Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1406 – ^{18}F-FDG PET for indolent non-Hodgkin's lymphoma

Applicant: **Clinical Associate Professor Judith Trotman**
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Date of MSAC consideration: **MSAC 68th Meeting, 24-25 November 2016**

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

1.   Purpose of application and links to other applications

An application requesting expansion of the current Medicare Benefits Schedule (MBS) item descriptors for ^{18}F-FDG PET/CT for lymphoma by removing the restriction for indolent non-Hodgkin's lymphoma (NHL) was received by the Department of Health from the Concord Hospital, Haematology Department.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness MSAC supported the MBS funding of fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in place of CT for indolent non-Hodgkin's lymphoma for initial staging, assessment of response to therapy and restaging following confirmation of recurrence.

MSAC advised that this item should not be used for surveillance of patients, which was not clinically justified and would significantly increase the frequency of utilisation per patient, and recommended monitoring this item for inappropriate or excessive use and also for co-claiming with other imaging services.

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

^{18}F-FDG PET is a minimally invasive nuclear medicine imaging technique which provides information about function and metabolism that is complementary to the structural information provided by anatomical imaging techniques such as x-ray computed tomography (CT). The use of ^{18}F-FDG PET combined with CT for anatomic correlation and attenuation correction (hereafter referred to as PET/CT) is considered as current standard of care and has replaced stand-alone ^{18}F-FDG PET in Australia. PET/CT is currently reimbursed through the MBS for 20 oncology indications including multiple listings for NHL.

NHL can be divided into indolent, aggressive or highly aggressive lymphomas, based on their natural history of progression. Indolent NHLs progress slowly, reflected in the measurement of survival of untreated disease in years. Follicular lymphoma is the most common sub-type of indolent NHL, accounting for 22% of people diagnosed with NHL in Australia in 2012.

PET/CT is currently reimbursed for stage I or IIA indolent NHL scheduled for definitive radiotherapy with curative intent (MBS item 61616). An additional four items for PET/CT studies for Hodgkin's lymphoma or NHL are also reimbursed — MBS items 61620, 61622, 61628 and 61632 — however, the item descriptors explicitly exclude indolent NHL. MSAC noted that this application seeks to expand the current MBS item descriptors for PET/CT for lymphoma by removing the restrictions for indolent NHL.

MSAC noted that the proposed clinical management algorithm recommends use of PET/CT in indolent NHL:
- in addition to and/or replacement for conventional staging in initial staging;
- as replacement for conventional imaging in restaging relapsed indolent FDG-avid NHL; or
- as replacement for CT± bone marrow aspiration and trephine (BMAT) to assess response of FDG-avid indolent NHL to first-line treatment.

While a number of tests are used in those who are newly diagnosed or have experienced a relapse and require staging of the disease, CT is the key test to which PET/CT would add additional information. For patients who require assessment of response to treatment, the comparator is CT with or without BMAT.

MSAC recalled that PET/CT had been previously reviewed by the Committee on multiple occasions and found to have acceptable safety. MSAC noted that no new safety concerns were raised by the studies included in the current assessment.

MSAC noted that no direct evidence to support the effectiveness of PET/CT in indolent NHL was identified. Instead, a linked evidence approach was adopted, with information provided on the comparative diagnostic performance, prognostic evidence, therapeutic efficacy and therapeutic effectiveness of the proposed imaging.

Evidence on comparative diagnostic performance (accuracy) was reviewed for the three scenarios for the use of PET/CT outlined in the proposed clinical management algorithm. MSAC accepted that very low quality evidence suggests that:
- PET/CT as a replacement test to CT would detect additional sites of disease not detected by CT in initial staging and restaging; and
- PET/CT as a replacement test to CT detects more true responders to treatment than CT (increase in sensitivity of 48%), but may also misclassify more patients as responders to treatment (decrease in specificity of 11%) with PET/CT likely to be a superior test overall.

MSAC noted that one comparative prognostic study of PET/CT compared to CT was identified (Trotman J et al 2014). The study was a pooled analysis of 246 centrally reviewed PET/CT scans from patients enrolled in three follicular lymphoma trials. PET/CT results were dichotomised, however CT-based response assessment was not; therefore, it was difficult to directly compare the two tests.

Response to treatment based on PET/CT was predictive of both progression free and overall survival. While not directly comparable, due to the exclusion of patients with progressive and

stable disease, response to treatment based on CT was weakly predictive of progression free but not overall survival. In multivariate analysis, PET/CT based response remained more predictive than CT based response.

MSAC considered the evidence of the impact PET/CT on clinical management. Two studies were identified that reported a change in patient management as a result of having undergone PET/CT at initial staging of indolent NHL (Scott AM et al 2009, Fulham MJ et al 2006). No studies reporting on changes in clinical management following PET/CT as a replacement in restaging or assessing response to first line treatment in indolent NHL were identified. MSAC noted that two randomised controlled trials of PET/CT response-adapted therapy were ongoing.

