Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1195 – F-18 fluorodeoxyglucose positron emission tomography (FDG PET) for the diagnosis of Alzheimer's disease

Applicant: **The Department of Nuclear Medicine and Centre for PET, Austin Health, Prof Christopher Rowe**

Date of MSAC consideration: **MSAC 63rd Meeting, 1-2 April 2015**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

In September 2013, the Department of Health received an application from the Department of Nuclear Medicine and Centre for Positron Emission Tomography (PET) at Austin Health, Victoria, requesting Medicare Benefits Schedule (MBS) reimbursement for the use of F-18 fluorodeoxyglucose (FDG) PET imaging to establish a diagnosis of Alzheimer's disease (AD) where other diagnostic methods are inconclusive.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of F-18 fluorodeoxyglucose positron emission tomography (FDG PET) for the diagnosis of Alzheimer's disease where other diagnostic methods are inconclusive, MSAC did not support the public funding because of uncertain cost effectiveness compared to single-photon emission computed tomography (SPECT) due to weak clinical comparative data and unclear translation of imaging performance to improved health outcomes.

MSAC considered that any reapplication should include:

- analysis of the paired SPECT and FDG PET patient data from the Austin Health Department of Molecular Imaging to assess analytical validity with a potentially larger sample than existing head-to-head studies;
- amendments to the proposed MBS item descriptor to more clearly specify the FDG PET analysis method (i.e. semi-quantitative), and the characteristics of the eligible patient population (i.e. suspected early stage Alzheimer's disease), and to limit the proposed service to no more frequently than once per patient per year; and
- a cost-minimisation analysis, considering costs to both the MBS and patients.

MSAC considered that any reapplication should be made via ESC.

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

MSAC noted that FDG PET is currently MBS funded for use predominantly related to oncology; however the technology is expensive and limited by the number of machines available. Therefore, it was noted that it is difficult for regional areas to access the technology.

MSAC was concerned that the proposed MBS item descriptor did not limit the number of services to one per year. MSAC noted that patient population and semi-quantitative analysis method should also be clearly stated in any MBS item descriptor.

MSAC agreed that single-photon emission computed tomography (SPECT) was the appropriate comparator. SPECT currently performs a similar function and is MBS-funded for the same purpose via MBS item 61402. MSAC accepted that FDG PET would be performed in place of SPECT for evaluating patients with suspected dementia following a standard workup where other tests are inconclusive. MSAC noted that SPECT usage through the MBS currently accounts for about 5,000 services per year or about 5% of the projected 100,000 dementia cases diagnosed per year (if none of these services were for any other purpose consistent with the SPECT item descriptor). MSAC considered that, where standard workup is inconclusive, SPECT was currently more likely to be performed due to its MBS funding, however, in some cases unfunded FDG PET is also performed. MSAC noted that it was unclear whether FDG PET and SPECT would be performed in a complementary fashion or whether the imaging modalities, which are each imperfect, would diagnose the same patients. MSAC considered that the two imaging technologies should be used as substitutes for each other rather than being used in addition to each other. Any MBS item for FDG PET in this indication may need to stipulate that it cannot be used before or after SPECT.

The scientific basis of the comparison relied mainly on two head-to-head studies of the two imaging technologies to discriminate the presence dementia or not in patients who were cognitively impaired, with variability between readers and small sample sizes (31 true positives out of a sample of 55 for Ito et al, 2014; and 4 true positives out of a sample of 24 for Döbert et al, 2005). The combined results from these small direct comparison suggested that FDG PET and SPECT had similar diagnostic accuracy for detecting Alzheimer's disease: FDG PET had a sensitivity and specificity of 71% (95% CI: 57% to 83%) and 60% (95% CI: 41% to 77%), respectively; while SPECT had a sensitivity and specificity of 69% (95% CI: 55% to 82%) and 57% (95% CI: 35% to 77%), respectively.

Eleven other studies that reported the diagnostic accuracy of either FDG PET or SPECT were also presented to construct an "indirect" comparison. The comparison across these studies was likely to be confounded by differences in their patient populations. Overall, the combined results from this less reliable comparison were consistent with the results of the small direct comparison, also suggesting that FDG PET and SPECT had similar diagnostic accuracy for detecting Alzheimer's disease: FDG PET had a sensitivity and specificity of 84% (95% CI: 78% to 89%) and 76% (95% CI: 67% to 83%), respectively; while SPECT had a sensitivity and specificity of 85% (95% CI: 79% to 90%) and 72% (95% CI: 60% to 83%), respectively. MSAC noted that these results also sent a signal that FDG PET may be better than SPECT at identifying very mildly affected brain regions so that there may be some predictive value in mild cognitive impairment, but this signal would need to be confirmed.

MSAC noted data from a case series of 194 consecutive patients (Elias et al, 2014) that suggested a potential advantage for FDG PET over SPECT in distinguishing between Alzheimer's disease and other types of dementia. However, MSAC was concerned that this

data was still at the research level, that there were inconsistencies in the data, and that the data did not compare FDG PET with SPECT.

