

***F-18
Fluorodeoxyglucose
(FDG) Positron
Emission
Tomography (PET)
for the diagnosis of
Alzheimer's disease***

February 2015

MSAC application no.

1195

Assessment Report

Assessment 1195 – F-18 Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) for the diagnosis of Alzheimer’s disease – February 2015

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MSAC’s advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Abbreviations

AChEI	acetylcholinesterase inhibitor
ACR	American College of Radiology
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive Subscale
ADI	Alzheimer's Disease International
ADL	activities of daily living
AE	adverse event
AHEAD	Assessment of Health Economics in Alzheimer's Disease
AIHW	Australian Institute of Health and Welfare
ALS	amyotrophic lateral sclerosis
AQoL	Assessment of Quality of Life
ARTG	Australian Register of Therapeutic Goods
CACP	Community Aged Care Package
CBA	cost benefit analysis
CBF	cerebral blood flow
CBT	cognitive behavioural therapy
CDR	Clinical Dementia Rating
CEA	cost-effectiveness analysis
CERAD	Consortium to Establish a Registry in Alzheimer's Disease
CI	confidence interval
CMA	cost-minimisation analysis
CMRgl	cerebral metabolic rate for glucose
CSF	cerebrospinal fluid
CT	computed tomography
CUA	cost-utility analysis

DLB	Dementia with Lewy bodies
DPMQ	dispensed price per maximum quantity
DUSC	Drug Utilisation Sub-Committee
ECD	ethyl cysteinate dimer
EMA	European Medicines Agency
FDG	fluorodeoxyglucose
FP	false positive
FN	false negative
FTD	frontotemporal dementia
GP	general practitioner
GPCOG	General Practitioner Assessment of Cognition
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HESP	Health Expert Standing Panel
HMPAO	^{99m} Tc-hexamethylpropylene
HRQoL	health-related quality of life
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
IMP	iodoamphetamine
LOCF	last observation carried forward
LYG	life year gained
MAUI	multi-attribute utility instrument
MBS	Medicare Benefits Schedule
MCI	mild cognitive impairment
MIX	mixed-type dementia
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging

MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NIA-AA	National Institute on Aging and the Alzheimer's Association
NICE	National Institute for Health and Clinical Excellence
NSW	New South Wales
OC	observed case
PASC	Protocol Advisory Sub-Committee
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Schedule
PET	positron emission tomography
PI	Product Information
PPICO	population, prior test, intervention, comparator, outcomes
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QLD	Queensland
QoL	quality of life
RACGP	Royal Australian College of General Practitioners
RACP	Royal Australian College of Physicians
rCBF	regional cerebral blood flow
RCT	randomised controlled trial
ROI	region of interest
RPBS	Repatriation Pharmaceutical Benefits Scheme
RRL	relative radiation level
RUDAS	Rowland Universal Dementia Assessment Scale
SD	standard deviation
SMMSE	Standardised Mini-Mental State Examination

SPECT	single-photon emission computed tomography
SSP	stereotactic surface projections
TGA	Therapeutic Goods Administration
TP	true positive
TN	true negative
VD	vascular dementia
VIC	Victoria
WA	Western Australia

Executive summary

Assessment of (intervention name/diagnostic test)

Purpose of application

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.

Current arrangement for public reimbursement

Currently, public reimbursement of FDG-PET for the diagnosis of AD is not available, although FDG-PET is funded through the MBS for a range of other indications, predominately relating to oncology.

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.

Background

Diagnosis of AD usually involves:

- clinical evaluation (history, examination, cognitive testing) for the assessment of cognitive function;
- routine blood testing (routine biochemistry, haematology, thyroid function, vitamin B12, folate) to exclude potentially treatable causes of cognitive decline; and
- structural imaging (magnetic resonance imaging or computed tomography) to exclude surgically treatable causes of cognitive decline and/or identify findings specific for AD (brain atrophy).

All of these diagnostic tests are currently funded through the MBS. The intention of the application is that FDG-PET would supplement rather than replace those MBS items in the diagnostic pathway.

Clinical need

Structural imaging, in combination with other prior tests, will often provide enough information to confidently diagnose AD in moderate to severe cases. However, the presence of AD in a mildly affected brain is more difficult to diagnose using MRI, particularly due to difficulty in distinguishing it from the mild decline in memory that can occur with normal aging and from mild cognitive manifestations of other neuropsychiatric conditions. Functional imaging, including PET and single-photon emission computed tomography (SPECT), is able to identify changes in glucose and oxygen metabolism, respectively, that are characteristic of AD before widespread atrophy occurs. The clinical need for such diagnostic techniques is therefore very high in patients with early signs of AD, who have not yet passed the optimal window for therapeutic intervention.

Physician confidence in a dementia diagnosis can also be challenging in younger patients, in atypical presentations, in patients with comorbid depressive and cognitive symptoms, and in patients with a higher level of education, who can experience a substantial decline of cognitive function before reaching the lower normal limits of standardised neuropsychological tests. More accurate assessment of dementia diagnosis can help to better select appropriate patients for anti-dementia therapy and family prognostic planning.

Despite the fact that there is currently no cure for AD, there are numerous advantages associated with early diagnosis. Several treatments are available on the Pharmaceutical Benefits Scheme (PBS) that have been reported to slow cognitive and functional decline and diminish the severity of behavioural and psychiatric symptoms. Patients with AD that is diagnosed at an early stage could benefit from the optimal use of the available drugs, with the possibility of delayed progression to more debilitating stages of disease.

However, functional imaging techniques such as FDG-PET have very limited utility in patients with severe AD, as less advanced diagnostic techniques (e.g. cognitive tests and/or structural imaging) would be sufficient to provide a confident diagnosis. Furthermore, in Australia patients with severe AD are excluded from the PBS-eligible population for AD drugs and therefore would not benefit from access to subsidised therapy.

Proposed MBS item

The proposed wording of the MBS item descriptor and the proposed Schedule fee for service are 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 ES.1 Proposed MBS item descriptor

Category 5 – DIAGNOSTIC IMAGING SERVICES
<p>MBS [item number]</p> <p>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)</p> <p>Fee: \$918.00 Benefit: 75% = \$688.50 85% = \$839.60</p>

Comparator

The assessment of cerebral perfusion with SPECT is currently funded through 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.

Clinical claim

The clinical claim in the Final Protocol is that FDG-PET results in improved patient selection compared with SPECT, based on superior diagnostic accuracy. This leads to

changes in treatment to target those patients that would benefit most, in turn leading to improved patients outcomes.

Diagnostic accuracy

There are a limited number of comparative studies evaluating FDG-PET and SPECT for the diagnosis of AD. Both diagnostic tests are able to detect temporoparietal changes, typical of AD, with a relatively high degree of accuracy. However, the comparative studies generally found that FDG-PET was marginally superior at identifying very mildly affected brains or brain regions (e.g. the frontal cortex) when compared with SPECT. A major limitation of the direct evidence is that, in most cases, validation was against clinical diagnostic criteria rather than histopathologic diagnosis. In the two studies that compared FDG-PET with SPECT in differentiating AD from non-AD dementia, the sensitivity and specificity of FDG-PET (71% and 60%) and SPECT (69% and 57%) were similar.

A larger number of low quality studies have assessed the diagnostic accuracy of either FDG-PET or SPECT. The Assessment Report included such studies, but only those that sought pathological confirmation of diagnosis. Ultimately, the combined results 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%. However, the pooling and comparison of indirect evidence is prone to bias due to inevitable differences between the patient populations across the different studies, which compromises the reliability of the estimates.

Importantly, some studies assessed the ability of FDG-PET and SPECT to distinguish between AD patients and normal controls, while other studies assessed the extent to which the test could differentiate between various types of dementia (e.g. AD and frontotemporal dementia). The most applicable studies are those that include the full range of patients likely to be seen in clinical practice, which could include patients with very early signs of disease (e.g. MCI) through to patients with manifest disease (Panegyres et al, 2009). Assessing highly selected subsets of patients limits the clinical applicability of the results.

Safety

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

Change in patient management

There was limited evidence available regarding change in management brought about by FDG-PET. One study found that FDG-PET resulted in a change in diagnosis in 29% of patients, and increased the use of AChEIs after diagnosis. These findings are supported by the only available Australian evidence (Elias et al, 2014), which reported a change in diagnosis in 35% of dementia patients who underwent FDG-PET.

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 required to provide data on the health outcomes of those who are correctly diagnosed.

Evidence regarding the effectiveness and safety of anti-AD drugs is relatively limited. In particular, the effect of anti-AD drugs on outcomes beyond cognition, function, behaviour and global impact, remains fairly uncertain. Of relevance to this assessment, there is limited evidence for the impact of treatment on quality of life (QoL), admission to full-time care and resource use, which underpin claims of cost-effectiveness. Furthermore, long-term follow-up (especially beyond one year) on the effect of anti-AD drugs on any outcome remains a major evidence gap.

Pre-modelling studies

Section C presents each of the translation issues identified to enable the transition from the clinical evidence discussed above to the economic evaluation presented in Section D. Applicability, extrapolation and transformation issues were considered in turn. In each instance, a focused analytical plan is presented prior to presenting the results of the pre-modelling study and the relationship between these and the economic evaluation presented in Section D.

Table ES.2 below summarises all potential translation issues/pre-modelling studies considered in Section C.