MSAC noted that, while it was assumed that the use of PET/CT for the three scenarios outlined in the clinical management algorithm would result in health benefits from changes in management, there was no direct evidence identified to support this assumption.

Overall, MSAC accepted that while the evidence base for clinical effectiveness was weak it was unlikely to improve as indolent NHL was an uncommon cancer.

MSAC considered the cost-consequence analysis undertaken from the economic evaluation. MSAC noted that the effect of PET/CT on upstaging was chiefly informed by a multicentre study of follicular lymphoma (Luminari S et al 2013), and that change of stage was used as a proxy for change in management. However, MSAC was concerned that many of the assumptions in the model were informed by expert opinion. The model indicated that if PET/CT were to replace CT in patients with indolent NHL the cost per patient would be $10.02 less. If PET/CT were to be used in addition to CT, the additional cost was estimated to be $549.98. The cost of PET/CT and the cost of CT were noted as key drivers of the model along with the proportion of asymptomatic patients, with MSAC considering the figure used for the latter to be a conservative estimate.

MSAC noted that, if the economic model were accepted, PET/CT may be modestly cost-saving to the MBS, but may modestly increase costs to the PBS due to increased use of immunochemotherapy. MSAC considered that there were multiple areas of uncertainty in the financial estimates, but noted that the impact of this was likely to be small given that indolent NHL is a uncommon cancer.

MSAC noted that epidemiological estimates of utilisation compared with current MBS item utilisation indicate that providers may have different interpretations of existing items for NHL. MSAC acknowledged that such differences may lead to inequity in patient access. MSAC also noted that the prognostic information provided was of value to patients and may have an important impact on quality of life and societal costs. MSAC considered that this information may be of particular importance in a disease which tends to affect people in late middle age and often has a long clinical course.

MSAC noted that amendment of the MBS item descriptors of 61620, 61622, 61628 and 61632 to remove the indolent NHL restrictions would make item 61616 redundant. MSAC was concerned that broadening of the item descriptors could lead to over-use and recommended that the descriptors be worded to deter unnecessary scans. MSAC noted that the item descriptor should reflect the intent that PET/CT replace CT for FDG-avid NHL rather than being used in addition to CT. MSAC recommended that consideration be given to the framework required to monitor the use of these items. MSAC foreshadowed that this

would include a review of co-claimed PET/CT and CT items and sequencing of claims to ensure that such imaging is not being used together unnecessarily.

MSAC suggested the Department consider assessment of PET in oncology as a modality, similar to the review of Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT) to treat cancer, rather than by separate indications which is likely to provide a weaker evidence base.

4.   Background

FDG PET has been considered by MSAC previously for other indications, including NHL.

5.   Prerequisites to implementation of any funding advice

Several PET, PET/CT and PET/MRI machines and related software are registered on the ARTG, as is the radiopharmaceutical, FDG. Radiolabelled FDG is available commercially and is also currently produced at several Australian hospitals.

To be eligible for a MBS rebate, the medical service must be requested by a recognised specialist or consultant physician, consistent with other PET items.

6.   Proposal for public funding

Proposed MBS item descriptors, based on simplifying the existing lymphoma items, are listed in Table 1.

Table 1 Proposed MBS item descriptors

Category 5 – Diagnostic imaging services
61616 - Replaced by 61620
61620 Whole body FDG PET study for the initial staging of newly diagnosed or previously untreated Hodgkin's or non-Hodgkin's lymphoma. (R) Bulk bill incentive Fee: $953.00 Benefit: 75% = $714.75 85% = $873.50
61622 Whole body FDG PET study to assess response to first line therapy either during treatment or within three months of completing definitive first line treatment for Hodgkin's or non-Hodgkin's lymphoma, (R) Bulk bill incentive Fee: $953.00 Benefit: 75% = $714.75 85% = $873.50
61628 Whole body FDG PET study for restaging following confirmation of recurrence of Hodgkin's or non-Hodgkin's lymphoma. (R) Bulk bill incentive Fee: $953.00 Benefit: 75% = $714.75 85% = $873.50
61632 Whole body FDG PET study to assess response to second-line chemotherapy when stem cell transplantation is being considered, for Hodgkin's or non-Hodgkin's lymphoma. (R) Bulk bill incentive Fee: $953.00 Benefit: 75% = $714.75 85% = $873.50

7. Summary of Public Consultation Feedback/Consumer Issues

Consumer impact statements supported the impact of PET/CT response assessment on patient quality of life; however, no published evidence was identified. Three consumer impact statements were included in the assessment which relate to the value of PET/CT assessment of treatment response. The prognostic information provided by PET/CT may assist patients make major life decisions, such as whether to continue to work, and may assist them to live with a disease which is both incurable and indolent.

8. Proposed intervention's place in clinical management

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of over 40 different histological sub-types of lymphoid malignancies that originate in B-lymphocytes, T-lymphocytes or natural killer (NK) lymphocytes with a wide spectrum of disease manifestations, therapies and prognoses. NHL can be divided into indolent, aggressive or highly aggressive lymphomas, based on their natural history of progression. Indolent NHLs tends to progress slowly and the survival of untreated disease is usually measured in years.