MSAC concluded that the evidence overall suggested that FDG PET is non-inferior to SPECT rather than significantly better than SPECT at diagnosing dementia.

MSAC noted from the pre-MSAC response that the applicant had ongoing access to a large and relevant data set that is currently unpublished that could be analysed. MSAC recommended that analysis of paired FDG PET and SPECT results for individual patients be performed by an independent statistician to assess comparative analytical validity and include this analysis in any reapplication via ESC for evaluation. MSAC expected that this might provide more conclusive comparative evidence for the use of FDG PET in the diagnosis of Alzheimer's disease as requested, especially if it would involve a larger sample size than the two small directly comparative studies reported to date. If necessary, the MSAC Executive could liaise with the applicant to provide guidance on the statistical analysis. This might be particularly helpful if there are insufficient comparisons with an accepted reference standard, and so might involve a 2-stage assessment with clinical follow-up, or a 3-way latent class analysis using the fair "bronze standard" principle.

MSAC noted the limited direct evidence for a change in clinical management or an improvement in health outcomes from treating any additional cases detected.

MSAC noted that there were no primary studies reporting on the comparative safety of FDG PET and SPECT in the diagnosis of Alzheimer's disease. However, MSAC accepted that FDG PET is a comparatively safe diagnostic procedure.

The MBS fee proposed by the applicant was $1,180, however, the current MBS fee of $918 for item 61559 (FDG PET study of the brain for refractory epilepsy being evaluated for surgery) was used in the economic model. MSAC noted the pre-MSAC response, which disputed whether the $100 Medicare payment available for CT done as part of a nuclear medicine scan would apply to PET. MSAC accepted advice from the Department that this extra $100 reflected the current practice for most of these services charged to the MBS.

Economic modelling was performed assuming that FDG PET improves the early diagnosis of Alzheimer's disease which leads to avoiding/slowing progression of disease by 50% through early treatment with anti-Alzheimer's disease drugs as well as leading to elongated patient productivity. However, MSAC noted that the evidence on the effectiveness of the drugs was uncertain and therefore there was uncertainty around the validity of claims of improved health outcomes. MSAC was concerned that the downstream consequences of early diagnosis were overly optimistic. In particular, MSAC did not accept the basis of the magnitude of effect of anti-Alzheimer's disease drugs. The sensitivity of the model to a reduced effect size would need to be more extensively assessed in any reapplication retaining this model.

MSAC noted that the 5-year model suggested that FDG PET would be dominant (both saving costs at $1160 per patient and improving health outcomes at 0.03 quality-adjusted life-years (QALYs) gained) compared to SPECT with an incremental cost per QALY of -$42,991. This result arose because the increased costs of the improved diagnostic accuracy with FDG PET and increased use of anti-Alzheimer's disease drugs were projected to be outweighed by larger downstream cost offsets associated with progression to severe Alzheimer's disease such as the avoidance of large nursing home care costs incurred by the individual. However, based on the evidence available, MSAC considered that a cost minimisation analysis would be more appropriate due the conclusion of FDG PET being non-inferior to SPECT. Cost-

minimisation would therefore not include any increased use of drugs or any decreased use of nursing home care costs. From the MBS perspective, this could be achieved by setting the proposed FDG PET MBS fee equal to the current fee of $605.05 for the comparator SPECT MBS item 61402. However, MSAC was not sure whether the out-of-pocket payments for FDG PET and SPECT would also be similar in order to achieve cost-minimisation for patients as well.

MSAC noted that the financial implications may be underestimated, but that uptake would be limited by the small number of FDG PET machines available. If currently 5% of Alzheimer's disease diagnoses are inconclusive and so are referred for SPECT, then any MBS funding for FDG PET should be introduced in such a way as to not increase the overall extent of such referrals.

4. Background

Although FDG PET has been considered by MSAC previously for other indications (most recently under application 1357 – FDG PET for Breast Cancer), MSAC had not previously considered FDG PET for the diagnosis of Alzheimer's disease.

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 FDG injection. Radiolabelled FDG is also currently produced several Australian hospitals.

The requested MBS listing for FDG PET was consistent with the TGA-approved indication.

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

6. Proposal for public funding

FDG is a slightly radioactive form of glucose that can be safely injected into a patient. After 30 minutes a scan can then be performed with a PET camera, which takes approximately 15 minutes.

FDG PET was currently listed on the MBS for a range of other indications, predominately relating to oncology, but was not listed for the diagnosis of Alzheimer's disease.

Alzheimer's disease is the most common cause of dementia. It is progressive and leads to severe disability and morbidity – on average seven years from diagnosis. Symptoms of Alzheimer's disease are present for several years before diagnosis and the pathological process that leads to the dementia of Alzheimer's disease begins a decade or more before diagnosis.