Table ES.2 Summary of translation issues considered in Section C

Translation issue	Methods and data sources	Relationship with Section D
Applicability issues	-	-
Population and circumstances of use (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 AD treatment (Section C.3)	On the basis of published data, duration of treatment was estimated for mild AD patients treated with AChEIs and moderate AD 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 AD (Section C.4)	Following a literature search, published transition probabilities that considered the impact of disease progression (according to mild AD, moderate AD and severe AD 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 AD drugs (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 AD 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 AD.	Treatment effect was applied to the natural history estimates of an untreated population to slow progression in individuals treated for AD. The uncertainty around the estimates used, which is acknowledged to be considerable, was examined in sensitivity analyses.

Translation issue	Methods and data sources	Relationship with Section D
Utility weights applied to the economic model (Section C.6)	A literature search was undertaken to source utility weights for individuals with AD, 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 sensitivity analyses.
Healthcare resource use and associated costs (Section C.7 and Section C.8)	Using published data, costs associated with AD 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 (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; AD, Alzheimer's disease; GPs, general practitioners

Economic evaluation

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. Nonetheless, a cost-utility analysis (CUA) has been undertaken, as suggested by PASC, assuming inferiority of SPECT but at a much lower cost.

There are a large number of CUAs relating to treatment of AD, many of which incorporate complex modelling approaches with microsimulation and probabilistic sensitivity analysis. The PBAC considered a CUA for AD at their December 2000 meeting when they recommended listing rivastigmine on the PBS. All other AD medications were recommended on a cost-minimisation basis.

There is a vast literature of studies undertaking economic evaluations of AD treatment using progressive models of AD's natural history, with evidence of at least 10 general modelling frameworks to assess the cost-effectiveness of AD treatment. These general models each present a different method to model the statistical relationship between risk factors and health states. One of the most widely used of all the models, and the model best able to differentiate patients by disease severity and residential setting, was first presented in the cost-effectiveness study by Neumann et al (1999).

The approach taken in support of the current Assessment Report was to construct a Markov model based on the treatment model by Neumann et al (1999), which characterises progression of AD through different disease stages and residential settings. In any time period, patients are classified into one of three disease stages – mild, moderate or severe AD. Conditional on disease stage, patients are also assigned a probability of being in one of two settings: in the community or institutionalised in a nursing home.

The Neumann model did not, however, incorporate diagnostic testing. Although there are some diagnostic models available, they do not adequately capture imaging test accuracy for a diagnostic model. Therefore, this Assessment Report presents a de novo

model commencing with diagnostic testing in terms of true positive (TP), true negative (TN), false negative (FN) and false positive (FP) results.

The structure of the model differentiates patients according to three characteristics:

1. disease severity (i.e. mild AD, moderate AD, no AD and, in later stages of the model, severe AD);
2. institutional setting (i.e. whether individuals are community-based or institutionalised in nursing homes); and
3. treatment status (i.e. whether individuals are receiving drug therapy for their AD or suspected AD).

The model takes the form of a state-transition semi-Markov model with non-constant transition probabilities applied where appropriate. The model was intentionally constructed in way that would avoid the unnecessary technical complexity of previous models by avoiding microsimulation/Monte Carlo methods. Instead, 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 (based on an Australian study) 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 appropriately applied to the model, which was constructed using TreeAge Pro 2014. All costs and outcomes were discounted at an annual rate of 5%, in accordance with MSAC Guidelines.

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

Table ES.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: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; QALY, quality-adjusted life year; SPECT, single-photon emission tomography
 Note: Rounding may impact on some figures

It was estimated that FDG-PET will save \$1,160 per patient over a five-year period, while also delivering an incremental QALY gain of 0.03. While this renders the ICER itself somewhat difficult to interpret, the key conclusion to draw from this result is that FDG-PET is more effective and less costly than SPECT in the diagnosis of AD.

Consequently, if the assumptions of the base case analysis are to be accepted, the decision-making process is simple: FDG-PET is to be accepted as a cost-effective alternative to SPECT for the requested listing. Sensitivity analyses presented in Section D.6, however, explore the impact alternative assumptions have on the result.

The cost difference is driven by larger downstream cost offsets associated with progression to severe AD. In particular, this is best understood as avoidance of the large nursing home care costs individuals incur in the severe AD health state. By avoiding/slowing progression to this health state (due to the effectiveness of AD drugs), there are large 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 AD detected.

The results of the model were shown to be 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. Of these, the second two are particularly noteworthy.

The cost savings generated in the base case are highly dependent on the inclusion (and magnitude) of these costs. If the assumptions of the base case are called into question, the conclusions drawn from the result could require re-examination.

In the case of diagnostic accuracy, sensitivity analyses reported in Section D.6 serve to highlight the complex relationship between diagnostic accuracy and cost-effectiveness. They also highlight the sensitivity of the base case results to the assumptions therein. If the data used in the base case can be accepted, it would appear that FDG-PET is a cost-effective alternative to SPECT in the diagnosis of AD. If, however, there is doubt regarding the acceptability of these data, it is clear that the conclusions of the base case may not be valid and particular caution should be taken to ensure that the impact of alternative data are well understood. In cases such as the present, where the incremental cost and QALY results are so close to zero, the conclusions are particularly sensitive and this should be accounted for in the decision-making process.

Estimated utilisation and financial implications

The estimated financial implications of a successful listing of FDG-PET on the MBS would ideally rely on either robust 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 AD across Australia and how diagnosis is achieved using functional imaging.

A scarcity of data of either type, however, 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 AD.

That is, the analysis follows an epidemiological approach which aimed to estimate the current use of SPECT in identifying AD from estimates of projected dementia incidence (Access Economics, 2009) and estimates regarding the proportion of these cases which are due to AD (Alzheimer's Disease International, 2014). These data were used in conjunction with assumptions regarding the rate at which SPECT is used to diagnose AD 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.

Note that, while SPECT was assumed to be the relevant comparator for this analysis, the MBS item fee for SPECT is shared with other diseases/indications. That is, while SPECT may be used under the MBS for use in diagnosing AD, it is also used for epilepsy, stroke, acute brain injury, etc. Consequently, it was not possible to derive estimates from MBS usage statistics, as there is no way to estimate what proportion of use relates to dementia/AD diagnosis.

In addition to these data and assumptions to estimate the use of FDG-PET for diagnosis of AD, the analysis also considered the possibility of increased expenditure on PBS-listed medications to treat AD. That is, with the increased use of FDG-PET, it is anticipated that more positive diagnoses would be made (both true positives and false positives). Since this will lead to greater use of PBS-listed medication, the financial impact of this has been accounted for. This part of the analysis relied on data considered in Section C (i.e. daily treatment costs and treatment duration estimates). These were described previously and are referred to again in detail below.

Table ES.4 below presents estimates of the number of SPECT services currently utilised under the MBS for diagnosis of AD as well as the number of SPECT and FDG-PET services anticipated in the event of a positive listing for FDG-PET on the MBS. These estimates account for replacement of SPECT with FDG-PET as well as increased use of functional imaging in the event of a positive listing for FDG-PET on the MBS.

Table ES.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 AD diagnosis via the MBS	1324	1387	1455	1513	1581
FDG-PET services undertaken to attempt AD diagnosis via the MBS	0	0	0	0	0
With MBS listing for FDG-PET	-	-	-	-	-
FDG-PET services replacing SPECT to attempt AD diagnosis via the MBS	199	416	655	908	1106
Net SPECT services undertaken to attempt AD 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 AD via the MBS in the event of a positive listing	199	451	728	1021	1264

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule

Accounting for associated specialist consultations, the total MBS costs with and without a successful FDG-PET listing on the MBS are presented in Table ES.5.

Table ES.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 AD diagnosis	\$699,987	\$733,778	\$769,502	\$799,947	\$835,871
Total cost of FDG-PET for AD 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 AD diagnosis	\$594,989	\$513,645	\$423,226	\$319,979	\$250,761
Total cost of FDG-PET for AD 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
<i>Total net financial impact of a successful listing for FDG-PET on the MBS</i>	<i>\$62,133</i>	<i>\$166,142</i>	<i>\$280,159</i>	<i>\$401,361</i>	<i>\$509,718</i>

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule

Additionally, however, as discussed in Section C.9, it is anticipated that FDG-PET will lead to more positive test results than in the case of SPECT. A consequence of this is a greater proportion of individuals moving on to PBS-listed therapies to treat AD. This has obvious cost implications, further increasing the total financial impact to the total Government health budget. Although this is expected to be modest, it was important to account for nonetheless. The total net financial impact to the MBS and PBS budgets is presented in Table ES.6.

Table ES.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

Background

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. The application was initially considered in April 2014 by the Protocol Advisory Sub-Committee (PASC) of the Medical Services Advisory Committee (MSAC) and the Final Protocol was published in September 2014.

In October 2014, HealthConsult Pty Ltd was contracted to conduct an assessment of the safety, effectiveness and cost-effectiveness of FDG-PET for the diagnosis of AD in order to inform a decision as to whether this service should be reimbursed through the MBS.

Section A. Details of the proposed medical service and its intended use

A.1. Address all items in the Protocol

This Assessment Report follows the framework that was provided in the Final Protocol, as agreed by PASC when they considered the application at their April 2014 meeting.