NHL is the 5th most prevalent cancer in Australia with 30,646 people diagnosed in the past 26 years still alive at the end of 2007 (Australian Institute of Health and Welfare 2016b).

The proposed patient population for this assessment are those who have already been diagnosed with indolent NHL and who are either:
  a)   newly diagnosed or relapsed and require staging or restaging of the disease or
  b)   require assessment of response to treatment.

The following types of lymphoma were considered as indolent for this assessment:
- Follicular lymphoma (accounting for ~70% of indolent NHL)
- Nodal marginal zone lymphoma
- Small lymphocytic lymphoma (excluding any features of CLL).

The proposed clinical management algorithm is presented in Figure 1.

PET/CT is already funded for staging of stage I-IIA indolent NHL. The proposal is to expand this to allow for staging of all newly diagnosed and relapsed indolent NHL: compared to staging without PET/CT, this would provide
1. More accurate staging
2. A baseline for post-treatment PET/CT interpretation.

PET/CT is funded for the assessment of response to treatment in aggressive but not indolent NHL. The proposal is to expand this indication to allow for assessment of response to treatment in indolent NHL: compared to response assessment without PET/CT, this would provide
- more accurate assessment of treatment effectiveness
- simpler, less invasive and more reproducible assessment of treatment response
- improved prognostic information.

Treatment intensification or de-escalation based on PET/CT response assessment is also possible and currently being assessed in clinical trials.

Figure 1   Proposed clinical management algorithm for the use of PET-CT in (1.) the initial and subsequent staging of (orange) and (2.) the assessment of response to treatment (purple) in indolent lymphoma
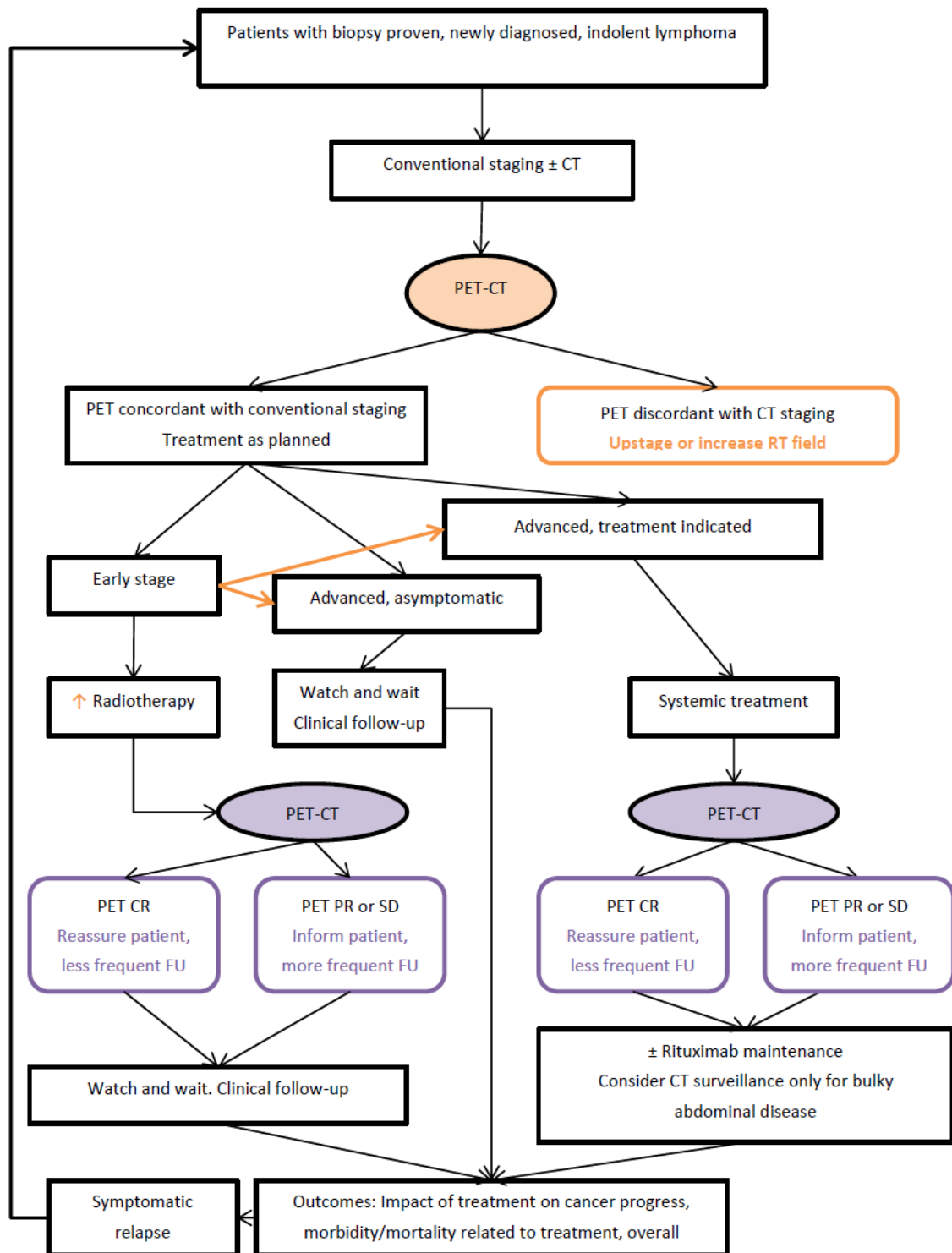
Where there is discordance between the PET and CT staging, the changes marked in orange may occur (increase in RT field or upstaging). Where there is no discordance then these pathways will not occur.