The rationale for using FDG-PT to diagnose dementia is that it detects hypometabolic areas of the brain which do not take up the radioactive glucose. It thus may also be useful in distinguishing between types of dementia. It was proposed that FDG PET be used and funded only in a particular subset of patients. The clinical utility of FDG PET in the diagnosis of AD was considered to be its potential to *augment* clinical diagnosis (including the use of neurological assessment, blood tests and structural brain imaging) in patients with *suspected* AD. It was accepted that, in patients with an unequivocal diagnosis of AD or no AD, FDG

PET provides no diagnostic value. The value of accurately identifying patients with early AD was argued to be that this phase of the disease is when treatment with anti-AD drugs (acetylcholine esterase inhibitors (AChEIs), NMDA antagonists) may provide benefit. However, it was accepted that, once AD has progressed to a more severe disease stage, these pharmacological agents are ineffective.

The proposed wording of the MBS item descriptor and a Schedule fee for the service were based on MBS item 61559 (FDG PET study of the brain, performed for the evaluation of refractory epilepsy which is being evaluated for surgery).

Table 1 Proposed MBS item descriptor

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS [item number] FDG PET study of the brain, performed for the diagnosis of Alzheimer's disease where clinical evaluation by a specialist, or in consultation with a specialist, and MRI are equivocal (R) Fee: $918.00 Benefit: 75% = $688.50 85% = $839.60

7. Summary of Public Consultation Feedback/Consumer Issues

No specific Consumer Impact Statement was provided in the assessment. However, the assessment report noted that "…due to the high capital cost, PET machines are typically located at large, metropolitan public hospitals. Access to PET scans in Australia is therefore restricted, particularly in regional areas, although the number of PET facilities (both public and private sector) is increasing with more widespread application in oncology for diagnosis and monitoring."

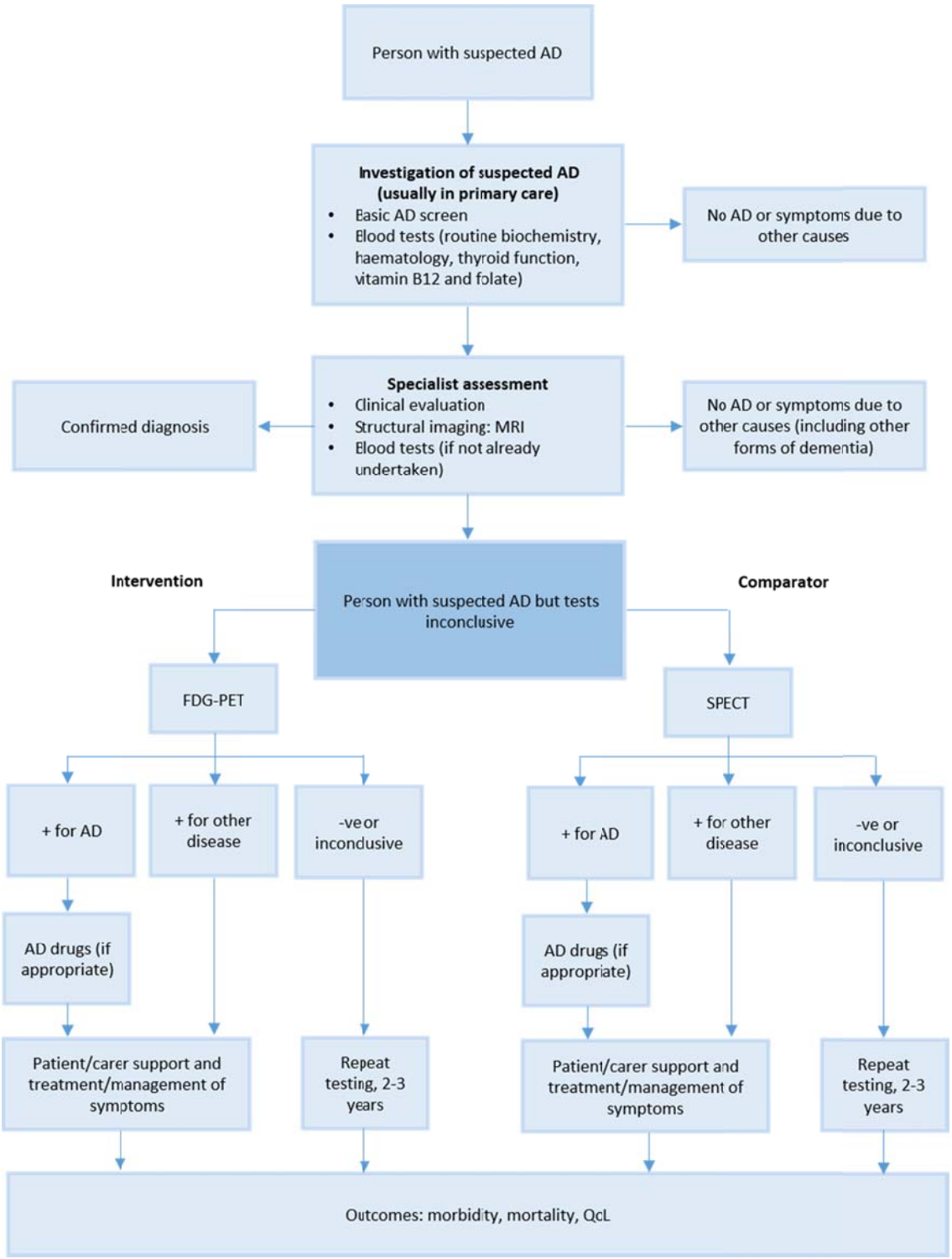
8. Proposed intervention's place in clinical management