Table A.1-1 Items addressed in the Protocol and Assessment Report

Items in the Final Protocol	Location in Assessment Report	Concurs with Protocol	Change and justification
Proposed MBS listing	Section A.3	Yes	NA
Comparator	Section A.4	Yes	NA
Clinical management algorithm	Section A.5, Figure A.5-1	Yes	NA
Clinical outcomes assessed	Section A.8, Section B.5, Section B.6	Yes	There was limited evidence available for some of the outcomes specified in the Protocol. Linked evidence was required to address patient outcomes resulting from the diagnostic intervention. Evidence for the effectiveness and safety of anti-dementia medicines for AD was addressed using the summarised findings from recent systematic reviews.
Healthcare resources	Section A.3, Section C.7 and C.8	NA	The Protocol did not provide a list of healthcare resources. The only costs considered in the Protocol were those of the proposed MBS item and the MBS item for the comparator. AD medications are also mentioned in the Protocol and are considered in the economic model and financial estimates.
Economic evaluation structure	Section D.3	Yes	Consistent with the Protocol (p13), Section D presents a CUA. The decision analytic structure of the economic evaluation was not provided in the Protocol.

Abbreviations: AD, Alzheimer's disease; CUA, cost-utility analysis; MBS, Medicare Benefits Schedule; NA, not applicable

A.2. Proposed medical service

The proposed medical service involves an FDG-PET study of the brain in patients with suspected AD, where the diagnosis remains uncertain after specialist assessment (routine blood tests, clinical evaluation, and structural imaging).

A.2.1. Alzheimer's disease

AD is the most common form of dementia, accounting for up to 75% of all cases (AIHW, 2012). It is a progressive neurodegenerative condition which is characterised by short-term memory loss, changes in personality, behavioural abnormalities, and a progressive intellectual and cognitive deterioration (EMA, 2008). While AD is not a natural part of ageing, the prevalence of AD and other forms of dementia increases rapidly with age. According to 2011 data from the Australian Institute of Health and

Welfare (AIHW), 9% of Australians aged 65 and over and 30% of Australians aged 85 and over had dementia (AIHW, 2012).

The pathologic hallmarks of AD are amyloid plaques caused by an accumulation of beta-amyloid ($A\beta$) peptide and neurofibrillary tangles, which result from abnormal phosphorylation of the tau protein (Kolarova et al, 2012). The development of amyloid plaques and neurofibrillary tangles occurs in a preclinical phase of disease. Over time the accumulation of plaques and tangles lead to synapse dysfunction and loss of neurons, at which point early signs of cognitive impairment become apparent. As AD progresses, gross atrophy occurs in specific brain regions, leading to more noticeable and progressive cognitive decline (Sperling et al, 2011).

According to The Royal Australian College of General Practitioners (RACGP), confirmation of suspected dementia (including AD) would initially involve consultation with a general practitioner (GP). GPs should undertake a patient history, perform a comprehensive physical examination, and conduct basic cognitive assessments (RACGP, 2012). In Australia, the standard diagnostic tools used for cognitive assessment in patients with suspected AD are:

- (1) Mini-Mental State Examination (MMSE);
- (2) General Practitioner Assessment of Cognition (GPCOG);
- (3) Clock drawing test; and
- (4) Rowland Universal Dementia Assessment Scale (RUDAS) – a multicultural cognitive assessment scale that has been used to detect dementia across cultures.

The ambiguity of early AD symptoms makes it challenging for GPs to exclude alternative diagnoses on the basis of patient history and cognitive assessment(s) alone (Phillips et al, 2011). As such, routine blood tests (e.g. full blood count, thyroid function, vitamin B12, folate) are typically undertaken to rule out other unrelated and readily treatable causes of cognitive decline such as infections, metabolic disturbances, and malnutrition. GPs may also request a computed tomography (CT) scan before referral to a specialist.

In cases where the diagnosis remains inconclusive (i.e. other potential causes of cognitive impairment have not been excluded), further investigations including magnetic resonance imaging (MRI), neuropsychological assessment, and functional imaging would be considered by a specialist (Pond, 2012).

A.2.2. Semi-quantitative FDG-PET

PET is a minimally invasive nuclear medicine imaging technique that uses radiopharmaceuticals that mimic endogenous molecules to detect and assess perfusion and metabolic activity in various organ systems (Kostakoglu and Goldsmith, 2003). It provides information about function and metabolism that is complementary to the structural information provided by anatomical imaging techniques such as MRI and CT.

PET scanning is non-invasive, but it does involve exposure to ionising radiation. ^{18}F -FDG, which is now the standard radiotracer used for PET neuroimaging and cancer patient management, has an effective radiation dose of 14 mSv.

Importantly, the proposed medical service is limited to PET using the radiolabelled glucose analogue F-18 fluorodeoxyglucose (FDG), which is the most common

radiopharmaceutical used in PET scanning. FDG is administered intravenously and has a half-life of 110 minutes, making FDG-PET a practical tool for the diagnosis and staging of cancers compared with other short-lived positron emitters. Additionally, it is a valuable tool in the detection of early signs of cancer recurrence and has superior utility in the evaluation of early response to therapy compared with CT or MRI (Kostakoglu and Goldsmith, 2003).

In addition to clinical utility in oncology, FDG has been recognised for several decades as a biomarker that allows the assessment of the presence or extent of neuronal injury, with application in the diagnosis of neurodegenerative conditions (Filippi et al, 2012). PET is used to evaluate the uptake of FDG by brain tissue, measured as the regional cerebral metabolic rate for glucose (CMRgl). The CMRgl provides information about the entity of neuronal loss or synapse dysfunction, which are important indicators of AD (Vacante et al, 2013). In particular, AD is typically characterised by a pattern of hypometabolism or hypoperfusion in the temporoparietal lobe (Herholz, 2002). Another biomarker (Pittsburgh Compound B (PiB)) used in conjunction with PET has gained recent attention but is not the focus of the current Assessment Report.

Similar to other imaging modalities, accurate diagnostic interpretation of the brain FDG-PET scans depends on the experience and skill of the person interpreting the results. FDG-PET measurements often lack clearly defined cut-offs to distinguish between normal and pathologic findings and therefore visual ratings depend heavily on the observer's prior experience and training (Bohnen et al, 2012). Several automated tools are now available, with the most common being voxel-based analysis techniques with statistical parametric mapping procedures. This allows observer-independent, quantitative mapping of regional glucose metabolic abnormalities, through statistical comparison of the ¹⁸F-FDG pattern in the individual brain against the mean and standard deviation (SD) of a control population. While there is some evidence that the addition of quantitative information improves diagnostic accuracy (Frisoni et al, 2013), subjective (visual) interpretation of the brain scan may still be common in clinical practice.

A.2.3. Clinical need

Currently, there is no single test that can diagnose AD and a definitive diagnosis can be made only through brain autopsy (Hyman et al, 2012). The exclusion of other causes of the early, non-specific symptoms of AD is therefore a fundamental part of the diagnostic process and a major challenge faced by GPs. Specialist examination and routine blood tests are undertaken to rule out differential diagnoses including dementia and delirium, hypothyroidism, and severe vitamin B12 deficiency (Vacante et al, 2013). Structural imaging (preferably MRI) is used to exclude underlying conditions such as subdural haematoma and brain tumours. In addition to ruling out differential diagnoses, structural MRI may, depending on the stage of the disease, reveal cerebral alterations that are characteristic of AD (e.g. brain atrophy).

As such, structural imaging, in combination with other prior tests, will often provide enough information to confidently diagnose AD in moderate to severe cases. However, the presence of AD in a mildly affected brain is more difficult to diagnose using MRI, particularly due to difficulty in distinguishing it from the mild decline in memory that can occur with normal aging and from mild cognitive manifestations of other neuropsychiatric conditions (Silverman et al, 2008). In contrast, functional imaging, including PET and single-photon emission computed tomography (SPECT), is able to

identify changes in glucose and oxygen metabolism, respectively, that is characteristic of AD before widespread atrophy occurs (Bloudek et al, 2011). The clinical need for such diagnostic techniques is therefore very high in patients with early signs of AD, who have not yet passed the optimal window for therapeutic intervention.

Physician confidence in a dementia diagnosis can also be challenging in younger patients, in atypical presentations, in patients with comorbid depressive and cognitive symptoms, and in patients with a higher level of education, who can experience a substantial decline of cognitive function before reaching the lower normal limits of standardised neuropsychological tests (Bohnen et al, 2012). More accurate assessment of dementia diagnosis can help to better select appropriate patients for anti-dementia therapy and family prognostic planning.

In Australia, there are currently around 300,000 people living with dementia (predominantly AD) and the figure is projected to rise to around one million in 2050 as the population rapidly grows and ages (Phillips et al, 2011). Currently, symptoms of dementia are detected by family members an average of 1.9 years prior to the first medical consultation and an average of 3.1 years passes before a firm diagnosis is made (Phillips et al, 2011). Rates of early diagnosis in a mild stage of AD may be improved if FDG-PET was made more readily available and accepted into the standard diagnostic pathway for mild or diagnostically challenging AD. With the availability of effective treatment, the detection of AD at an early stage could have a significant effect on downstream medical and residential aged care expenditure.