9.   Comparator

For patients who are newly diagnosed or relapsed and require staging of the disease, the comparator is prior tests alone. These prior tests usually include:
- Physical examination

- Laboratory studies (i.e. full blood counts, β2-microglobulin, lactate dehydrogenase, liver function tests)
- ± contrast enhanced CT (neck, chest, abdomen, pelvis)
- ±MRI
- Biopsy (bone marrow, lymph node, or organ with suspected lesions).

Computed tomography (CT) is the key test to which PET/CT would provide additional information. For initial staging, PET/CT could replace CT in some patients given the latter test is incorporated in the former.

For restaging and assessment of response to treatment, PET/CT is proposed to replace stand-alone CT for lymphomas which have been shown to be FDG-avid on initial staging.

BMAT is a bone marrow biopsy in which both aspirate (liquid) and trephine (sections) are examined. PET/CT could replace BMAT in assessment of response to treatment for those patients with bone marrow involvement.

The reference standard for all tests was specified in the PICO confirmation as pathology, or clinical follow-up (≥6 months). This is an imperfect reference standard.

10. Comparative safety

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.

11. Comparative effectiveness

Accuracy
A reliable and feasible reference standard is not available for PET/CT imaging, and therefore all studies are at some risk of bias. The reference standard is usually differentially applied based on the test results (positive tests undergo histopathology or directed conventional imaging and negative tests have follow-up for disease progression) leading to verification bias. Furthermore, any histopathology or further imaging is directed based on the positive test result, leading to incorporation bias.

PET/CT in addition to conventional staging in the initial staging of indolent NHL
Three studies (Adams et al. 2013; Lee et al. 2015; Perry et al. 2016) reported the incremental accuracy of PET/CT over bone marrow biopsy (BMB) in patients with indolent NHL. The studies were small and used different positivity thresholds. PET/CT identified additional lesions in 16-36% of patients who were negative on BMB. The number of these additional lesions which were true positive ranged from 15% to 100% (Table 2).

PET/CT as a replacement for conventional imaging in the initial staging of newly diagnosed NHL and the restaging of relapsed indolent NHL
One study (Fueger et al. 2009) reported the accuracy of PET/CT compared to CT for a mixed population of patients undergoing both staging and restaging. For the detection of nodal regions on a per lesions basis, PET/CT was found to have the same specificity as CT (0.98, 95% CI: 0.97-0.99) and a higher sensitivity than CT (PET/CT 0.77, 95% CI 0.69-0.84 versus CT 0.54, 95% CI: 0.45-0.63) (Table 2   Summary of findings for the accuracy of PET/CT relative to CT±BMAT, in patients with indolent NHL). The study used dual modality PET/CT scans and compared the fused PET/CT data with the CT component alone and is therefore not an ideal study design.

PET/CT as a replacement for CT ±BMAT in the assessment of response to first line treatment in indolent NHL

One study (Le Dortz et al. 2010) reported the accuracy of PET/CT compared to CT for the assessment of response to therapy. The study found PET/CT to have higher specificity than CT (1.00 [95% CI: 0.87-1.00] versus 0.52 [95% CI 0.32-0.71]) and lower sensitivity (0.72 [95% CI: 0.47-0.90] versus 0.83 [95% CI: 0.59-0.96]) (Table 2   Summary of findings for the accuracy of PET/CT relative to CT±BMAT, in patients with indolent NHL). The study was small, did not specify the reference standard and did not provide clear data for the calculation of sensitivity and specificity. The specificity and sensitivity values reported in the paper differ from those calculated based on the evaluators' interpretation.

Table 2   Summary of findings for the accuracy of PET/CT relative to CT±BMAT, in patients with indolent NHL

Clinical question	Number of participants (number of studies)	Summary accuracy PET/CT [95% CI]	Summary accuracy CT [95% CI]	Quality of evidence	Comments
PET/CT in addition to conventional staging (CT±BMAT) for newly diagnosed indolent NHL	130 (3)	Additional lesions detected in 16 to 36% of patients with negative BMB. PPV of additional lesions ranged from 0.15 [0.04-0.36] to 1.00 [0.22-1.00]	NA	⊕⊙⊙⊙	Different positivity thresholds for PET/CT Poor reporting in one study Reference standard not well defined High variability in findings
PET/CT as a replacement to CT for staging newly diagnosed and relapsed indolent NHL	45 (1)	specificity 0.98 [0.97-0.99] sensitivity 0.77 [0.69-0.84]	specificity 0.98 [0.97-0.99] sensitivity 0.54, [0.45-0.63]	⊕⊙⊙⊙	Per lesion data Incorporation of CT scan into PET/CT scan A single small study
PET/CT as a replacement to CT for assessment of response to treatment in indolent NHL	45 (1)	specificity 1.00 [0.87-1.00] sensitivity 0.72 [0.47-0.90]	specificity: 0.52 [0.32-0.71] sensitivity 0.83 [0.59-0.96]	⊕⊙⊙⊙	Reference standard not defined Poor reporting A single small study