The clinical management algorithm for the diagnosis of patients with suspected Alzheimer's disease is shown in. As shown in the algorithm (Figure 1), current clinical evaluation involves taking a patient history, cognitive assessments, routine blood tests, and structural imaging with MRI in some cases. It was proposed that FDG PET be used in addition to these tests and investigations, and instead of SPECT.

The various tests outlined in the algorithm were all currently available for suspected Alzheimer's disease patients in Australia; however, under the current funding arrangements, an MBS rebate was not available for FDG PET. Under proposed funding arrangements an MBS rebate would be available for all diagnostic tests shown in the clinical algorithm.

The clinical management algorithm shows that SPECT was currently used to resolve difficult cases in which prior tests have been inconclusive. In particular, it was understood that SPECT provides information that assists with the differentiation between different types of dementia.

Figure 1 Clinical management algorithm for Alzheimer's disease diagnosis with FDG PET



Abbreviations: AD, Alzheimer's disease; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; QoL, quality of life; SPECT, single-photon emission computed tomography.

Each FDG- PET scan has a cost associated with the purchase and transport of radiochemicals. Because the half-life of fluorine (F)-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

9. Comparator

The nominated comparator was assessment of cerebral perfusion with SPECT currently billed via MBS item 61402. The most commonly used tracer to examine cerebral blood flow (CBF) using SPECT is 99m-Tc-hexamethylpropylene (HMPAO); however, several other tracers have been investigated in clinical studies.

Like FDG PET, SPECT can be analysed using semi-quantitative methods. SPECT is technically less demanding and more widely available than PET, but is reported to have lower resolution. FDG PET is proposed as a replacement test to SPECT, although the availability of FDG PET may limit the extent to which it replaces SPECT, particularly in rural and regional areas.

10. Comparative safety

No primary studies were identified that reported on the comparative safety of FDG PET and SPECT for the diagnosis of Alzheimer's disease. However, it was widely accepted that PET is a safe diagnostic procedure.

FDG PET and SPECT are associated with similar levels of radiation exposure: the techniques have been assigned the same Relative Radiation Level.

11. Comparative effectiveness

Change in patient management
One Canadian study found that FDG PET resulted in a change in diagnosis in 29% of patients, and increased the use of AChEIs after diagnosis (Laforce et al, 2010). This was consistent with the only available Australian study (Elias et al, 2014), which reported a change in diagnosis in 35% of dementia patients who underwent FDG PET.

No information was provided regarding the impact of SPECT on patient management, so no conclusions could be drawn regarding the relative impact of FDG PET versus SPECT on changes in patient management.

Change in patient outcomes
No studies were identified that assessed the direct health impact (effectiveness) of FDG PET versus SPECT in the target population. A 'linked evidence' approach was therefore used to derive data on the health outcomes of those who are correctly diagnosed. Evidence regarding the effectiveness and safety of anti-Alzheimer's disease drugs was relatively limited. In particular, the effect of anti-Alzheimer's disease drugs on outcomes beyond cognition, function, behaviour and global impact, remained uncertain. Of relevance to this assessment, there was limited evidence for the impact of treatment on quality of life, admission to full-time care and resource use, which underpinned claims of cost-effectiveness. Long-term follow-up (especially beyond one year) on the effect of anti-Alzheimer's disease drugs on any outcome remained a major evidence gap.

Comparative diagnostic accuracy

The assessment report considered 20 head-to-head and single-arm studies that reported on the diagnostic performance of FDG PET and/or SPECT. The studies were found to be generally of poor quality and limited by the recruitment of patients not relevant to the proposed MBS indication, and insufficient use of appropriate reference standards.

The evidence base ultimately relied on for the base case of the modelled economic evaluation comprised two small studies (Dobert et al, 2005 and Ito et al, 2014) with 24 and 55 subjects, respectively. These two studies had the greatest applicability to the proposed indication (in terms of patients recruited), but both were of limited quality. Consequently, the assessment report added the true positives, false positives, false negative and true negatives to derive combined estimates of sensitivity and specificity.

Pre-modelling studies

Table 2 presents each of the translation issues identified to enable the transition from the clinical evidence discussed above to the economic evaluation presented in Section 12 below.

