Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1357.1 – F-18 Fluorodeoxyglucose (FDG) positron emission tomography (PET) for the evaluation of breast cancer

Applicant: **Australasian Association of Nuclear Medicine Specialists (AANMS)**

Date of MSAC consideration: **MSAC 74th Meeting, 22-23 November 2018**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) for the evaluation of breast cancer in patients who have locally advanced disease where other imaging does not provide sufficient information to determine appropriate treatment (population 1) and in patients in whom recurrent or metastatic disease is suspected and for whom active therapy is likely to be pursued (population 2) was received from the Australasian Association of Nuclear Medicine Specialists by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding of FDG PET scanning for the evaluation of patients with breast cancer who are considered candidates for active treatment and:

- who have locally advanced (stage III) disease, or
- in whom recurrent or metastatic disease is suspected.

MSAC considered there was reasonable evidence of improved diagnostic accuracy and acceptable cost-effectiveness, with the potential to be cost-saving.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application is a resubmission of Application No. 1357, considered by MSAC at its November 2014 meeting.

The proposed service is FDG PET scanning for the evaluation of breast cancer in patients who have locally advanced disease where other imaging does not provide sufficient information to determine appropriate treatment (population 1) and in breast cancer patients in whom recurrent or metastatic disease is suspected and for whom active therapy is likely to be

pursued (population 2). MSAC noted that this resubmission included a different patient population: the previous patient populations 2 and 3 are now assessed as population 2 in the economic model (as 'suspected recurrent or metastatic disease'). The other PICO items remained the same.

As previously accepted by MSAC, FDG PET is routinely used in conjunction with computerised tomography (CT) and thus MSAC assessed PET/CT as the current standard, rather than standalone FDG PET.

The clinical rationale for using PET/CT to evaluate breast cancer in these populations is that PET is safe, has improved diagnostic accuracy (low false negatives and low false positives), and has clear clinical utility in terms of consequences for changes in use of effective treatments with plausible improvements in health outcomes.

MSAC considered that the cost-utility analysis used in the initial assessment report prepared for the resubmission was unreliable; it partially relied on an assumed ICER of $50,000/QALY for the cost-effectiveness of treatment and worked backwards to obtain implied estimates of the effectiveness of this treatment. Following comments from ESC, a supplementary cost-consequence analysis comparing PET/CT with conventional imaging over a 10-year time horizon was developed (as previously recommended by MSAC), using a decision tree and Markov cohort model and linked evidence approach to measure impacts on health outcomes. As was also previously recommended by MSAC, the cost-consequence analysis also evaluated two scenarios applicable to both populations 1 and 2: the use of PET/CT *in addition to* conventional imaging (when the results of conventional imaging were equivocal – scenario 1); and the use of PET/CT *as a replacement for* conventional imaging (scenario 2). This showed net reduced costs and likely dominance for population 1 in scenario 1 and for both populations in scenario 2. MSAC noted the estimates of net reduced costs were robust despite changes to treatment costs. The revised economic model showed that the expected benefits were driven by the improved diagnostic accuracy of PET/CT leading to more appropriate use of available treatments.

MSAC concluded that these analyses supported scenario 2 over scenario 1, and thus advised against including the proposed requirement for previous equivocal conventional imaging in the proposed item descriptors. MSAC also noted that the evidence of comparative diagnostic accuracy was stronger for scenario 2 over scenario 1. Thus, consistent with scenario 2, MBS-funded PET/CT should be used earlier in the diagnostic pathway than proposed in the application, and should replace, not complement, conventional imaging to realise the greatest cost offsets of using PET/CT in these breast cancer populations.

MSAC noted that the standard wording in similar MBS item descriptors specifies the requesting professional as 'specialist or consultant physician', does not refer to CT, and also does not include a requirement for prior imaging. Therefore, MSAC advised that the item descriptor for proven locally advanced breast cancer (LABC) should be as follows:

> Whole body FDG PET study, where the patient is referred by a specialist or consultant physician, performed for the staging of locally advanced (Stage III) breast cancer in a patient considered potentially suitable for active therapy.
>
> Fee: $953.00 Benefit: 75% = $714.75 85% = $871.30

Similarly, MSAC advised that the item descriptor for suspected local or regional recurrence, or suspected metastatic disease should be as follows:

> Whole body FDG PET study, where the patient is referred by a specialist or consultant physician, performed for the evaluation of suspected metastatic or suspected locally or regionally recurrent breast carcinoma in a patient considered suitable for active therapy.
>
> Fee: $953.00 Benefit: 75% = $714.75 85% = $871.30

MSAC acknowledged that its preference for PET/CT to be used earlier in the diagnostic pathway may require time for clinicians to change their practice. MSAC will communicate to professional bodies for oncologists, radiation oncologists and surgeons to encourage that best practice be switched to replacing conventional imaging with PET/CT in these breast cancer populations.

4. Background

Application 1357 was considered by MSAC at its November 2014 meeting. MSAC did not support public funding of PET/CT for the evaluation of breast cancer because of uncertain clinical effectiveness, cost-effectiveness and financial impact due to weak comparative data and no translation of imaging performance to improved health outcomes.