Despite the fact that there is currently no cure for AD, there are numerous advantages associated with early diagnosis. Several treatments are available that have been reported to slow cognitive and functional decline and diminish the severity of behavioural and psychiatric symptoms (Vacante et al, 2013). Patients with AD that is diagnosed in its early stages could benefit from the optimal use of the available drugs (see Table A.2-1), with the possibility of delayed progression to more debilitating stages of disease. In addition, they may be able to trial newly developed interventions and will have a greater opportunity to plan care strategies and organise legal matters such as power of attorney (Phillips et al, 2011).

Importantly, functional imaging techniques such as FDG-PET have very limited utility in patients with severe AD, as less advanced diagnostic techniques (e.g. cognitive tests and/or MRI) would be sufficient to provide a confident diagnosis (McMahon et al, 2003). Furthermore, in Australia, patients with severe AD are excluded from the Pharmaceutical Benefits Scheme (PBS)-eligible population for AD drugs and therefore would not benefit from access to subsidised therapy.

As the Australian population rapidly ages, the addition of FDG-PET into the diagnostic pathway of mild and difficult-to-diagnose AD will mean that less patients miss the optimal window in which the condition responds to therapy (i.e. before the onset of severe symptoms). The timely diagnosis of AD is therefore paramount and FDG-PET may be an important diagnostic tool where other tests and imaging modalities are unable to provide a confident diagnosis of AD.

As well as its utility in the diagnosis of AD, FDG-PET has utility in providing greater prognostic information than other diagnostic tools. Hypometabolism in the temporoparietal lobe would indicate underlying AD and the patient would therefore know at an early stage that their cognitive decline is irreversible.

A.2.4. Regulatory status and prerequisites

Regulation

According to the Final Protocol, there are three PET machines registered on the Australian Register of Therapeutic Goods (ARTG):

- GE Healthcare Australia Pty Ltd. ARTG #156649 and ARTG #114476
- Phillips Electronics Australia Pty. ARTG #147067

There are two registered PET/CT machine types¹:

- Siemens Ltd. ARTG #144218
- Philips Electronics Australia Ltd. ARTG #118077

There are two registered PET/MRI machine types:

- Siemens Ltd. ARTG #188470
- Philips Electronics Australia Ltd. ARTG #193622.

There are also four registered types of PET imaging software available:

- Siemens Ltd. ARTG #181848 and ARTG #178420
- GE Healthcare Australia Pty Ltd. ARTG #154936 and ARTG #153390.

There are two registered entries for FDG injection:

- 2-deoxy-2-(¹⁸F)fluoro-D-glucose; Austin Health, in Melbourne, ARTG #54251
- FDGen (Fludeoxyglucose [¹⁸F] Injection); PETNET Australia Pty Ltd, with ARTG #78935 (Licence number MI-2009-LI-03349-3).

Only the FDG product from Austin Health lists neurological disorders as an indication.

Additionally, there is a second commercial supplier of radiolabelled FDG in Australia, Cyclotek which is a TGA approved manufacturer (Licence number MI-12092005-LI-000904-2). Radiolabelled FDG is also produced at the Royal Prince Alfred Hospital (NSW), Peter MacCallum Cancer Institute (VIC), Royal Brisbane Hospital (QLD), Wesley Hospital (QLD) and Sir Charles Gairdner Hospital (WA).

The requested MBS listing for FDG-PET is consistent with the regulatory body approved indication.

Prerequisites

Reimbursement of the proposed medical service would require referral from a recognised specialist (e.g. geriatrician, psychiatrist, neurologist) or consultant physician.

PET scanners are often confined to large, metropolitan, public hospitals due to the high capital cost of the scanner and ongoing costs to maintain and operate the machine.

Additionally, each 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

¹ In this assessment, the term 'PET' is used to refer to either PET or PET/CT. The term 'PET/CT' is used where specific reference to this modality is made. Most current and future practice will relate to the use of PET/CT machines, as all PET machines sold now in Australia are PET/CT machines.

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.

A.2.5. Co-administered and associated services

There are no diagnostic tests or other MBS services that would typically be co-administered with FDG-PET.

The proposed listing of FDG-PET could marginally increase the number of associated GP attendances (MBS item 23) if a greater number of patients are diagnosed with AD and regularly see their GP to monitor and/or manage their condition. Conversely, the potential earlier diagnosis of AD through FDG-PET could minimise GP visits, as ongoing GP attendances to investigate the non-specific symptoms of undiagnosed AD would be avoided. These potential downstream costs or savings are highly uncertain.

Anti-dementia medicines for AD

There are four drugs subsidised through the PBS and Repatriation Pharmaceutical Benefits Scheme (RPBS) for patients who have a diagnosis of AD (see Table A.2-1).

Table A.2-1 List of PBS-subsidised drugs used for the treatment of AD

Drug class	Drug name	Trade name	PBS codes
Acetylcholinesterase inhibitor	Donepezil	Aricept®	2479L, 2532G, 8495D, 8496E
Acetylcholinesterase inhibitor	Galantamine	Reminyl® Galantyl®	2463P, 2531F, 2537M, 8770N, 8771P, 8772Q
Acetylcholinesterase inhibitor	Rivastigmine	Exelon®	2475G, 2476H, 2477J, 2493F, 2494G, 2526Y, 2551G, 8497F, 8498G, 8499H, 8500J, 8563Q, 9161E, 9162F
NMDA receptor antagonist	Memantine	Memaxa® Ebixa® APO-Memantine®	1956Y, 2492E, 2513G, 9306T

Abbreviations: AD, Alzheimer's disease; NMDA, N-methyl-D-aspartate; PBS, Pharmaceutical Benefits Scheme.

The acetylcholinesterase inhibitors (AChEIs) work by stopping the breakdown of acetylcholine in the brain, effectively increasing the level of this chemical. Acetylcholine is used by the nerve cells in the brain and is important for memory. Increasing the level of acetylcholine can increase communication between nerve cells and may improve or stabilise the symptoms of AD.

Memantine acts quite differently to the AChEIs. It works by blocking the chemical glutamate. This prevents too much calcium entering the brain's nerve cells, which can damage or affect the function of the cells.

The four medicines listed on the PBS do not cure AD but give some relief from symptoms, and may slow decline in progression of the disease for a period of time in some patients (PBS Review, 2012)². These medicines also have significant side effects, which means that some people do not tolerate these medicines and will need to stop treatment within months of starting. Starting at a low dose with upward titration has been reported to overcome some of these issues (PBS Review, 2012).

² Summary and PBAC Minutes available on the PBS website ([PBS website](#)); full report available by request to the PBAC Secretariat.

Access to the PBS subsidy is restricted to cases confirmed by (or in consultation with) a specialist or consultant physician, subject to specific clinical criteria being met (MMSE or Standardised Mini-Mental State Examination (SMMSE) scores).

As discussed in Section A.2.3, patients with severe AD are unable to access PBS-subsidised AD drugs and generally require an MMSE or SMMSE score of 10 or more (on a 30-point scale) for initial therapy. A patient with an (S)MMSE score of 9 or less may be able to access the PBS-subsidised therapy provided that they are unable to register a higher score for reasons other than AD (e.g. intellectual disability, lack of competence in English, limited education).

In 2009–10, a total of 392,796 subsidised dementia-specific medications were dispensed with an average annual growth in the dispensing of subsidised dementia-specific medications of 8% each year between 2002–03 and 2009–10 (AIHW, 2012). Based on PBS and RPBS data, Australian Government expenditure on dementia-specific medications in 2009–10 was \$58.7 million (AIHW, 2012).

The proposed listing of FDG-PET to diagnose AD could marginally increase the rate of uptake of these medications but any effect is likely to be small (see Section E.5).

A.2.6. Current reimbursement arrangements

Currently, public reimbursement of FDG-PET for the diagnosis of AD is not available, although FDG-PET is funded through the MBS for a range of other indications: MBS items 61523 to 61646 (Group I4 – Nuclear Medicine Imaging), which are predominately whole body scans relating to oncology.

In the absence of public funding for FDG-PET for the diagnosis of AD, patients with suspected AD who undergo FDG-PET have to pay for the service out-of-pocket. There is no private health insurance rebate for PET services.

A.2.7. Existing MBS services for the diagnosis of AD

As discussed in Section A.2.1, the diagnosis of AD in Australia involves an initial clinical and cognitive evaluation by a GP and blood tests for routine biochemistry, haematology, thyroid function, vitamin B12 and folate. The GP may also conduct a CT scan before referring the patient to a specialist (e.g. neurologist, neuropsychiatrist, geriatrician) who will conduct a further clinical evaluation and may request an MRI. All of the aforementioned tests are currently funded through the MBS and the intention of the application is that FDG-PET would supplement rather than replace those MBS items in the diagnostic pathway.

In contrast, it is proposed that FDG-PET would replace SPECT in the diagnostic pathway, where other diagnostic methods are inconclusive. The assessment of cerebral perfusion with SPECT is currently funded through MBS item 61402. SPECT for the diagnosis of AD is discussed further in Section A.4.

A.3. Proposed MBS listing sought

A.3.1. Proposed descriptor for the service

Table A.3-1 presents the MBS descriptor for the proposed medical service, as shown in the Final Protocol (Table 1, p8). The Applicant did not recommend specific wording for

the proposed MBS item; however, they did state that the technique is the same as for MBS item 61559 (FDG-PET study of the brain, performed for the evaluation of refractory epilepsy which is being evaluated for surgery). Based on MBS item 61559, the Assessment Group who prepared the Final Protocol developed the proposed item descriptor. The fees shown in Table A.3-1 have been updated to reflect the current fees according to MBS Online (accessed 12 November, 2014).