Table 2 Summary of translation issues

Translation issue	Methods and data sources	Relationship with Section D
Applicability issues	-	-
Population and circumstances of use (Assessment report Section C.2)	Characteristics of the requested listing and the modelled population/circumstances of use were considered in isolation and compared.	Requested listing was modelled in Section D as closely as possible given data limitations; potential differences were identified and flagged for testing in sensitivity analyses.
Extrapolation issues	-	-
Duration of Alzheimer's disease treatment (Assessment report Section C.3)	On the basis of published data, duration of treatment was estimated for mild Alzheimer's disease patients treated with AChEIs and moderate Alzheimer's disease patients treated with memantine.	Drug discontinuation rates were applied to the model using the available data. In the case of memantine, the use of non-Australian data meant that PBS restrictions were not inherent in the data; this was therefore flagged for further testing in sensitivity analyses.
Transformation issues	-	-
Modelling the natural history of Alzheimer's disease (Assessment report Section C.4)	Following a literature search, published transition probabilities that considered the impact of disease progression (according to mild Alzheimer's disease, moderate Alzheimer's disease and severe Alzheimer's disease classifications) and residential status were sourced. Adjustments were made where appropriate and discussed in Section C.	Transition probabilities were applied to the model and tested in sensitivity analyses.
Treatment effect of Alzheimer's disease drugs (Assessment report Section C.5)	A literature search was used to source estimates of treatment effect for AChEIs and memantine which could be merged with the health states (and technical structure) considered in the economic model. In the case of AChEIs, a relevant relative risk was sourced and applied to individuals with mild Alzheimer's disease on treatment. In the case of memantine, a relative risk was calculated from transition probabilities in a published economic evaluation. This was applied to moderate patients on treatment for Alzheimer's disease.	Treatment effect was applied to the natural history estimates of an untreated population to slow progression in individuals treated for Alzheimer's disease. The uncertainty around the estimates used, which is acknowledged to be considerable, was examined in sensitivity analyses.
Utility weights applied to the economic model (Assessment report	A literature search was undertaken to source utility weights for individuals with Alzheimer's disease, which considered both disease severity and the impact of institutionalisation in nursing home care.	Utility weights were applied to health states in accordance with the evidence. The impact of these data and the assumptions applied were examined in

Translation issue	Methods and data sources	Relationship with Section D
Section C.6)		sensitivity analyses.
Healthcare resource use and associated costs (Assessment report Section C.7 and Section C.8)	Using published data, costs associated with Alzheimer's disease drugs, ongoing care from GPs and costs associated with both care in nursing homes and in the community were estimated.	Estimated costs were applied to health states as required, considering each health state's requirements in terms of drug and other treatment/care. The estimates were varied in sensitivity analyses to determine their impact on the base case result.
Diagnostic accuracy (Assessment report Section C.9)	True positive, true negative, false positive and false negative data from the published literature.	Base case assumptions regarding diagnostic accuracy were applied to the model but tested in sensitivity analyses to determine the impact of any uncertainty on these point estimates on the cost-effectiveness.

Abbreviations: AChEIs, acetylcholinesterase inhibitors; GPs, general practitioners

12. Economic evaluation

Although the assessment report indicated that it could not be concluded that the diagnostic accuracy of FDG PET was statistically significantly superior to SPECT in patients with suspected Alzheimer's disease, a cost-utility analysis (CUA) was undertaken in line with PASC advice, assuming inferiority of SPECT but at a lower cost.

The model takes the form of a state-transition semi-Markov model with non-constant transition probabilities applied where appropriate. The model followed a cohort of patients from diagnostic testing through transition to disease progression or death over a five-year period using cycles of six weeks. Individuals were assumed to be 72.4 years of age at the beginning of the model and gender was distributed with 61.98% of the cohort female (using data from the Australian Institute of Health and Welfare).

Half-cycle correction was applied to the model and costs and outcomes were discounted at an annual rate of 5%, in accordance with MSAC Guidelines.

Table 3 presents the base case results in terms of the QALY gain offered by FDG PET.

Table 3 Incremental cost-effectiveness ratio of FDG PET versus SPECT

Parameter	FDG PET arm	SPECT arm	Incremental
Cost	$98,242	$99,585	-$1160
QALY	2.41	2.39	0.03
Incremental cost per QALY	-	-	-$42,991

Abbreviations: FDG PET, fluorodeoxyglucose positron emission tomography; QALY, quality-adjusted life year; SPECT, single-photon emission tomography
Note: Rounding may impact on some figures

The assessment report estimated that FDG PET would save $1,160 per patient over a five-year period, and deliver an incremental QALY gain of 0.03. The assessment report drew the conclusion that, if it is accepted that the non-significant small numerical difference in diagnostic accuracy between FDG PET and SPECT is clinically meaningful, then FDG PET is more effective and less costly than SPECT in the diagnosis of Alzheimer's disease.