MSAC considered that any reapplication should include:

- amendments to the descriptor, better definitions of what constitutes standard prior imaging and equivocal prior diagnostic work-up; and to specify specialist referral;
- an amended decision tree to consider earlier use of PET/CT (noting that PET/CT, not stand-alone PET, is the current standard);
- any evidence for a consequential change in clinical management and patient outcomes;
- a cost consequence analysis; and
- a longer time horizon in the economic evaluation.

5. Prerequisites to implementation of any funding advice

It was envisioned that the MBS descriptor for the proposed services would be consistent with the regulations on the MBS for delivering PET services for other diseases (i.e. 'Note DIN Group I4 - Nuclear Medicine Imaging' for MBS items 61523 to 61646).

6. Proposal for public funding

The proposed service is FDG PET scanning for the evaluation of breast cancer in patients who have locally advanced disease where other imaging does not provide sufficient information to determine appropriate treatment (population 1) and in breast cancer patients in whom recurrent or metastatic disease is suspected and for whom active therapy is likely to be pursued (population 2).

Table 1 and Table 2 present the revised item descriptors proposed in the Supplementary Report for the resubmission. Removing the text in italics in these tables changes the proposals from scenario 1 (the use of PET/CT *in addition to* conventional imaging when the results of conventional imaging were equivocal) to scenario 2 (the use of PET/CT *as a replacement for* conventional imaging).
Given that prior testing may comprise one or more of a range of tests (including CT, bone scintigraphy, magnetic resonance imaging [MRI] and ultrasound), the initial assessment

report for the resubmission proposed that a more precise description of prior testing, as requested by MSAC, may not be necessary, and could be left to the discretion of the treating clinician.

Table 1 Proposed MBS item descriptor for PET/CT for proven LABC (i.e. population 1)

Category 5—DIAGNOSTIC IMAGING SERVICES
MBS [item number]
Whole body ^{18}F-FDG PET/CT study, where the patient is referred by a specialist, performed for the staging of locally advanced (Stage III) breast cancer in a patient considered potentially suitable for active therapy*, where prior investigations have provided either equivocal results or findings suspicious for metastatic disease*.*
Fee: $953.00 Benefit: 75% = $714.75 85% = $871.30

* Removing the text in italics changes the proposal from scenario 1 (the use of PET/CT in addition to conventional imaging when the results of conventional imaging were equivocal) to scenario 2 (the use of PET/CT as a replacement for conventional imaging)
Abbreviations: ^{18}F-FDG PET/CT = F-18 fluorodeoxyglucose positron emission tomography//computed tomography

Table 2 Proposed MBS item descriptor for PET/CT for suspected locally or regionally recurrent or suspected metastatic breast cancer (i.e. population 2)

Category 5—DIAGNOSTIC IMAGING SERVICES
MBS [item number]
Whole body ^{18}F-FDG PET/CT study, where the patient is referred by a specialist, performed for the evaluation of suspected metastatic or suspected locally or regionally recurrent breast carcinoma in a patient considered suitable for active therapy*, where prior investigations have provided either equivocal results or findings suspicious for recurrent or metastatic disease*.*
Fee: $953.00 Benefit: 75% = $714.75 85% = $871.30

* Removing the text in italics changes the proposal from scenario 1 (the use of PET/CT in addition to conventional imaging when the results of conventional imaging were equivocal) to scenario 2 (the use of PET/CT as a replacement for conventional imaging)
Abbreviations: ^{18}F-FDG PET/CT = F-18 fluorodeoxyglucose positron emission tomography/computed tomography

7. Summary of public consultation feedback/consumer issues

See Public Summary Document for Application 1357 on the MSAC website.

8. Proposed intervention's place in clinical management

For the purposes of both populations in this resubmission, the alternative scenarios were examined for the positioning of PET/CT in the proposed clinical management algorithm (Figure 1):

- Scenario 1: the use of PET/CT in addition to conventional imaging when the results of conventional imaging were equivocal; and
- Scenario 2 the use of PET/CT as a replacement for conventional imaging.