[a] GRADE Working Group grades of evidence (Guyatt et al. 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Prognosis

PET/CT as a replacement for CT ±BMAT in the assessment of response to first line treatment in indolent NHL

One comparative prognostic study (Trotman et al. 2014) was included. It was a pooled analysis of 246 centrally reviewed PET/CT scans from patients enrolled in three follicular lymphoma trials.

PET/CT results were dichotomised but CT based response assessment was not; therefore, it is difficult to directly compare the two tests. Response to treatment based on PET/CT was

predictive of both progression free (HR 3.9 (95% CI: 2.5-5.9), p<0.0001) and overall survival (HR 6.7 (95%CI: 2.4-18.5), p=0.0012) (
Table 3). Response to treatment based on CT was weakly predictive of progression free (HR 1.7 (95% CI 1.1-2.5), p=0.017) but not overall survival (HR 1.4 [95% CI 0.4-4.6], p=0.58.

In multivariate analysis, PET/CT based response remained more predictive than CT based response.

Table 3   Summary of results for the prognostic value of PET/CT compared with CT in the assessment of response to treatment

Test	Category	n (%)	4-year PFS [95% CI]	HR [95% CI]	4-year OS [95% CI]	HR [95% CI]
PET/CT	Negative	205 (83%)	63.4% (55.9-70.0)	-	97.1% (93.2-98.8)	-
-	Positive	41 (17%)	23.2% (11.1-37.9)	3.9 (2.5-5.9), p<0.0001	87.2% (71.9-94.5)	6.7 (2.4-18.5), p=0.0012
CT	CR & CRu	168 (70%)	63.1% (54.7-70.4)	-	96.8% (92.5-98.7)	-
-	PR	62 (26%)	49.4 (35.9-61.5)	1.7 (1.1-2.5), p=0.017*	95.9 (83.9-99.0)	1.4 (0.4-4.6), p=0.58*
-	PD & SD	10 (4%)	12.5 (0.7-41.8)	-	62.5 (22.9-86.1)	-

* HR for CR/CRu vs PR (CR: complete response; CRu: complete response, unconfirmed; PR: partial response; SD: stable disease [International Workshop Criteria, 2009])

Therapeutic efficacy (change in management)

PET/CT in addition and/or replacement to conventional staging in the initial staging of indolent NHL

Two Australian studies were included based on post-hoc inclusion criteria. The prospective Australian data collection study (Scott et al. 2009) reported a change in management plan in 34% of patients (95% CI: 24-45%). A change from radiotherapy to chemotherapy was documented in 6/74 (8%) and from observation to chemotherapy in 4/74 (5%). A change from chemotherapy to observation was documented in 2/74 (3%) and from radiotherapy to observation in 4/74 (5%). This study was considered in the MSAC Ref. 35c Assessment Report.

The second Australian study reported that 27/39 (69%) of patients who were upstaged had a change in management but details of the management change were not reported (Fulham et al. 2006 – abstract only).

PET/CT as a replacement for conventional imaging in the restaging of relapsed indolent NHL

No studies were identified which reported on changes in clinical management following restaging of clinically suspected disease relapse in patients with indolent NHL.

PET/CT as a replacement for CT ±BMAT in the assessment of response to first line treatment in indolent NHL

No studies were identified which reported on changes in clinical management following PET/CT response assessment in indolent NHL. Two ongoing randomised controlled trials of PET/CT response-adapted therapy were identified.

Therapeutic effectiveness (health benefit from change in management)

PET/CT in addition and/or replacement to conventional staging in the initial staging of indolent NHL

In order to make a case for the effectiveness of PET/CT in initial staging of patients with indolent NHL (particularly stage III-IV), it must be assumed that in selected patients who have additional disease detected and consequently a change in the duration and/or intensity and/or combination of chemotherapy, the improvements in progression free and overall survival will outweigh the side effects of intensified chemotherapy.

Where PET/CT is used during staging merely to provide a baseline scan for comparison with a post-treatment PET/CT scan, it is not intended to influence initial management or thereby to alter patient outcomes. Although MSAC noted that the initial PET can influence management by:

- More accurate definition of active disease extent for involved-site RT in Stage I-IIa disease (the current intent of 61616);
- Upstaging of apparent Stage I-II disease to Stage III-IV disease, in which case "curative" RT would not be indicated and systemic Rx (immunochemotherapy) would be applicable to symptomatic patients (GELF criteria).