The assessment report noted that the cost difference was driven by larger downstream cost offsets associated with progression to severe Alzheimer's disease, including the large nursing home care costs individuals incur. Avoiding or slowing progression to this health state through the use of Alzheimer's disease drugs resulted in savings of $1,225 per patient

(discounted), which more than fully offset the additional costs of FDG PET and the drug treatment in those additional patients with Alzheimer's disease detected.

The results of the model were sensitive to the duration of the model, the more expensive home and nursing care resources that occur downstream as an individual's condition worsens, and diagnostic accuracy. The cost savings generated in the base case were highly dependent on the inclusion (and magnitude) of home and nursing care resources costs.

The assessment report also highlighted the complex relationship between diagnostic accuracy and cost-effectiveness. It noted that the base case results were highly sensitive to these assumptions. If the data used in the base case could be accepted, it would appear that FDG PET is a cost-effective alternative to SPECT in the diagnosis of Alzheimer's disease. If, however, there was doubt regarding the acceptability of these data, it was clear that the conclusions of the base case might not be valid and particular caution would need to be taken to ensure that the impact of alternative data is well understood.

The assessment report noted that the incremental cost and QALY results were both very close to zero, so the conclusions were particularly sensitive.

13. Financial/budgetary impacts

A scarcity of data relating to the availability of FDG PET facilities throughout Australia (both now and in the next five years), and/or accurate data describing the incidence of Alzheimer's disease across Australia, and how diagnosis is achieved using functional imaging, meant that the analysis was undertaken using more general data derived from incidence of dementia and associated estimates of how this is made up, in part, from individuals with Alzheimer's disease.

The analysis used an epidemiological approach to estimate the use of SPECT in identifying Alzheimer's disease from estimates of projected dementia incidence (Access Economics, 2009) and estimates regarding the proportion of these cases which were due to Alzheimer's disease (Alzheimer's Disease International, 2014). These data were used in conjunction with assumptions regarding the rate at which SPECT is used to diagnose Alzheimer's disease and how FDG PET would be used to substitute for SPECT in the event of a successful MBS listing. Assumptions regarding the possibility of increased use of functional imaging in the event of a MBS listing for FDG PET were also applied.

The assessment report noted that it was not possible to derive estimates of the volume or proportion of SPECT services which relate to dementia or Alzheimer's disease from MBS data, the SPECT item may be for a range of indications.

Table 4 shows estimates of the number of SPECT services currently utilised under the MBS for diagnosis of Alzheimer's disease and the number of SPECT and FDG PET services which could occur. These estimates account for replacement of SPECT with FDG PET as well as increased use of functional imaging.

Table 4 FDG PET and SPECT services under the current scenario and the future scenario in the event of a positive listing on the MBS for FDG-PET

	2015	2016	2017	2018	2019
No MBS listing for FDG-PET	-	-	-	-	-
SPECT services undertaken to attempt Alzheimer's disease diagnosis via the MBS	1324	1387	1455	1513	1581
FDG-PET services undertaken to attempt Alzheimer's disease diagnosis via the MBS	0	0	0	0	0
With MBS listing for FDG-PET	-	-	-	-	-
FDG-PET services replacing SPECT to attempt Alzheimer's disease diagnosis via the MBS	199	416	655	908	1106
Net SPECT services undertaken to attempt Alzheimer's disease diagnosis via the MBS	1125	971	800	605	474
Additional FDG-PET services due to increased used of functional imaging	0	35	73	113	158
Total FDG-PET services expected for attempted diagnosis of Alzheimer's disease via the MBS in the event of a positive listing	199	451	728	1021	1264

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule

Table 5 shows the total financial impact on the MBS with and without FDG PET listing.

Table 5 Total MBS costs with and without a successful FDG-PET listing on the MBS

	2015	2016	2017	2018	2019
No MBS listing for FDG-PET	-	-	-	-	-
Total cost of SPECT for Alzheimer's disease diagnosis	$699,987	$733,778	$769,502	$799,947	$835,871
Total cost of FDG-PET for Alzheimer's disease diagnosis	$0	$0	$0	$0	$0
Total cost of associated specialist consultations	$254,793	$267,093	$280,097	$291,179	$304,255
Total cost to the MBS	$954,780	$1,000,872	$1,049,599	$1,091,126	$1,140,125
With MBS listing for FDG-PET	-	-	-	-	-
Total cost of SPECT for Alzheimer's disease diagnosis	$594,989	$513,645	$423,226	$319,979	$250,761
Total cost of FDG-PET for Alzheimer's disease diagnosis	$167,131	$379,599	$612,430	$859,491	$1,064,402
Total cost of associated specialist consultations	$254,793	$273,771	$294,102	$313,017	$334,680
Total cost to the MBS	$1,016,913	$1,167,014	$1,329,757	$1,492,487	$1,649,843
Total net financial impact of a successful listing for FDG-PET on the MBS	*$62,133*	*$166,142*	*$280,159*	*$401,361*	*$509,718*

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule

The assessment report also anticipated that FDG PET would lead to more positive test results than in the case of SPECT. This would result in a greater proportion of individuals moving on to PBS-listed therapies to treat Alzheimer's disease. The total net financial impact to the MBS and PBS budgets is presented in Table 6.