Table A.3-1 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

Source: Final Protocol September 2014, p8, updated to reflect changes introduced 01 November 2014 in the calculation of 85% benefit

FDG-PET scans for the diagnosis of AD will be provided by a nuclear medicine specialist upon receipt of a written referral from a medical specialist. The professional groups most likely to order this test are neurologists, geriatricians and psychiatrists.

Importantly, while a characteristic AD pattern of hypometabolism may be observed visually (i.e. qualitatively) using FDG-PET, the Applicant proposed that MBS funding should be restricted to FDG-PET assessments that use a semi-quantitative method of analysis. This is not explicitly stated in the proposed MBS item descriptor. Compared with visual interpretation, computer software programs such as NEUROSTAT 3D-SSP allow for a more objective analysis of the pattern of hypometabolism by comparing the pattern of tracer uptake in the patient’s scan with a reference data set (Filippi et al, 2012).

As discussed in the Final Protocol, it is expected that patients would only have one FDG-PET scan for the diagnosis of AD. While the item descriptor does not preclude multiple FDG-PET scans in one patient, it is likely that patients in whom the diagnosis remains equivocal would only have a repeat scan 2-3 years later³. Similarly, patients with a negative test who experience persistent symptoms of cognitive decline may undergo a repeat scan after 2-3 years.

A.3.2. Proposed fee for the service

As discussed in the Final Protocol, the Applicant has proposed a fee of \$1,180, which is greater than the fee current fee of \$918.00 for MBS item 61559. No explicit justification for the higher fee was provided; however it may have been to offset the cost of the computer software discussed in Section A.3.1. The Applicant stated that the programs cost up to \$40,000; however PASC subsequently advised that certain programs (e.g. NEUROSTAT 3D-SSP) are available as freeware.

A.4. Comparator details

The assessment of cerebral perfusion with SPECT is currently funded through MBS item 61402 as shown in Table A.4-1. 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.

³ Advice provided by Health Expert Standing Panel (HESP) member

Table A.4-1 MBS item descriptor and fee for MBS item 61402

Category 5 – DIAGNOSTIC IMAGING SERVICES
<p>MBS 61402</p> <p>CEREBRAL PERFUSION STUDY, with single photon emission tomography and with planar imaging when undertaken (R)</p> <p>Fee: \$605.05 Benefit: 75% = \$453.80 85% = \$526.65</p>

Source: MBS Online, accessed 12 November 2014.

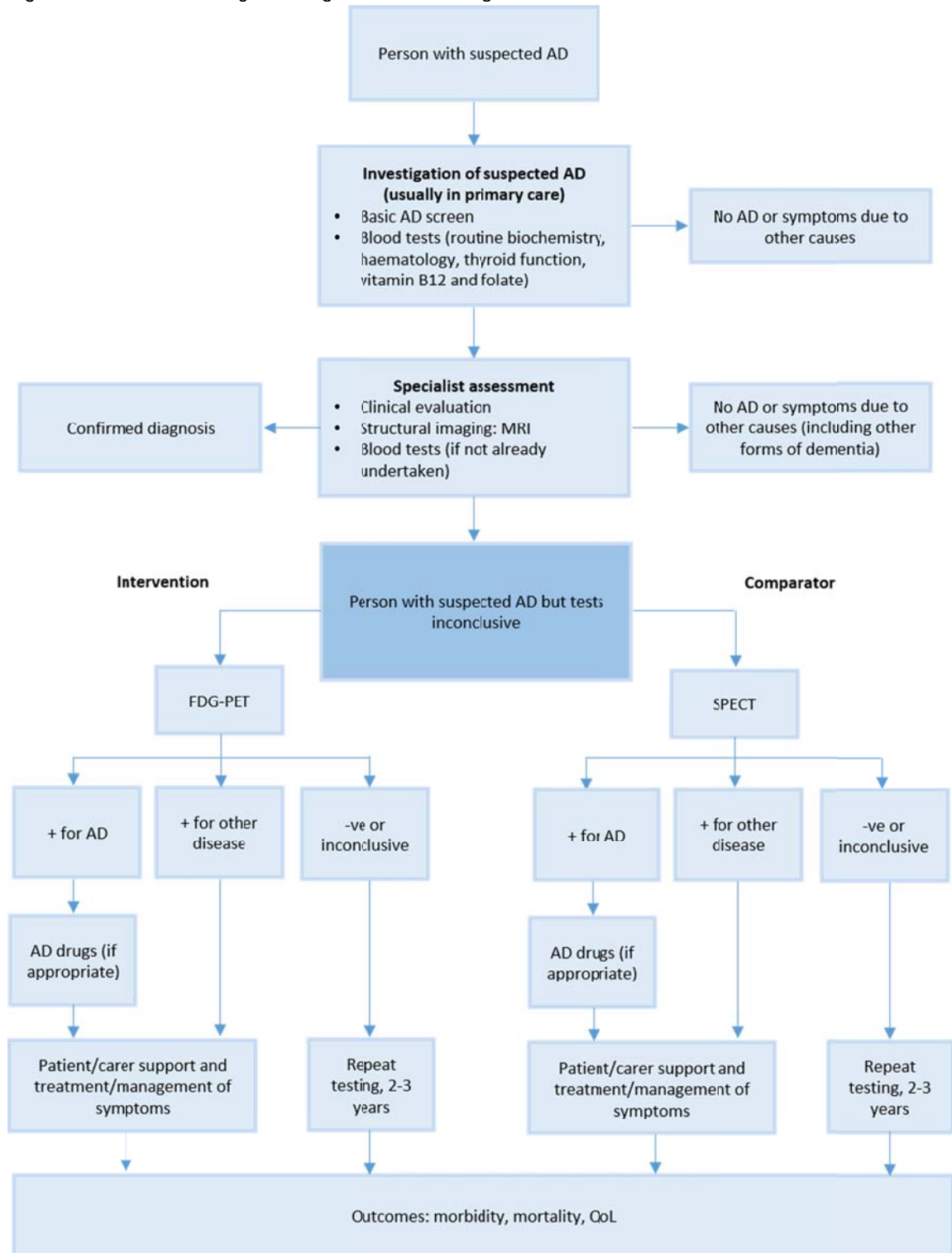
Like FDG-PET, SPECT can be analysed using semi-quantitative methods. Both CBF and CMRgl (assessed using FDG-PET) reflect brain metabolism and can assist in diagnosing AD. SPECT is technically less demanding and more widely available than PET but also has lower resolution (Filippi et al., 2012). FDG-PET 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.

A.5. Clinical management algorithm

The clinical management algorithm for the diagnosis of patients with suspected AD is shown in Figure A.5-1. The various tests outlined in the algorithm are all currently available for suspected AD patients in Australia; however, under the current funding arrangements an MBS rebate is not available for FDG-PET. Under proposed funding arrangements an MBS rebate is available for all diagnostic tests shown in the clinical algorithm.

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

Figure A.5-1 Clinical management algorithm for AD 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.

A.6. Differences between the proposed medical service and the main comparator

Both SPECT and PET have different advantages and disadvantages. Equipment needed for SPECT is cheaper and more widely available. Access to PET scanning in Australia is more restricted, particularly in regional areas, although the number of PET facilities is increasing with more widespread application in oncology for diagnosis and monitoring. SPECT is still most frequently used in Europe to aid diagnosis of dementia (Ebmeier, 2010) whereas PET is used more widely in the USA.

Unlike PET, SPECT scanning relies on photon-emitting isotopes instead of radioisotopes. SPECT isotopes have longer half-lives and are relatively cheap compared with PET isotopes (Colloby and O'Brien, 2004). While FDG-PET is used to detect characteristic patterns of glucose hypometabolism in patients with AD, SPECT imaging is used to assess characteristic patterns of regional blood flow (Gaugler et al, 2013). SPECT tracers provide a 'snapshot' of blood flow around the time of injection; in contrast, FDG-PET images are 'real time' representations of metabolism while the subject is in the scanner. PET has advantages with respect to spatial resolution, with resolution of 4-6 mm as compared with SPECT resolution of 8-16 mm (Colloby and O'Brien, 2004).

A.7. Clinical claim

Existing MBS-funded tests for the diagnosis of AD have significant limitations in terms of reaching a confident diagnosis of AD. In its early stages, AD is particularly difficult to differentiate from other conditions (see Section A.2.3). Structural imaging techniques are mainly used to exclude surgically treatable causes of cognitive impairment (e.g. subdural haematoma) but are typically unable to differentiate between the various types of dementia. SPECT, the only functional diagnostic tool that is currently listed on the MBS, can provide diagnostic support in challenging cases; however, SPECT is associated with limitations in image resolution and is claimed to be inferior to FDG-PET in terms of diagnostic accuracy in cases of suspected AD.

The improved patient selection afforded by FDG-PET may significantly reduce the number of mild or diagnostically challenging cases of AD that remain undiagnosed, or in which diagnosis is delayed until the onset of more severe cognitive symptoms. Overall, when compared with SPECT, FDG-PET may improve patient outcomes by providing the opportunity to pursue treatment strategies at a disease stage that is responsive to treatment.