PET/CT as a replacement for conventional imaging in the restaging of relapsed indolent NHL

There was insufficient evidence to determine the effectiveness of restaging PET/CT in modifying therapy.

Where restaging PET/CT is used merely to provide a new baseline scan for comparison with a PET/CT scan following maintenance or intensification of treatment, it is not intended to influence initial management or thereby to alter patient outcomes.

PET/CT as a replacement for CT ±BMAT in the assessment of response to first line treatment in indolent NHL

The following differences between PET/CT response assessment and CT ±BMAT response assessment are proposed to improve patient quality of life:

- non-invasive compared to BMAT
- dichotomous output, replacing multiple CT categories based on size of mass
- less complex and therefore more reproducible than CT assessment
- metabolic response (PET/CT) more sensitive, and therefore more predictive, than anatomical response (CT).

In order to make a case for the clinical effectiveness of PET/CT for response assessment using a linked evidence approach, the following assumptions must be made:

- the initiation of PET/CT response-adapted maintenance therapy as currently being tested in clinical trials would also translate to routine clinical practice, and a proportion of these patients would not have undergone such a management change if response assessment had been based on conventional assessment alone; and

- PET/CT response-adapted maintenance therapy will improve PFS and OS, and those benefits will outweigh the morbidity (and associated quality of life detriments) and mortality associated with escalated therapy.

12. Economic evaluation

PET/CT is considered to have non-inferior safety and uncertain effectiveness compared to the comparator. A cost-consequence analysis was undertaken for the economic evaluation (Table 4).

Table 4 Summary of the economic evaluation

Perspective	Healthcare
Comparator	CT
Type of economic evaluation	Cost-consequence
Sources of evidence	Systematic review, clinical opinion
Time horizon	Max: 27 months
Outcomes	Costs
Methods used to generate results	Decision-analytic model
Discount rate	N/A
Software packages used	Microsoft Excel 2010

Key structural assumptions of the model are:
- That all stage I-II indolent NHL patients currently receive staging PET/CT
- That a change in stage at initial staging will result in a change in management
- That PET/CT based assessment of treatment response will result in a different follow-up schedule to CT based assessment of treatment response
- Relapsed indolent NHL (staging and response assessment) is not included in the model.

The overall costs, and incremental costs as calculated for the testing strategy and comparative testing strategy in the model, and using the base case assumptions, are shown in Table 5 assuming replacement of CT at initial staging by PET/CT and in Table 6 assuming addition of PET/CT to CT at initial staging.

Table 5   Implications for the base case economic evaluation of applying the results of the clinical evaluation (PET/CT in replacement of CT)

	PET/CT	CT	Incremental Cost
Staging			
Immuno-chemotherapy	$5,906.11	$5,864.35	$95.76
Radiotherapy	$1,537.91	$1,645.70	-$107.79
Watch & Wait	$906.99	$686.11	$220.89
Total	$8,404.90	$8,196.05	$208.84
Response to Treatment			
Immuno-chemotherapy	$333.29	$552.16	-$218.86
Radiotherapy	$0.00	$0.00	$0.00
Watch & Wait	$0.00	$0.00	$0.00
Total	$333.29	$552.16	-$218.86
Total			
Immuno-chemotherapy	$6,293.41	$6,416.51	-$123.10
Radiotherapy	$1,537.91	$1,645.60	-$107.79
Watch & Wait	$906.99	$686.11	$202.89
Total	**$8,738.19**	**$8,748.21**	**-$10.02**

Table 6 **Implications for the base case economic evaluation of applying the results of the clinical evaluation (PET/CT in addition to CT)**

	PET/CT	CT	Incremental Cost
Staging			
Immuno-chemotherapy	$6,082.82	$5,864.35	$218.47
Radiotherapy	$1,673.81	$1,645.60	$28.22
Watch & Wait	$1,208.27	$686.11	$522.16
Total	$8,964.90	$8,196.05	$768.84
Response to Treatment			
Immuno-chemotherapy	$333.29	$552.16	-$218.86
Radiotherapy	$0.00	$0.00	$0.00
Watch & Wait	$0.00	$0.00	$0.00
Total	$333.29	$552.16	-$218.86
Total			
Immuno-chemotherapy	$6,416.11	$6,416.51	-$0.40
Radiotherapy	$1,673.81	$1,645.60	$28.22
Watch & Wait	$1,208.27	$686.11	$522.16
Total	**$9,298.19**	**$8,748.21**	$549.98

The modelled results were most sensitive to the prevalence of asymptomatic patients, as these patients receive observation rather than immuno-chemotherapy, and the proportion of patients with stage I-II disease who are treated with immuno-chemotherapy (which is determined by the proportion with bulky disease)(Table 7).