Table 6 Net financial impact to the Government health budget

	2015	2016	2017	2018	2019
Net impact to the MBS	$62,133	$166,142	$280,159	$401,361	$509,718
Net impact to the PBS	$4,111	$9,337	$15,064	$21,141	$26,181
Total net impact	$66,244	$175,479	$295,222	$422,502	$535,898

Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Schedule

14. Key issues from ESC for MSAC

ESC noted that there were no primary studies which reported on the comparative safety of FDG PET and the main comparator, single-photon emission computed tomography (SPECT), for the diagnosis of Alzheimer's disease.

ESC considered that key safety issues would relate to the use of the radiopharmaceutical rather than the procedure as a whole. ESC noted that FDG PET and SPECT have been assigned the same Relative Radiation Level. ESC noted that the interventions would therefore have equivalent safety issues.

ESC noted that that PET was generally accepted as safe.

ESC noted that the limited body of directly comparative evidence contributed to significant uncertainty in the assessment of the comparative diagnostic performance of FDG PET versus SPECT.

ESC considered the quality of evidence to be poor, with small sample sizes, variable control groups, poor quality of reporting and insufficient use of reference standards within and across studies. ESC also noted that, in the majority of studies, the study populations were not applicable to the proposed MBS population.

ESC agreed with the assessment report's cautionary conclusion: "based on the limited body of evidence presented in Section B, it cannot be concluded that the diagnostic accuracy of FDG PET is superior to SPECT in patients with suspected AD. Although the results numerically favour FDG PET, it is unclear whether this would represent a true difference between the imaging modalities in clinical practice."

ESC agreed with the assessors who considered the only useful head-to-head studies to be Döbert et al, 2005 and Ito et al, 2014, which were conducted in applicable patient populations, and included partial reference standards (i.e. clinical but not histopathological confirmation). ESC considered it appropriate to disregard the six other available studies directly comparing FDG PET and SPECT because these studies compared performance of the tests using cognitively normal controls as well as diagnosed cases.

ESC noted that the estimates of sensitivity and specificity were quite different between the Döbert et al, 2005 and Ito et al, 2014 studies, and that there was a wide range of values across the two studies. ESC noted that the assessors had replicated the methodology of a published meta-analysis by Cure et al (2014) by simply adding the true positives and true negatives from each study and then reconstructing a two by two table to yield 'combined' measures of comparative diagnostic accuracy. ESC considered this to be simplistic and questioned whether the Döbert et al, 2005 and Ito et al, 2014 studies were sufficiently similar to be combined. ESC also considered that a mean or weighted mean would have been useful. Overall, ESC considered that a Receiver Operating Characteristic (ROC) curve may have been more beneficial in graphically presenting the two studies separately for both FDG PET and SPECT.

ESC noted that the assessors' combined results of indirect studies showed very similar diagnostic accuracy between the two imaging techniques, with FDG PET demonstrating a sensitivity and specificity of 84% and 76%, while SPECT had a sensitivity and specificity of 85% and 72%. Despite the low quality studies, ESC also noted FDG PET seemed marginally

superior at identifying very mildly affected brains or brain regions (e.g. the frontal cortex) when compared with SPECT.

ESC noted that validation against clinical diagnostic criteria rather than histopathologic diagnosis was a major limitation of most of the evidence, including the Döbert et al, 2005 and Ito et al, 2014 studies.

ESC considered that an Australian study undertaken by the applicant regarding changes in patient management was valuable in providing external validation for the economic model (ie. that the use of FDG PET does indeed change the prescribing of AChEIs). However, ESC noted that patient management studies were only provided for FDG PET and therefore no conclusions could be drawn regarding relative changes to patient management with FDG PET versus SPECT.

ESC noted that the absence of verification of true disease status in patients with discordant test results added further to the uncertainty regarding these results. However, ESC acknowledged that definitive diagnosis for Alzheimer's disease could only be achieved via autopsy, and that this would present problems for measuring diagnostic accuracy in a clinical setting.

Longer term clinical follow-up was accepted by ESC as an alternative (albeit imperfect) reference standard, but ESC noted that only one of the two key studies included subsequent clinical confirmation of AD diagnosis (Döbert et al, 2005).

ESC noted that the applicant, in its pre-ESC response, had focused on diagnostic sensitivity, but ESC agreed that specificity would be the most relevant measure for the proposed use of FDG PET. This view was noted to be consistent with published European guidelines for the diagnosis and management of AD: *"the quest should be to increase specificity to augment clinical diagnostic criteria and structural imaging"* (Waldemar et al. European Journal of Neurology 2007;14:e1 – e26).