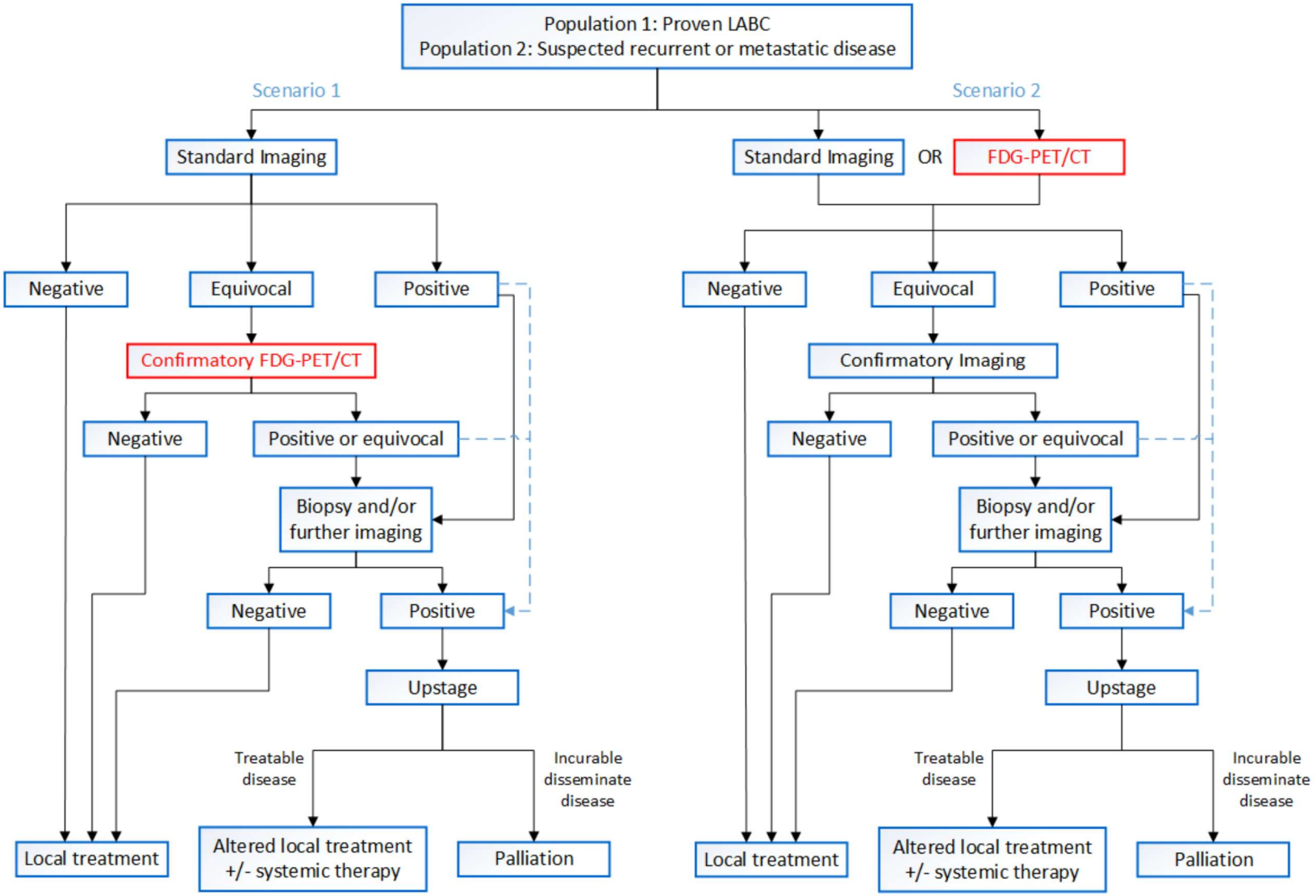

Figure 1 **Proposed clinical management algorithms depicting alternative scenarios for PET/CT in proposed populations for breast cancer**

9. Comparator

The main comparator nominated is standard confirmatory diagnostic imaging (i.e. conventional imaging). This may include a variety of imaging techniques, such as plain radiography, ultrasound, bone scintigraphy (i.e. nuclear medicine), CT and MRI. However, the imaging tests most commonly used for staging breast cancer are CT and bone scintigraphy.

10. Comparative safety

As per the PSD for MSAC Application 1357, MSAC concluded that "PET has been reviewed previously by MSAC on multiple occasions and found to be a safe procedure. The studies included in this assessment did not raise any new safety concerns." Consequently, the resubmission did not seek to provide further assessment of safety of PET/CT.

11. Comparative effectiveness

The resubmission stated that, in the absence of any direct evidence for the effectiveness of PET/CT, effectiveness evidence is presented with a linked approach, considering the evidence for diagnostic accuracy (new k=10), change in management (new k=16) and the expected benefit of changes in treatment on health outcomes. These studies were relevant to Scenario 2 (where PET/CT and conventional imaging are compared as alternatives). The Supplementary Report for the resubmission confirmed that there are no data on the accuracy of alternative confirmatory conventional imaging techniques following equivocal or negative results, i.e. relevant to Scenario 1.

Diagnostic accuracy

The resubmission presented a meta-analysis for the diagnostic accuracy of PET/CT versus conventional imaging in detecting metastatic disease (LABC) or in detecting metastatic or recurrent disease (suspected recurrent or metastatic breast cancer) (Table 3).

Table 3 Overview of diagnostic accuracy in detecting metastatic or recurrent disease by population for PET/CT over conventional imaging

Population	Sensitivity – pooled result [95% CI]		Specificity – pooled result [95% CI]	
	PET/CT	CvI	PET/CT	CvI
Locally advanced BC	97.7 [95.2, 98.9] (k=4)	89.2 [78.6, 94.9] (k=4)	98.4 [96.3, 99.3] (k=4)	94.4 [88.4, 97.4] (k=4)
Suspected recurrent or metastatic BC	96.1 [93.8, 97.5] (k=14)	77.4 [65.9, 85.9] (k=14)	93.8 [87.2, 97.1] (k=14)	89.7 [62.3, 97.8] (k=14)

BC = breast cancer; CvI = conventional imaging; k = number of studies

Therapeutic efficacy (change in clinical management)

The resubmission summarised the results for clinical utility of PET/CT versus conventional imaging (Table 4).