Table 7 **Key drivers of the economic model**

Description	Method/Value	Estimate	Impact
Prevalence of asymptomatic patients	72.5% (58% to 87%)	High	Base case parameter favours CT
Proportion of Stage I/II patients treated with immunochemotherapy	21.3% (17% to 25.5%)	High	Base case parameter favours CT
Cost of PET/CT	$953 ($762.40 to $1143.60)	Low	Base case parameter favours PET/CT
Cost of CT	$560 ($448 to $672)	Low	Base case parameter favours CT
Proportion of Patients in Stage I/II	33% (26.4% to 39.6%)	High	Base case parameter favours PET/CT
Proportion of PET/CT Patients who upstage	10.8% (8.6% to 13%)	Low	Base case parameter favours CT
Proportion of Patients with Rituxumab Maintenance	50% (40% to 60%)	High	Base case parameter favours CT
Cost of Radiotherapy	$5377.9 ($4302.32 to $6453.48)	Indifferent	-
Cost of Immunochemotherapy	$20195.81 ($16156.64 to $24234.97)	Low	Base case parameter favours CT
Proportion of PET/CT patients who respond to treatment	83.3% (66.6% to 100%)	Unknown	Unknown

Description	Method/Value	Estimate	Impact
Cost of Observation (CT PR)	$2616.5 ($2093.20 to $3139.80)	Indifferent	-
Proportion of PET/CT Patients who downstage	3.6% (2.9% to 4.3%)	Unknown	Unknown
Cost of Observation (CT CR)	$1410.50 ($1128.40 to $1692.60)	Indifferent	-
Proportion of CT with Complete Response	38% (30.4% to 45.6%)	Unknown	Unknown
Cost of Observation (CT CRu)	$1453.50 ($1162.80 to $1744.20)	Indifferent	-
Proportion of CRu patients	32% (25.6% to 38.4%)	Unknown	Unknown
Cost of Rituximab Maintenance Therapy	$5377.90 ($8936.13 to $13404.20)	High	Low
Cost of Observation over 6 months	$527.50 ($422.00 to $633.00)	Indifferent	-
Cost of Increased Observation (PET/CT)	$1216.5 ($973.20 to $1459.80)	Indifferent	-
Cost of Reduced Observation (PET/CT)	$204.50 ($163.60 to $245.40)	Indifferent	-
Proportion of PR patients	30% (24% to 36%)	Unknown	Unknown
Cost of BMAT	$709.20 ($567.36 to $851.04)	Indifferent	-
Proportion of CT patients who are BMAT+	43.8% (35% to 52.5%)	Unknown	Unknown

The information needed to identify the total costs associated with PET/CT is minimal, and when available may not be representative of real practice. To account for these uncertainties, the values of parameters have been chosen when these inputs favour CT and therefore provide a conservative estimate. Table 7 shows how these values will impact the model and the only parameter which may underestimate the true value and favour the PET/CT arm, the cost of PET/CT, would be offset by the underestimate of the cost of CT.

While sensitivity analyses have shown that, using conservative estimates, the cost of PET/CT is favourable compared with CT, the main uncertainty of the model is structural, that is, whether clinicians would actually follow the clinical pathway proposed.

13.   Financial/budgetary impacts

An epidemiological approach has been used to estimate the financial implications of the proposed listing of PET/CT for indolent NHL.

The financial implications to the MBS resulting from the proposed listing of PET/CT are summarised in

Table 8. These estimates are based on the 100% MBS rebate under the assumption that the proposed population would be eligible for the Medicare safety net. The base case assumes that PET/CT replaces:

- 25% CT for initial staging;
- CT & BMAT for assessment of response to immunochemotherapy;
- 50% CT for restaging suspected relapse.

Although a cost saving has been estimated for the MBS, this is offset by a cost to the PBS due to the increased use of immunochemotherapy (Table 9) which is estimated to cost the PBS $225,740 in 2020.

Table 8   Estimated total costs to the MBS associated with expanding PET/CT for indolent NHL and the impact of this on subsequent interventions

Description	2016	2017	2018	2019	2020
Number of services	2,144	2,209	2,271	2,335	2,401
Cost of PET/CT	$2,043,526	$2,105,691	$2,163,667	$2,225,656	$2,287,554
Associated interventions	-	-	-	-	-
Change in CT	-2133.00	-2,322	-2,422	-2,523	-2,625
Cost of CT	-$1,194,528	-$1,300,355	-$1,356,120	-$1,412,609	-$1,469,738
Change in BMAT	-427	-440	-452	-465	-478
Cost of BMAT	-$303,082	-$312,302	-$320,900	-$330,094	-$339,274
Increase in radiotherapy	-12	-12	-13	-13	-13
Cost of radiotherapy	-$64,189	-$66,142	-$67,963	-$69,910	-$71,854
Increase in chemoimmunotherapy	8	8	8	8	9
Cost of chemoimmunotherapy	$158,750	$163,579	$168,083	$172,899	$177,707
Initial Consultation	170	175	180	185	190
Cost of initial consultation	$25,677	$26,458	$27,186	$27,965	$28,743
Follow-up consultation	-595	-613	-630	-648	-666
Cost of follow-up consultation	-$44,936	-$46,303	-$47,578	-$48,941	-$50,302
Follow-up CT scan	-839	-864	-888	-914	-939
Cost of follow-up CT scan	-$469,471	-$484,031	-$497,358	-$511,607	-$525,836
Total cost	**$151,478**	**$86,597**	**$69,018**	**$53,359**	**$37,001**