A.8. Primary elements of the decision analysis

As the proposed medical service is a diagnostic test, the research question that underpins this evidence-based assessment is formulated around the PPICO criteria, in which the key components are the target population (P), prior tests (P), the intervention (I), comparator (C) and target outcomes (O). The specific components of the PPICO criteria (shown in Table A.8-1) are used to inform the literature search strategy and the economic evaluation.

As per the Final Protocol, the question for public funding addressed in this review is:

In people with suspected Alzheimer's disease in whom prior tests (clinical evaluation, MRI and blood tests) have been inconclusive, what is the safety, effectiveness and cost-effectiveness of FDG-PET as a replacement for SPECT for establishing a diagnosis?

Table A.8-1 Summary of PPICO criteria to define research question that assessment will investigate

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcomes to be assessed
People with suspected AD in whom prior tests have been inconclusive	1) Clinical evaluation 2) Structural imaging: MRI (or CT only where MRI is contraindicated) 3) Blood tests <ol style="list-style-type: none"> Routine biochemistry Haematology Thyroid function Vitamins B12 and folate 	Semi-quantitative FDG-PET	SPECT	Histopathologic diagnosis via autopsy or biopsy, or long-term clinical follow-up	<u>Safety</u> Adverse events Radiation exposure <u>Diagnostic accuracy</u> Sensitivity Specificity Additional TP & FP <u>Change in management</u> Treatment instigated Treatment avoided Other changes occurring in ≥10% patients <u>Patient outcomes</u> Disease-specific mortality Disease progression <ul style="list-style-type: none"> • Cognitive function • Global outcome • Activities of daily life Quality of life Prognostic value <u>Cost-effectiveness</u>

Abbreviations: AD, Alzheimer's disease; CT, computed tomography; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; FP, false positive; SPECT, single-photon emission computed tomography; TP, true positive.

There are important considerations relating to the two reference standards presented in Table A.8-1. For studies that followed patients longitudinally (i.e. long-term clinical follow-up), a patient may have been deemed to have a non-progressive course after two or three years of stable cognitive status. However, some of these patients may have developed signs of progressive dementia after the period of follow-up in the study. If these patients had a negative FDG-PET or SPECT scan, they would have been categorised as true negatives when in fact they were false negatives, so the sensitivity reported would be falsely elevated. If patients had an abnormal FDG-PET or SPECT scan with no progression detected during follow-up (but progression evident on longer term follow-up), they would have been classified as false positives when in fact they were true positives, and the specificity reported would be lower than the true specificity.

Although postmortem pathologic diagnosis of AD is considered the 'gold standard', it is becoming increasingly apparent that it is not a perfect reference standard in practice. There is no universally accepted set of pathologic diagnostic criteria, and the various diagnostic algorithms place discordant degrees of reliance on varying diagnostic factors (Bohnen et al, 2013). Thus, a patient's autopsy diagnosis will be dependent on the criteria used, which potentially limits the specificity of any studies correlating FDG-PET or SPECT with postmortem diagnosis. This is particularly relevant given emerging evidence of pre-symptomatic AD in otherwise healthy elderly persons (Aizenstein et al, 2008).

Furthermore, mixed pathologies can be detected in patients diagnosed with AD at the time of autopsy (Kovacs et al, 2008) and in these instances it can be difficult, if not impossible, to determine the relative pathologic contributions to the patient's cognitive abnormalities. These concerns have prompted recent revisions to the guidelines on neuropathologic criteria for AD from the National Institute on Aging-Alzheimer's Association (NIA-AA) (Hyman et al, 2012).

Section B. Clinical evaluation for the main indication

This assessment uses the theoretical framework outlined in the MSAC *Guidelines for the Assessment of Diagnostic Technologies* (August 2005).

This means that evidence of the clinical effectiveness of FDG-PET for the diagnosis of AD requires either:

- evidence of the effectiveness of FDG-PET from high-quality comparative studies evaluating the use of FDG-PET and subsequent treatment compared to the use of SPECT and subsequent treatment (direct evidence). Randomised controlled trials (RCTs) provide the highest quality evidence for this comparison. Or, if this is not available:
- evidence of treatment effectiveness from high-quality comparative studies evaluating the treatment for AD, linked with applicable and high-quality evidence of the accuracy of FDG-PET compared to SPECT to diagnose AD. This is called 'linked evidence'.

There was no direct evidence available assessing the impact of FDG-PET on the diagnosis and subsequent treatment of AD, so in this assessment a linked evidence approach was required. That means that evidence from studies that report on diagnostic test performance (diagnostic accuracy), the impact on clinical decision-making, and the impact of the treatment of diagnosed patients on health outcomes, was narratively linked in order to infer the effect of the diagnostic test on patient health outcomes.

For the last step of the linked analysis, a search was conducted to identify systematic reviews of RCTs (Level I evidence) on treatment effectiveness in patients with AD. This provides data on the health outcomes of those who are correctly diagnosed (i.e. true positives). The same studies can then be used to infer the implications associated with inappropriately treating people who are incorrectly diagnosed with AD (false positives) and the implications of not properly treating people who are incorrectly given an alternative diagnosis to AD (false negatives). For people initially suspected of AD but who are eventually given an alternative diagnosis (true negatives), it is assumed that their management/treatment would be optimised as a consequence of obtaining the correct diagnosis.

B.1. Description of search strategies

B.1.1. Literature search strategy and sources

AD diagnosis using FDG-PET

A systematic literature search was conducted to identify studies that report diagnostic accuracy, safety, and change in patient management as a result of imaging using FDG-PET compared with SPECT in the target population.

Electronic searches of EMBASE.com and the Cochrane Library were conducted using the search terms outlined in Appendix 2. The search terms were broad enough to ensure that economic studies relating to FDG-PET and AD would also be captured. The search

of EMBASE.com (which concurrently searches Medline and EMBASE) was conducted on 3 November, 2014 and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Economic Evaluation Database) was searched on 22 November, 2014.

In addition, reference lists of relevant reviews and primary studies were hand-searched to identify additional studies. Databases maintained by health technology assessment (HTA) agencies were also reviewed for relevant reports.

Treatment for AD

A separate literature search was conducted of PubMed, the Cochrane Library (Cochrane Reviews, Other Reviews) and the websites of HTA agencies to identify recent systematic reviews and meta-analyses relating to the efficacy and safety of pharmacotherapies for AD. In order to capture the most recent evidence, the search was limited to systematic reviews published from 2010 onwards. The search terms are outlined in Appendix 2.

B.1.2. Selection criteria

AD diagnosis using FDG-PET

The eligibility criteria for inclusion in this Assessment Report were underpinned by the main components of the research question (prior test, population, intervention, comparator and outcomes), as outlined in Table A.8-1. Specifically, studies were excluded for the following reasons:

- Wrong publication/study type – literature reviews, case reports, studies not fully published or peer-reviewed (editorials, letters, conference proceedings, abstracts), non-human and in vitro studies.
- Wrong intervention – not FDG-PET.
- Wrong population – not AD, suspected AD, mild cognitive impairment (MCI) or other unspecified dementia.
- Wrong outcomes – no diagnostic accuracy, change in management, safety or patient outcomes reported.
- Wrong comparator – not SPECT.

Although HMPAO is the most commonly used tracer to examine CBF using SPECT, studies that reported the diagnostic accuracy of SPECT using other tracers (e.g. ethyl cysteinate dimer (ECD), iodoamphetamine (IMP)) were also included in the Assessment Report.

Treatment for AD

The interventions considered relevant to the treatment of AD were those medicines currently listed on the PBS:

- AChEIs (donepezil, galantamine, rivastigmine); and
- N-methyl-d-aspartate antagonists (memantine).

Only recent (2010 onwards) high-level evidence was considered. Studies were excluded for the following reasons:

- Wrong publication/study type – non-systematic literature reviews, primary studies, case reports, studies not fully published or peer-reviewed (editorials, letters, conference proceedings, abstracts), non-human and in vitro studies.
- Wrong intervention – not donepezil, galantamine, rivastigmine or memantine.
- Wrong population – not AD.
- Wrong outcomes – no patient outcomes reported or outcomes not relevant to the economic model.
- Wrong comparator – not placebo or no treatment.

B.1.3. Search results

AD diagnosis using FDG-PET

The search of EMBASE.com yielded 2,205 potentially relevant publications. The titles and abstracts were screened using the selection criteria outlined in Section B.1.2.

A total of 2,187 studies were excluded (including 13 duplicates), leaving 18 publications for which the full texts were retrieved. The full papers were assessed for inclusion/exclusion. Six studies were subsequently excluded, leaving 12 included publications. Two of the 284 potentially relevant citations identified through the Cochrane Library included information on the diagnostic accuracy of FDG-PET versus SPECT. Both of these publications were already captured in the search of EMBASE.com.

A summary of the literature review process is presented in Table B.1-1.

Table B.1-1 Summary of the process used to identify relevant studies of diagnostic effectiveness

	EMBASE.com	Cochrane Library
Number of citations retrieved by search	2,205	284
Number of duplicate citations removed	13	1
Number of citations screened by title and abstract review	2,192	283
Number of citations excluded after title/abstract review:	-	-
• Wrong publication type or not in English	518	39
• Wrong intervention	275	111
• Wrong population	547	42
• Wrong outcomes	605	16
• Wrong comparator	229	73
Total excluded	2,174	281
Number of citations screened by full text review	18	2
Number of citations excluded after full text review:	-	-
• Wrong publication type	2	0
• Wrong outcomes	2	0
• Wrong comparator	2	0
Total excluded	6	0
Total number of citations included from each database	12	2
Total number of citations (excluding duplicates)	12	-

One additional systematic review was identified through hand-searching of grey literature. The systematic review and meta-analysis of test accuracy in studies with autopsy-confirmed diagnosis was not identified in the search, possibly due to its recent

publication date (Cure et al, 2014). The rationale behind the inclusion of Cure et al (2014) is discussed further in B.2.2, as it did not meet the eligibility criteria of the Assessment Report.