Table 4 Overview of clinical utility results by population for PET/CT over conventional imaging

Population	Locally advanced breast cancer	Suspected metastatic breast cancer, or suspected local or regional recurrence
% change in management, any	Mean: 19.2% Weighted average: 16.6% Median: 18% Range: 6.5–39.5% Number of studies = 9	Mean: 44.8% Weighted average 48% Median: 50% Range: 11–57% Number of studies = 7

For population 1, results from an included Australian study (Ng 2015) reported a change in management of 20.8% after PET/CT in patients with locally advanced breast cancer (population 1) and 57.1% after PET/CT in patients with suspected locally or regionally recurrent or suspected metastatic breast cancer (population 2).

The clinical management changes in LABC were mostly to commence treatment with palliative intent rather than curative intent where metastases were detected, as the more aggressive curative treatment would be futile and more harmful. The clinical management changes in suspected metastatic or recurrent breast cancer were more diverse.

Clinical claim

The proposed clinical claim is that confirmatory PET/CT imaging is superior to confirmatory standard diagnostic imaging in terms of diagnostic accuracy and clinical utility.

12. Economic evaluation

The resubmission's economic evaluation was a cost-utility analysis (Table 5). The structure remained unchanged from the previous submission, however, multiple variables, including accuracy estimates, assumptions regarding the number of repeated imaging tests and the decision impact of results were revised or updated.

Table 5 Summary of the economic evaluation

Perspective	Health care system	
Comparator	Conventional imaging	
Type of economic evaluation	Cost-utility analysis	
Sources of evidence	Linked evidence approach	
Time horizon	10 years	
Outcomes	Cost, LYG, QALY, incremental cost per QALY gained	
Methods used to generate results	Combined decision tree model and Markov cohort model	
Health states[a]	<u>Population 1</u> MET Optimal tx MET Suboptimal tx LOC Optimal tx Dead	<u>Population 2</u> MET Optimal tx MET Suboptimal tx MET Untreated LOC Optimal tx LOC Untreated NO C Untreated Dead
Cycle length	6 months	
Discount rate	5% per annum	
Software package used	TreeAge Pro 2017	

[a] The disease states listed in this summary reflects a combination of the patient's true health status and the treatment they are receiving based on their imaging results.

Abbreviations: MET: Optimal tx: Patient has metastatic disease; correctly identified; treated accordingly; MET: Suboptimal tx: Patient has metastatic disease; local disease identified and treated but metastatic disease is not detected; MET: Untreated: Patient has metastatic disease, no cancer detected, no treatment initiated; LOC: Optimal tx: Patient has local disease; local disease identified and treated; LOC: Untreated: Patient has local disease, no cancer detected, no treatment initiated; NO C: Patient has no disease, no cancer detected, no treatment initiated

However, in response to advice from ESC, supplementary economic analyses presented cost-consequence analyses for the two scenarios:

- Scenario 1: patients in population 1 or population 2 receiving PET/CT when the results of conventional imaging were equivocal – i.e., PET/CT would be an additional test for some patients in these populations; and
- Scenario 2: patients in population 1 or population 2 receiving PET/CT as an alternative staging or diagnostic tool which would replace conventional imaging for all patients in these populations.

Tables 6 to 8 summarise the costs of imaging estimated in the supplementary economic analyses.

Table 6 PET/CT imaging costs (both scenarios)

Parameter	MBS item	Cost
PET/CT	61523	$953.00
Physician consultation (subsequent attendance)	116	$75.50
Total cost		**$1,028.50**

Table 7 Confirmatory conventional imaging costs (scenario 1)

Parameter	MBS item	Cost	Weighted
CT (chest, abdomen, and pelvis)	56807	$560.00	26%
CT (chest)	56307	$400.00	26%
CT (brain)	56007	$250.00	14%
MRI (brain) + MRI (brain - contrast medium)	63001+63491	$448.00	15%
MRI (spine) + MRI (spine - contrast medium)	63154+63491	$403.20	1%
Bone study (for bone scintigraphy) with low dose CT	61425+61505	$700.70	17%
Abdomen ultrasound	55036	$111.30	-
Physician consultation (subsequent attendance) – added to all investigations	116	$75.50	100%
Total average cost			**$550.45**

Table 8 Conventional imaging costs (scenario 2)

Parameter	MBS item	Cost
Computed tomography (chest, abdomen, and pelvis)	56807	$560.00
Bone study (for bone scintigraphy)	61425+61505	$700.70
Abdomen ultrasound – assumed to occur in 50% of cases	55036	$111.30 x 50%
Physician consultation (subsequent attendance)	116	$75.50
Total cost		**$1,336.20**

In the Scenario 1 analyses (Table 9), the economic model determined PET/CT (relative to conventional imaging) to be either cost saving of $277 per patient in population 1 (locally advanced disease) or additional cost of $845 per patient in population 2 (suspected recurrent or metastatic disease).

