent MSAC/PBAC submission in February 2018 would provide further detailed information on the utilisation of both the test and olaparib.

PASC noted the clinical expert comment that there would likely be higher utilisation in the first year, but usage should level off to less than 500 patients per year over time. PASC noted that utilisation of post-test genetic counselling would also increase, although again, this is expected to level off over time.

PASC noted the applicant's claims for superior effectiveness over standard care and for non-inferior safety compared to standard care, and that the appropriate economic evaluation would be a cost-utility analysis.

Consultation feedback

PASC noted supportive responses following targeted consultation from:

- Royal College of Pathologists Australasia (RCPA)
- Breast Cancer Network Australia (BCNA)

Other issues

PASC noted that this test would require informed patient consent, and pathologists performing the test should be aware whether or not this has occurred. PASC suggested options such as including this in the MBS item explanatory notes, and confirmation on the request form could be considered. PASC noted that training for specialists on informed consent issues is currently occurring.

PASC acknowledged that gBCRAm testing is already subsidised, with test performance being high and patient risk being low. PASC noted that, although the projected utilisation still requires confirmation for this population, performance of the test itself is not an issue. PASC discussed the possibility of a streamlined approach, and agreed to refer this to MSAC Executive for advice on proceeding through the assessment phase. Subsequently, MSAC Executive (12 December 2017) agreed to a streamlined codependent submission.