Treatment for AD

The search of the Cochrane Library yielded 92 potentially relevant systematic reviews of the effectiveness and safety of pharmacotherapy (AChEIs and memantine) for AD. The titles and abstracts were screened using the selection criteria outlined in Section B.1.2.

A summary of the literature review process is presented in Table B.1-2.

Table B.1-2 Summary of the process used to identify relevant studies of treatment for AD

	Cochrane Library
Number of citations retrieved by search	92
Number of citations excluded after title/abstract review:	-
• Wrong intervention: not AChEI or memantine	53
• Wrong population: not AD	20
• Wrong or no outcomes	7
• Not in English	3
• Duplicate	1
Total excluded	84
Total number of citations included for further consideration	8

Abbreviations: AChEI, acetylcholinesterase; AD, Alzheimer's disease

A search of the Pharmaceutical Benefits Advisory Committee (PBAC) website identified an additional systematic review within a post-market review of PBS anti-dementia medicines for AD (PBS Review, 2012).

B.2. Listing of all studies

B.2.1. Direct evidence of diagnostic effectiveness

No studies were identified that assessed the direct health impact (effectiveness) of FDG-PET versus SPECT in the target population.

B.2.2. Diagnostic accuracy

In total, 12 studies met the eligibility criteria, including three systematic reviews and nine primary studies (see Table B.2-1). The nine primary studies identified from the systematic literature search all directly compared the diagnostic accuracy of FDG-PET and SPECT in a single patient population.

The three included systematic reviews all included some of those primary studies, with direct evidence comparing FDG-PET and SPECT. While other systematic reviews, which included evidence for both FDG-PET and SPECT were identified in the literature search, they were ultimately excluded as none of their included studies provided direct, comparative evidence. Furthermore, the evidence in the excluded reviews has been superseded by the more recent, comprehensive reviews, which are listed in Table B.2-1.

Table B.2-1 List of included studies comparing diagnostic accuracy of FDG-PET and SPECT

Study ID	Citation
Systematic reviews	-
Bloudek (2011)	Bloudek LM, Spackman DE, Blankenburg M & Sullivan SD (2011). Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. <i>Journal of Alzheimer's Disease</i> , 26(4):627-645.
Davison (2014)	Davison CM & O'Brien JT (2014). A comparison of FDG-PET and blood flow SPECT in the diagnosis of neurodegenerative dementias: A systematic review. <i>International Journal of Geriatric Psychiatry</i> , 29(6):551-561.
Frisoni (2013)	Frisoni GB, Bocchetta M, Chetelat G, Rabinovici GD, De Leon MJ, Kaye J, et al. (2013). Imaging markers for Alzheimer disease: Which vs how. <i>Neurology</i> , 81(5):487-500.
Primary studies	-
Döbert (2005)	Döbert N, Pantel J, Frolich L, Hamscho N, Menzel C & Grunwald F (2005). Diagnostic value of FDG-PET and HMPAO-SPET in patients with mild dementia and mild cognitive impairment: Metabolic index and perfusion index. <i>Dementia and Geriatric Cognitive Disorders</i> , 20(2-3):63-70.
Herholz (2002)	Herholz K, Schopphoff H, Schmidt M, Mielke R, Eschner W, Scheidhauer K, et al. (2002). Direct comparison of spatially normalized PET and SPECT scans in Alzheimer's disease. <i>Journal of Nuclear Medicine</i> , 43(1):21-26.
Ishii (1999)	Ishii K, Sasaki M, Sakamoto S, Yamaji S, Kitagaki H & Mori E (1999). Tc-99m Ethyl Cysteinate Dimer SPECT and 2-[F-18]fluoro-2-deoxy-D- glucose PET in Alzheimer's disease: Comparison of perfusion and metabolic patterns. <i>Clinical Nuclear Medicine</i> , 24(8):572-575.
Ito (2014)	Ito K, Shimano Y, Imabayashi E, Nakata Y, Omachi Y, Sato N, et al. (2014). Concordance between 99mTc-ECD SPECT and 18F-FDG PET interpretations in patients with cognitive disorders diagnosed according to NIA-AA criteria. <i>International Journal of Geriatric Psychiatry</i> , 29(10):1079-86.
Kuwabara (1990)	Kuwabara Y, Ichiya Y, Otsuka M, Tahara T, Fukumura T, Gunasekera R, et al. (1990). Comparison of I-123 IMP and Tc-99m HMPAO SPECT studies with PET in dementia. <i>Annals of Nuclear Medicine</i> , 4(3):75-82.
Messa (1994)	Messa C, Perani D, Lucignani G, Zenorini A, Zito F, Rizzo G, et al. (1994). High-resolution technetium-99m-HMPAO SPECT in patients with probable Alzheimer's disease: Comparison with fluorine-18-FDG PET. <i>Journal of Nuclear Medicine</i> , 35(2):210-216.
Mielke (1994)	Mielke R, Pietrzyk U, Jacobs A, Fink GR, Ichimiya A, Kessler J, et al. (1994). HMPAO SPET and FDG PET in Alzheimer's disease and vascular dementia: Comparison of perfusion and metabolic pattern. <i>European Journal of Nuclear Medicine</i> , 21(10):1052-1060.
Morinaga (2010)	Morinaga A, Ono K, Ikeda T, Ikeda Y, Shima K, Noguchi-Shinohara M, et al. (2010). A comparison of the diagnostic sensitivity of MRI, CBF-SPECT, FDG-PET and cerebrospinal fluid biomarkers for detecting Alzheimer's disease in a memory clinic. <i>Dementia and Geriatric Cognitive Disorders</i> , 30(4):285-292.
Nihashi (2007)	Nihashi T, Yatsuya H, Hayasaka K, Kato R, Kawatsu S, Arahata Y, et al. (2007). Direct comparison study between FDG-PET and IMP-SPECT for diagnosing Alzheimer's disease using 3D-SSP analysis in the same patients. <i>Radiation Medicine - Medical Imaging and Radiation Oncology</i> , 25(6):255-262.

Due to a paucity of good-quality, comparative studies, the Assessment Report also presents diagnostic accuracy findings from a number of studies that did not directly compare FDG-PET and SPECT. The citation details of those studies are provided in Table B.2-2. The additional 13 primary studies were excluded from the systematic evidence review based on wrong (or lack of) comparator, but ultimately were included in Section B to supplement the limited body of direct evidence.

The three systematic reviews shown in Table B.2-1 and the systematic review by Cure et al (2014) were used to identify the additional primary studies containing indirect

evidence. Importantly, studies of FDG-PET or SPECT alone were only included in the clinical evaluation if the diagnostic accuracy of the test was assessed against the reference standard (i.e. histopathologic diagnosis via autopsy or biopsy). None of the comparative studies included follow-up to autopsy/biopsy.

The most comprehensive list of applicable studies was found in Cure et al (2014), as the inclusion criteria was limited to those studies with autopsy confirmation of diagnosis; hence Cure et al (2014) was included in Section B despite not meeting the eligibility criteria of providing direct evidence for the diagnostic accuracy of FDG-PET versus SPECT. Most of the primary studies (indirect evidence) were also included in the systematic reviews by Bloudek et al (2011) and Davison et al (2014); however, studies with pathological confirmation of diagnosis were not their sole focus. As such, not all indirect evidence presented in those two systematic reviews is included in the Assessment Report as they were deemed to be of insufficient quality (i.e. they did not directly compare FDG-PET and SPECT, nor did they have pathologically confirmed AD diagnosis).

While the aforementioned systematic reviews were used to identify the primary studies in Table B.2-2, there were numerous discrepancies in the reporting of those studies between systematic reviews. As a result, most of the individual papers were retrieved for the purpose of data extraction.