Table 9 Economic evaluation results for Scenario 1

Model	Item	PET/CT	CI	Increment
Population 1:	Cost	$28,496	$28,773	-$277 (saving)
Proven local cancer	Indicative QALYs	4.903	4.897	0.006
	Indicative $/QALY gained			**Dominant**
Population 2:	Cost	$16,908	$16,063	$845
Suspected recurrent local	Indicative QALYs	3.873	3.829	0.044
or metastatic cancer	**Indicative $/QALY gained**			**$19,205**

CI = conventional imaging; PET/CT = positron emission tomography/computed tomography; QALY = quality-adjusted life year.

In the Scenario 2 analyses (Table 10), the economic model determined PET/CT (relative to conventional imaging) to be cost saving of $1,510 per patient in population 1 (locally advanced disease) and $832 per patient in population 2 (suspected recurrent or metastatic disease).

Table 10 Economic evaluation results for Scenario 2

Model	Item	PET/CT	CI	Increment
Population 1:	Cost	$26,934	$28,444	-$1,510 (saving)
Proven local cancer	Indicative QALYs	4.5998	4.5911	0.0087
	Indicative $/QALY gained			**Dominant**
Population 2:	Cost	$9,138	$9,970	-$832 (saving)
Suspected recurrent local	Indicative QALYs	4.1198	4.0912	0.0286
or metastatic cancer	**Indicative $/QALY gained**			**Dominant**

CI = conventional imaging; PET/CT = positron emission tomography/computed tomography; QALY = quality-adjusted life year.

13. Financial/budgetary impacts

The financial estimates for PET/CT (relative to conventional imaging) are presented in Table 11 for the two scenarios.

Table 11 Estimated utilisation of PET/CT and net financial impact to the MBS

Parameter	2019	2020	2021	2022	2023
Scenario 1 (requiring prior equivocal imaging)					
Proven locally advanced breast cancer (population 1)					
Services for PET/CT imaging	912	929	947	965	982
MBS costs of PET/CT imaging	$869,136	$885,146	$902,300	$919,454	$935,465
Alternative imaging MBS cost offsets	-$427,892	-$435,774	-$444,220	-$452,665	-$460,547
Net cost to MBS of PET/CT imaging	$441,244	$449,372	$458,081	$466,790	$474,918
Suspected recurrent or metastatic breast cancer (population 2)					
Services for PET/CT imaging	2211	2252	2295	2337	2379
MBS costs of PET/CT imaging	$1,926,091	$1,962,544	$1,999,845	$2,036,299	$2,073,176
Alternative imaging MBS cost offsets	-$1,037,167	-$1,056,796	-$1,076,882	-$1,096,512	-$1,116,369
Net cost to MBS of PET/CT imaging	$888,924	$905,748	$922,963	$939,787	$956,807
All eligible patients					
Services for PET/CT imaging	3,123	3,181	3,242	3,302	3,361
MBS costs of PET/CT imaging	$2,795,227	$2,847,691	$2,902,146	$2,955,753	$3,008,641
Alternative imaging MBS cost offsets	-$1,465,059	-$1,492,571	-$1,521,102	-$1,549,177	-$1,576,917
Net cost to MBS of PET/CT imaging	**$1,330,168**	**$1,355,120**	**$1,381,044**	**$1,406,577**	**$1,431,724**
Scenario 2 (no requirement for prior equivocal imaging)					
Proven locally advanced breast cancer (population 1)					
Services for PET/CT imaging	3,041	3,098	3,156	3,215	3,272
MBS costs of PET/CT imaging	$2,649,449	$2,699,636	$2,749,823	$2,801,055	$2,851,242
Alternative imaging (CT/BS) MBS cost offsets	-$3,424,549	-$3,489,418	-$3,554,287	-$3,620,508	-$3,685,377
Net cost to MBS of PET/CT imaging	-$775,100	-$789,782	-$804,464	-$819,453	-$834,135
Suspected recurrent or metastatic breast cancer (population 2)					
Services for PET/CT imaging	9914	10102	10294	10481	10669
MBS costs of PET/CT imaging	$8,638,227	$8,801,714	$8,969,004	$9,132,491	$9,295,979
Alternative imaging (CT/BS) MBS cost offsets	-$11,165,352	-$11,376,668	-$11,592,898	-$11,804,214	-$12,015,530
Net cost to MBS of PET/CT imaging	-$2,527,125	-$2,574,953	-$2,623,894	-$2,671,723	-$2,719,551
All eligible patients					
Services for PET/CT imaging	12,955	13,200	13,450	13,696	13,941
MBS costs of PET/CT imaging	$11,287,676	$11,501,350	$11,718,827	$11,933,547	$12,147,221
Alternative imaging (CT/BS) MBS cost offsets	-$14,589,901	-$14,866,086	-$15,147,185	-$15,424,722	-$15,700,907
Net saving to MBS of PET/CT imaging	**$3,302,225**	**$3,364,736**	**$3,428,359**	**$3,491,175**	**$3,553,686**

CT = computed tomography; PET = positron emission tomography; MBS = Medicare Benefits Scheme
Note: rounding has been applied