Given the lack of statistically significant difference in diagnostic performance between the two imaging modalities, ESC suggested remodelling on the basis of cost-minimisation, including a sensitivity analysis in which the diagnostic accuracy was varied within the range of confidence intervals. This was anticipated to give a better idea about whether PET is superior (or at least no worse) than SPECT.

ESC considered the structure and assumptions in the model to be generally sound, but noted the need for caution regarding how the results are interpreted. ESC considered that the base case and all one-way sensitivity analyses in the 'Alzheimer's disease model' should be treated with caution as they were based on non-statistically significant differences in sensitivity and specificity.

ESC noted that the modelled cost-utility analysis was highly sensitive to the values of diagnostic accuracy. ESC also noted that the transition probabilities and utility weights in the model were taken from a non-Australian longitudinal dataset. Whilst this data source may be the most appropriate available, and provides internal consistency for the model, the applicability of these variables to an Australian AD population was not clear.

ESC noted that the modelled benefits associated with a correct diagnosis of AD were driven by the assumption that treatment with anti-AD drugs slows disease progression by 50% and considered that this was a highly favourable assumption. ESC also noted that the assumption

regarding the effectiveness of the PBS Alzheimer's disease drugs in allowing patients to remain in the community was not clearly based on strong evidence.

ESC could not support superiority of FDG PET over SPECT in changing clinical management because the patient management studies that suggested FDG PET was effective at changing treatment did not consider whether SPECT would be associated with similar changes.

ESC noted that the ICER was highly sensitive to diagnostic accuracy and that reasonable evidence-based changes to the sensitivity/specificity would reverse the cost effectiveness conclusion. In one sensitivity analysis an ICER of $127,567 per QALY was reported, whilst in another sensitivity analysis FDG PET was associated with additional costs and poorer QALY outcomes. ESC considered that each of these modelled results was equally likely given that the incremental cost and QALY results were so close to zero.

ESC noted that the applicant proposed a fee of $1,180, for FDG PET, which is greater than the fee of $918 specified in the final Protocol as being equivalent to MBS item 61559 which is the lowest fee for FDG PET on the MBS. However, all financial analysis had been performed using the $918 fee.

ESC noted that no information was presented on the inputs to either fee, and that no conclusion could be made regarding their appropriateness.

ESC noted the fee of $918 had been set equal to that for MBS item 61599 (FDG PET for epilepsy), but also noted that the current fee for the comparator item for SPECT (MBS item 61402) is lower, at $605.05. ESC discussed the relevance of MBS item 61505 (nuclear medicine co-claimable item for a concurrent CT scan), the fee for which is $100. It was noted that this item can be co-claimed with PET or SPECT items, and that no information is available regarding the relative proportions of co-claiming for PET versus SPECT. However, given that all new PET and SPECT machines include CT capability, ESC agreed that co-claiming of item 61505 is likely to be similar for PET and SPECT. Consequently, ESC felt it was appropriate to exclude the costs associated with item 61505 as they would apply equally to both arms of the economic evaluation.

Although SPECT was agreed by PASC as the main comparator for this application, there was discussion by ESC regarding the extent to which SPECT is actually used in the population for whom FDG PET listing is sought. In particular, ESC noted the low rates of utilisation for MBS item 61402, which covers a range of indications for SPECT (eg, epilepsy, stroke, acute brain injury) in addition to AD (cf. Table E.2.1 in the contracted assessment report).

ESC requested that the Policy Area provide additional information to MSAC on the current use of SPECT as this may affect the financial and economic conclusions.

ESC noted that the applicant had not proposed any wording for the proposed MBS item descriptor, but stated that the technique is the same as MBS item 61559 (FDG PET study of the brain for refractory epilepsy being evaluated for surgery). ESC considered that careful specification of the eligible population would be important to ensure FDG PET is provided in the appropriate place in the diagnostic pathway. ESC also considered that the item could be limited to once per year.

ESC considered that restriction of the technique to 'semi-quantitative' might be warranted as the use of software algorithms to enhance visualisation of the images improves the performance of FDG PET in the diagnosis of Alzheimer's disease.

ESC proposed the following alternative MBS item descriptor.

Table 6 ESC-proposed MBS item descriptor

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS [item number] Semi-quantitative FDG PET study of the brain, performed for the diagnosis of suspected early stage Alzheimer's disease where clinical evaluation by a specialist, or in consultation with a specialist, and MRI are equivocal. (R) Fee: $918.00 Benefit: 75% = $688.50 85% = $839.60 Limit of one service per patient per year.

15. Other significant factors

Nil.

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

The applicant agrees that the suggested descriptor is appropriate and strongly favour the compulsory use of semi-quantitation to achieve best results given the highly variable experience and training of readers in clinical practice. It should be acknowledged that amyloid PET or CSF measurement of AD markers have very high accuracy for diagnosis of AD compared to post mortem histopathology and therefore provide a better "gold standard" diagnosis for Alzheimer's disease than clinical diagnosis, with or without follow-up, against which to compare the performance of other investigations including FDG PET and CBF SPECT.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.