Table 9   Estimated financial implications for Government health budgets

Description	2016	2017	2018	2019	2020
Total Cost to MBS	$143,363	$88,100	$73,397	$60,368	$46,737
Total Cost to the PBS	$201,658	$207,793	$213,514	$219,631	$225,740
Total Government Health Budget	$345,021	$295,893	$286,911	$279,999	$272,477

Key uncertainties in the estimation of the financial impact of the proposed listing are:

- the patient numbers for restaging of relapsed disease and assessment of response to second-line therapy
- the extent to which PET/CT would replace CT, especially in initial staging
- the treatment changes as a result of listing for staging; these were derived from the economic analysis which used change in stage as a proxy for change in management
- the treatment changes as a result of listing for assessment of treatment response; these were derived from the economic analysis which used clinical opinion to model reduced follow-up frequency in PET/CT responders.

14.   Key issues from ESC for MSAC

ESC raised the question whether MSAC assessment of combined positron-emission tomography / computed tomography (PET/CT) using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) as a modality rather than by each indication might be more efficient, similar to the MSAC assessment of IMRT and IGRT.

Clinical effectiveness of PET/CT:
ESC agreed that the clinical effectiveness of PET/CT for indolent non-Hodgkin's lymphoma (NHL) is uncertain due to the limited available evidence base. There was no available direct

effectiveness evidence. Evidence was presented from studies assessing test accuracy and therapeutic impact which was linked to evidence about treatment efficacy or improved prognosis.

- *PET/CT in addition to and/or replacement for conventional staging in initial staging:*
  - ESC noted that there was no new evidence of the impact of PET or PET/CT on changes in management since MBS item 61616 was listed (MSAC Reference 35c: Assessment Report and PSD, 2009); evidence of disease upstaging and, less commonly, downstaging was consistent with the findings of the review for Ref. 35c.

- *PET/CT as replacement for conventional imaging in restaging relapsed indolent NHL:*
  - ESC noted that there was no evidence presented.

- *PET/CT as replacement for CT ± bone marrow aspiration and trephine (BMAT) to assess response to first-line treatment:*
  - ESC noted there were no studies of clinical effectiveness although PET/CT did show superior prognostic value.
  - There are two randomised controlled trials of PET/CT response-adapted treatment ongoing.

ESC considered that clinical evidence for the therapeutic impact of PET/CT beyond the currently funded indication was not available and that the value of the prognostic information to patients and their quality of life is difficult to quantify.

Economic model:
ESC considered that the uncertainties and limitation of the clinical effectiveness data flowed on to the cost-consequence analysis presented. ESC was also concerned that the majority of assumptions included in the model were based almost entirely on expert opinion rather than being evidence based. Moreover, it was not clear how extensively expert opinion had been canvassed in order to arrive at the model assumptions.

Financial impact:
ESC noted that, comparing epidemiologic projections with actual usage of MBS items, it is likely that PET/CT items other than item 61616 are already being used in patients with indolent NHL.

ESC considered that the financial impact was highly uncertain; however, if the economic model were to be accepted, PET/CT may be modestly cost-saving to MBS, but may modestly increase costs to PBS.

15. Other significant factors

The assessment report noted three additional considerations:
1. *Equity:* MBS data use analysis suggested that it is likely that patients with indolent NHL are currently referred for PET/CT for staging and response assessment using items appropriate for aggressive NHL. This number is likely to be variable across providers.

2. *Value of prognostic information:* The value of prognostic information to patients was difficult to measure and to cost. Nevertheless, it may have a significant impact on quality of life (patient reassurance, making important life decisions etc.) and on societal costs (patients more likely to remain in the workforce). This information may

be of particular value in a disease which may have a long clinical course, which affects people in late middle age, and which patients may die with rather than from.

3. *Methodology of PET assessments:* Although little evidence was presented in this assessment, numerous previous assessments of PET in oncology have been undertaken. It may be valid to 'network' some consistent findings from these to the current assessment, particularly as PET/CT is now an established imaging modality in oncology and indolent NHL is relatively uncommon, therefore new high-quality evidence on accuracy or clinical effectiveness is unlikely.

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

With the improved prognosis for most, but not all, patients with indolent NHL in the modern therapeutic era there is an urgent need for reliable lymphoma staging and response assessment using the most sensitive and predictive imaging modality. Australian-led research demonstrates PET to be superior to standard contrast enhanced CT in predicting outcome after initial therapy of advanced stage follicular lymphoma. The inclusion of indolent lymphoma in the indications for MBS-funded PET scanning brings Australia into line with international guidelines for lymphoma imaging. It provides a platform for Australian participation in study of baseline metabolic tumour volume and PET-response adapted therapies, designed to improve outcomes for all patients with indolent lymphoma.

17. Further information on MSAC

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