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Amendments to the descriptor to give better definitions of what constitutes standard prior imaging and equivocal prior diagnostic work-up; and to specify specialist referral was requested by MSAC	The item descriptors have been amended to include the requirement for specialist referral, and equivocal results for recurrent disease in the descriptor for the use of PET/CT in recurrent and metastatic disease. The item descriptors and fees have also been amended to incorporate the use of CT in conjunction with PET. Defining what constitutes prior standard imaging or equivocal prior diagnostic work-up is difficult because clinicians use a variety of different modalities, and the 2017 National Comprehensive Cancer Network guidelines for breast cancer use the same terminology.
Amended decision tree to consider earlier use of PET/CT was requested by MSAC	Earlier use of PET/CT is difficult to clarify as some form of imaging will always be needed to establish the initial diagnosis of breast cancer and to stage local spread of disease. 'Earlier' might imply replacing conventional imaging with PET/CT as the initial staging modality. Uncertainty remains as to whether PET/CT is intended to be a replacement for conventional imaging or an 'add-on'.
Any evidence for a consequential change in clinical management and patient outcomes was requested by MSAC	Further evidence of change in patient management is provided in the resubmission and included in the linked evidence approach.
A cost-consequence analysis was requested by MSAC	A cost-utility analysis comparing PET imaging with confirmatory standard imaging was provided instead of a cost-consequence analysis. An HTA group was requested to undertake a cost-consequence analysis to give more certainty about the costs resulting from change in management.
A longer time horizon in the economic evaluation was requested by MSAC	The time horizon of the base case cost-utility analysis has been extended to 10 years.
Approach in the contracted assessment for developing the economic model	The model in the contracted assessment, which partially relied on an assumption of $50,000/QALY and working backwards to obtain implied effectiveness of treatment, cannot be relied on directly. The revised cost-utility analysis from the Critique corrected a number of errors in the contracted model, but it too maintained the approach of starting from an assumption of $50,000 per QALY to estimate effectiveness of treatment. Additional work is being undertaken by the HTA group who undertook the Critique.

ESC discussion

ESC noted that Application 1357.1 is a resubmission that proposes MBS listing of FDG PET for the evaluation of breast cancer. MSAC did not support funding at that time due to uncertain clinical effectiveness, cost effectiveness and financial impact caused by weak comparative data, and no translation of imaging performance to improved health outcomes.

ESC noted that FDG-PET imaging is already listed on the MBS for a number of other cancers including lung, colorectal, ovarian and cervical cancers, and melanoma. ESC noted that there is very high public demand for public funding of PET/CT scanning for breast cancer and that the current resubmission is supported by Breast Cancer Network Australia, Cancer Voices Australia, and the Royal Australian and New Zealand College of Radiologists.

ESC noted that over 18,000 new cases of breast cancer are diagnosed each year, and approximately 25–30% of patients will develop recurrent or metastatic disease. Although the five-year cure rate is now around 80%, the relative survival rate decreases to 55% in patients with locally advanced tumours and 18% in patients with metastatic disease. For patients with large tumours, the risk of distant metastasis is 8.3–15%. Precise knowledge of the extent of disease is therefore essential to allow adequate management and prognostic stratification in patients newly diagnosed with breast cancer.

ESC noted that all PET equipment sold in Australia is for PET combined with computed tomography (CT) imaging (PET/CT); PET/CT is the current clinical standard. The application proposes a role for PET/CT in breast cancer patients with locally advanced breast cancer (LABC) where other imaging does not provide sufficient information to determine appropriate treatment, and in patients with suspected recurrent or metastatic disease for whom active therapy is likely to be pursued.

ESC suggested amendments to the MBS item descriptors to include the requirement for specialist referral during evaluation, and equivocal results for recurrent disease in the descriptor for recurrent and metastatic disease. Proposed item descriptors have also been amended to incorporate use of CT in conjunction with PET.

ESC-proposed MBS item descriptor for PET/CT for proven LABC

Category 5—DIAGNOSTIC IMAGING SERVICES
MBS [item number] Whole body ^{18}F-FDG PET/CT study, where the patient is referred by a specialist, performed for the staging of locally advanced (Stage III) breast cancer in a patient considered potentially suitable for active therapy, where prior investigations have provided either equivocal results or findings suspicious for metastatic disease. Fee: $953.00 Benefit: 75% = $714.75 85% = $871.30

ESC-proposed MBS item descriptor for PET/CT for suspected locally or regionally recurrent or suspected metastatic breast cancer

Category 5—DIAGNOSTIC IMAGING SERVICES
MBS [item number] Whole body ^{18}F-FDG PET/CT study, where the patient is referred by a specialist, performed for the evaluation of suspected metastatic or suspected locally or regionally recurrent breast carcinoma in a patient considered suitable for active therapy, where prior investigations have provided either equivocal results or findings suspicious for recurrent or metastatic disease. Fee: $953.00 Benefit: 75% = $714.75 85% = $871.30

ESC noted that defining what constitutes 'standard prior imaging' or 'equivocal prior diagnostic work-up' is difficult as clinicians use a variety of different modalities, and the 2017 National Comprehensive Cancer Network (NCCN) guidelines for breast cancer use the same terminology. ESC noted that, for existing MBS items for PET for other cancers, there is no stipulation requiring that prior investigations have either equivocal results or findings suspicious for metastatic disease.

ESC expressed concerns about leakage beyond the intent of the item descriptor due to repeat imaging to monitor patients or provide reassurance. Leakage could potentially be high for the population with recurrent disease or suspected metastases. ESC suggested it may be useful to analyse the number of times patients with other cancers (e.g. colorectal cancer) receive repeat PET/CT for staging. ESC also considered that such leakage may already be occurring when using conventional imaging to reassure patients and that there is need for clarity about the placement of PET/CT in the clinical algorithm so that item descriptors are written to minimise leakage.

ESC noted that PET/CT is generally used for staging of disease by detecting lesions away from the breast rather than for imaging of breast lesions (although it may be used to assess response to neoadjuvant therapy). Glucose analogues such as ^{18}F-FDG are taken up by higher grade and more aggressive tumours, which are more likely to metastasise.

ESC noted that the comparator in the application is conventional imaging used for initial staging investigations or for restaging in cases of suspected metastatic disease. ESC noted that guidelines from the European Society of Medical Oncology (ESMO) recommend initial investigations with chest X-ray, abdominal ultrasound, CT and bone scan for patients with clinically positive axillary lymph nodes, large tumours or suspicion of metastatic disease. In Australia, the most usual standard or conventional staging imaging would be a combination of CT of the chest/abdomen/pelvis and an isotope bone scan. About a third of patients would also have a liver ultrasound depending on results of pelvic imaging.

ESC noted that PET/CT has better sensitivity and specificity, and both positive and negative predictive value, than conventional imaging (CT and bone scintigraphy) for detecting distant metastases in patients with LABC. In patients with suspected recurrent or metastatic breast cancer, PET/CT was more effective overall that CT alone in correctly identifying patients with or without recurrent or metastatic disease.

ESC noted that it is also essential to assess diagnostic tests such as PET/CT in terms of changes to clinical management and subsequent changes in health outcomes. Based on nine studies, a mean of 15% of patients with LABC had a change in clinical management after FDG-PET/CT. The majority of LABC patients had a change in treatment intent from curative to palliative due to detection of previously unknown metastases. Based on seven studies, a mean of 48% of patients with suspected recurrent or metastatic breast cancer had a change in management after PET/CT. This suggests that a significant proportion of patients with recurrent or suspected metastatic disease would have received inadequate treatment without a change in management resulting from the PET/CT result. ESC also noted results of a study by Cochet et al. (European Journal of Nuclear Medicine and Molecular Imaging, 2014) that compared PET/CT to conventional imaging as the primary staging tool for large breast cancers. In this study, 21% of patients were upstaged following PET/CT (including 8% changed from stage 2 or 3 to stage 4), and 16% were downstaged (including 3% changed from stage 4 to stage 2 or 3).

ESC noted that the clinical management algorithm in the application is outdated and does not reflect current practice in Australia. The most common scenarios for the use of PET/CT in breast cancer patients would be as a supplementary staging procedure if previous standard

imaging (chest/abdomen/pelvis CT and bone scan) were negative or equivocal, and when a patient has persistent systemic symptoms or abnormally raised tumour marker levels (such as CA15-3 or CEA). In this situation a PET/CT scan would be used to either confirm or exclude the presence of metastatic or recurrent breast cancer. The role and use of needle biopsies in this situation would be relatively infrequent. Biopsies of bone, mediastinal lymph nodes and lungs would be rarely undertaken, and in most cases treatment would be based on confirmatory imaging evidence. ESC considered that the costs of biopsies has probably therefore been overstated in the economic evaluation, and with PET/CT predictably less biopsies would be required.

ESC noted the lack of clarity about the placement of PET/CT in the clinical management algorithm. ESC queried whether PET/CT is intended to be a replacement for conventional imaging or an 'add-on', performed either as an alternative at the same point in the clinical pathway or only after conventional imaging. ESC noted that the placement of PET/CT in the pathway is difficult to clarify as some form of imaging will always be needed to establish the initial diagnosis of breast cancer and to stage local spread of disease. Placing PET/CT earlier in the pathway might imply replacing conventional imaging with PET/CT as the initial staging modality. ESC noted that this would have consequences for practice for other cancers as well.

ESC noted a comparison of the MBS costs of conventional imaging and PET/CT:

- Cost of chest/abdomen/pelvis CT (MBS item 56807; $560) plus isotope bone scan (MBS item 61421; $479.80) – total MBS cost of $1039.80
- Cost of chest/abdomen/pelvis CT (MBS item 55074; $560), isotope bone scan (MBS item 61421; $479.80) and abdominal ultrasound (MBS item 55036; $111.30) – total MBS cost of $1151.10
- Proposed MBS cost of PET/CT – $953.

ESC noted potential cost offsets that might apply with use of PET/CT. Conventional imaging can be time-consuming and potential false negative findings could delay therapy, whereas PET/CT involves a single radiological examination, and repeated conventional imaging and some biopsies could be avoided.

ESC noted the following clinical policy issues for MSAC:

- Currently patients with breast cancer either pay for PET scans privately or seek access via the public hospital system. This has been highlighted by the significant amount of correspondence that the Department has received from patients about the high out-of-pocket costs they incur for this service.
- As most patients receive PET/CT as outpatients, MBS listing could potentially result in a significant cost shift from the public to private sector for PET/CT evaluation of breast cancer.
- Consideration could be given to further amending the MBS item descriptor to remove the requirement for prior conventional staging investigations. Would mandating prior imaging effectively virtually double the costs?

ESC noted that a cost-utility analysis comparing PET imaging with confirmatory standard imaging is provided in the resubmission (not the cost-consequence analysis requested by MSAC). ESC reinforced that a cost-consequence analysis would give an informative estimate of the cost associated with the overall changes in clinical management.

ESC noted the concern expressed in the Critique that the method used by the assessment group to derive a key variable for the economic model was inappropriate. ESC noted that the

effectiveness of treatment for inclusion in the model was derived by working backwards from an assumed incremental cost-effectiveness ratio (ICER) of $50,000/QALY and estimated costs of treatment to derive implied outcomes gained and thus create 'treatment-specific hazard ratios which deliver the threshold cost per QALY ratio for treatment'. The cost-utility analysis was revised in the Critique, but maintained the assumption used to infer the extent of benefit of treatment.

ESC also noted that neither the analytical performance comparison for the model informed an assessment of the use of PET/CT earlier in the clinical pathway as requested by MSAC. ESC also noted that there is uncertainty about what constitutes conventional imaging, but most of the analysis was done using a combination of CT and bone scans, which is realistic.

ESC noted that the economic model was a decision tree and Markov cohort model. The original Application 1357 reported the cost per diagnostic error avoided. The resubmission incorporated additional outcomes (cost per biopsy avoided, cost per surgery avoided, cost per delayed biopsy avoided, and cost per QALY). The model used a six-month cycle and extended the time horizon of the base case cost-utility analysis to 10 years as requested by MSAC.

ESC noted that the model used a linked evidence approach, but queried the applicability of the evidence base in which prior equivocal imaging was generally not a prerequisite. This is inconsistent with the proposed placement of PET/CT in the clinical pathway included in the application. ESC noted that accuracy estimates for conventional imaging used as second or third-line confirmatory testing are non-specific and unlikely to be accurate. However, these estimates were maintained in the Critique due to a lack of alternative inputs. ESC noted that increasing the time horizon from 1 year to 10 years, while more realistic, introduces considerable uncertainty into modelled survival and treatment costs, as initial uncertainty is compounded over time.

ESC considered that there is substantial uncertainty in the transformation of modelled survival estimates into QALYs. The Critique model resulted in greater estimated health benefit as the increased accuracy of PET/CT is realised.

ESC considered that utility values are highly uncertain and that much of the uncertainty is not able to be quantified. This is important when interpreting the incremental QALYs and incremental cost-effectiveness ratios generated by the model.

ESC noted that in the Critique model, the ICER is dominant for the population of patients with proven LABC. For the population of patients with suspected recurrent local or metastatic disease, the ICER is $40,454/QALY if the claim of superior accuracy of PET/CT is accepted.

ESC noted that, although the economic data are uncertain, there is evidence for changed management in a significant proportion of patients, so benefit arises from treatment being tailored to an accurate diagnosis. However, ESC queried whether and how changes in treatment have been adequately identified and costed and expressed concern over the accuracy of the estimated costs and cost offsets by the model.

ESC considered that the sensitivity analyses provided in the application were of limited value. However, the sensitivity analyses were not revised in the Critique. ESC noted that the key drivers of uncertainty are survival, utility values and cost offsets.

ESC considered that there was uncertainty around the number of eligible patients with equivocal results of prior imaging. ESC noted that estimates of financial and budgetary

impact were also uncertain. If no cost offsets were realised, the cost to the MBS would be just under $2 million per year.

ESC noted the Department's concerns about leakage resulting from future uptake of PET/CT. According to advice received by the Department from experts, about a third of women would take it up. ESC noted that the Department's re-costing resulted in a cost of $2.4 million per year, not taking into account any extra cost offsets.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The AANMS warmly welcomes MSAC's recommendation that PET/CT for breast cancer receive public funding and urges the Government to accept this recommendation as access to publicly-funded PET for breast cancer will provide a very positive health benefit for Australian patients with breast cancer. We strongly support MSAC's and ESC's recommendations to remove equivocal and prior imaging requirements in order that implementing this service will be cost effective. We also welcome MSAC's agreement that PET/CT should be used earlier in the diagnostic pathway and note MSAC's acknowledgement that it may require time for clinicians to change their practice. In this regard, the AANMS supports MSAC's role in communicating with professional bodies for oncologists, radiation oncologists and surgeons to encourage that best practice be switched to replacing conventional imaging with PET/CT in these breast cancer populations. The AANMS also supports MSAC's project to develop a new approach that moves away from condition based assessment and instead seeks to assess the clinical utility of PET in relation to all fluorodeoxyglucose F18 (FDG) avid tumours, regardless of the origin or site of the cancer (*Proposed streamlining of MSAC assessment of positron emission tomography [PET]*) and will work with MSAC to progress this project. This is a logical approach that acknowledges PET/CT is a proven technology. Importantly this proposed new approach will also support the use of PET/CT for the assessment of patients with rare cancers.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website