Table B.2-2 List of studies reporting diagnostic accuracy of FDG-PET or SPECT

Study ID	Citation
Systematic reviews	-
Cure (2014)	Cure S, Abrams K, Belger M, Dell'agnello G & Happich M (2014). Systematic literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. <i>J Alzheimers Dis</i> , 42(1):169-82.
Primary studies	-
Bonte (1993)	Bonte FJ, Tintner R, Weiner MF, Bigio EH, White CL, III (1993) Brain blood flow in the dementias: SPECT with histopathologic correlation. <i>Radiology</i> , 186:361-365.
Bonte (1997)	Bonte FJ, Weiner MF, Bigio EH, White CL, III (1997) Brain blood flow in the dementias: SPECT with histopathologic correlation in 54 patients. <i>Radiology</i> , 202:793-797.
Bonte (2004)	Bonte FJ, Harris TS, Roney CA, Hynan LS (2004) Differential diagnosis between Alzheimer's and frontotemporal disease by the posterior cingulate sign. <i>J Nucl Med</i> , 45:771-774.
Bonte (2006)	Bonte FJ, Harris TS, Hynan LS, Bigio EH & White ICL (2006). Tc-99m HMPAO SPECT in the differential diagnosis of the dementias with histopathologic confirmation. <i>Clinical Nuclear Medicine</i> , 31(7):376-378.
Foster (2007)	Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, et al. (2007). FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. <i>Brain</i> , 130(10):2616-2635.
Hoffman (2000)	Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. (2000). FDG PET imaging in patients with pathologically verified dementia. <i>Journal of Nuclear Medicine</i> , 41(11):1920-1928.
Jagust (2001)	Jagust W, Thisted R, Devous MD Sr, Van Heertum R, Mayberg H, Jobst K, et al. (2001) SPECT perfusion imaging in the diagnosis of Alzheimer's disease: a clinical-pathologic study. <i>Neurology</i> , 56(7):950-956.
Jagust (2007)	Jagust W, Reed B, Mungas D, Ellis W & DeCarli C (2007). What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? <i>Neurology</i> , 69(9):871-877.
Jobst (1998)	Jobst KA, Barnetson LP, Shepstone BJ (1998) Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: The use of NINCDSADRDA and DSM-III-R criteria, SPECT, X-ray CT, and ApoE4 in medial temporal lobe dementias. Oxford Project to Investigate Memory and Aging. <i>Int Psychogeriatr</i> , 10:271-302.

Study ID	Citation
McNeill (2007)	McNeill R, Sare GM, Manoharan M, Testa HJ, Mann DM, Neary D, et al. (2007) Accuracy of single-photon emission computed tomography in differentiating frontotemporal dementia from Alzheimer's disease. <i>J Neurol Neurosurg Psychiatry</i> , 78:350-335.
Minoshima (2001)	Minoshima S, Foster NL, Sima AAF, et al. 2001. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. <i>Ann Neurol</i> 50:358-265.
Rusina (2010)	Rusina R, Kukul J, Belicek T, Buncova M & Matej R (2010). Use of fuzzy edge single-photon emission computed tomography analysis in definite Alzheimer's disease – a retrospective study. <i>BMC Med Imaging</i> , 10:20.
Silverman (2001)	Silverman DHS, Small GW, Chang CY, Lu CS, Kung de Aburto MA, Chen W, et al. (2001). Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome. <i>Journal of the American Medical Association</i> , 286(17):2120-2127.

The matrix in Table B.2-3 shows the four included systematic reviews and all of the primary studies that are discussed throughout Section B. Three of the systematic reviews included studies that directly compared the diagnostic accuracy of FDG-PET and SPECT in the diagnosis of AD. As discussed above, the only studies included in Section B that did not directly compare FDG-PET and SPECT are studies that had pathological confirmation of AD diagnosis (listed under 'Indirect evidence' in Table B.2-3).

Table B.2-3 Matrix showing primary studies included in each of the systematic reviews

Study ID	Cure (2014)	Davison (2014)	Frisoni (2013)	Bloudek (2011)
Direct evidence	-	-	-	-
Ito (2014)	-	-	-	-
Morinaga (2010)	-	-	✓	-
Nihashi (2007)	-	✓	✓	✓
Döbert (2005)	-	✓	-	-
Herholz (2002) ^a	-	✓	-	-
Ishii (1999)	-	✓	-	-
Messa (1994)	-	✓	✓	✓
Mielke (1994)	-	✓	-	-
Kuwabara (1990)	-	✓	-	-
Indirect evidence	-	-	-	-
Rusina (2010)	✓	-	-	-
Foster (2007)	✓	✓	-	✓
Jagust (2007)	✓	✓	-	✓
Silverman (2001)	✓	✓	✓	✓
Hoffman (2000)	✓	✓	-	✓
McNeill (2007)	-	✓	-	✓
Bonte (2006)	✓	✓	-	✓
Bonte (2004)	✓	-	-	✓
Jagust (2001)	-	✓	✓	-
Minoshima (2001)	-	✓	-	-
Jobst (1998)	✓	-	✓	✓
Bonte (1997)	✓	✓	-	✓
Bonte (1993)	✓	-	-	✓

^a Bloudek (2011) and Frisoni (2013) both included a different 2002 study by Herholz et al. It was included in the FDG-PET meta-analysis in Bloudek (2011); however it is not included individually in the Assessment Report as it reports the diagnostic accuracy of FDG-PET only and does not have autopsy confirmation of diagnosis.

Upon closer inspection, two potentially relevant studies (Minoshima et al, 2001; and Morinaga et al, 2010, shown in Table B.2-3) were excluded from the clinical evaluation. Morinaga et al (2010) compared the diagnostic sensitivity of MRI, CBF-SPECT, FDG-

PET and cerebrospinal fluid (CSF) biomarkers for detecting AD. Only 87 of the 207 patients included in the study underwent FDG-PET, while 163 underwent CBF-SPECT. It was unclear how many patients underwent both tests. As a result, there was no usable diagnostic accuracy data and the study was excluded.

Minoshima et al (2001) examined the ability of FDG-PET to distinguish Dementia with Lewy bodies (DLB) and AD, in cases where the DLB and AD diagnoses were later confirmed on autopsy. The study reported a sensitivity of 90% and specificity of 80% when discriminating DLB and AD; however it was not entirely clear to which of the diagnoses the results related. The reporting of the Minoshima study in Davison et al (2014) was also unclear.

Neither Morinaga et al (2010) nor Minoshima et al (2001) will be discussed beyond Section B.2 of this Assessment Report.

B.2.3. Safety

No primary studies were identified that specifically examined the safety of FDG-PET versus SPECT in patients with AD. Only one systematic review of FDG-PET for the evaluation of dementia included safety of FDG-PET as an outcome (Bohnen et al, 2012).

B.2.4. Change in patient management

There is limited clinical evidence reporting the downstream impact of functional imaging on change in patient management and patient outcomes. No studies were identified that compared change in patient management after FDG-PET compared with SPECT. However, one retrospective study was identified that reported on change in patient management after use of FDG-PET in the diagnosis of dementia in a memory clinic setting (Laforce et al, 2010). This study followed patients for an average of 1.5 years after their clinical diagnosis and is discussed in detail in Sections B.3-B.6.

An Australian study that reported on change in patient management after FDG-PET was also identified in the literature search but was excluded because the FDG-PET diagnosis was not confirmed by neuropathological examination or clinical follow-up (Elias et al, 2014). As acknowledged by the authors, “the benefits of the alterations in management by FDG-PET can only be inferred and are not proven”. Although the Elias et al (2014) study does not meet the eligibility criteria, the findings are briefly discussed in Section B.6, as it represents the only Australian evidence for change in patient management following FDG-PET.

B.2.5. Change in patient outcomes

To answer the question of whether a change in management leads to improved patient health outcomes, a literature search was conducted to identify systematic reviews on the effectiveness and safety of treatment (AChEIs and memantine) for AD.

Nine systematic reviews were identified in total (eight from the Cochrane Library and one from a search of the Department of Health website); however, four were excluded because they did not exclusively review evidence in patients with AD or assessed non-standard treatment regimens. An additional review was excluded because it assessed only one of the treatments available (memantine). Of the four remaining published reviews, two were related; an HTA by Bond et al (2012) and an associated publication by Hyde et al (2013).

Table B.2-4 List of systematic reviews of the effectiveness and safety of anti-dementia medicines for AD

Citation	Reason for exclusion
Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde C. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model. <i>Health Technol Assess</i> 2012; 16: 1-470.	Included.
Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. <i>BMJ Open</i> . 2012;11:2(3).	Excluded. Combination therapy only.
Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R, Jeffreys M, Davis S, Thokala P, Moxham T. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. <i>Age Ageing</i> . 2013;42(1):14-20.	Included. Publication based on Bond et al (2012) HTA for NICE.
Muayqil T, Camicioli R. Systematic review and meta-analysis of combination therapy with cholinesterase inhibitors and memantine in Alzheimer's disease and other dementias. <i>Dementia and Geriatric Cognitive Disorders Extra</i> . 2012;1:546-572.	Excluded. Population not restricted to AD.
Oremus M, Santaguida P, Raina P. Efficacy and safety of galantamine hydrobromide in the treatment of mild to moderate dementia. <i>Clinical Medicine Insights: Therapeutics</i> . 2010;4:809-824.	Excluded. Population not restricted to AD.
Post-market Review of Pharmaceutical Benefits Scheme anti-dementia medicines to treat AD, October 2012. Prepared for the Pharmaceutical Benefits Advisory Committee (PBAC) by Monash University, University of South Australia, and the Department of Health and Ageing. ⁴	Included.
Schneider, LS, Dagerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer disease. <i>Archives of Neurology</i> . 2011;8:991-998.	Excluded. Not a licensed indication for memantine.
Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC, Tan L. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. <i>J Alzheimers Dis</i> . 2014;41(2):615-631.	Review from China. Included – but not discussed further.
Yang Z, Zhou X, Zhang Q. Effectiveness and safety of memantine treatment for Alzheimer's disease. <i>Journal of Alzheimer's Disease</i> . 2013;3:445-458.	Excluded. Memantine only.

The systematic review by Tan et al (2014) will not be discussed further as the other two reviews (PBS Review, 2012; Bond et al, 2012) are of high-quality and have been used to underpin decision-making.

The Post-market Review of PBS anti-dementia medicines to treat AD was prepared for the PBAC by Monash University, the University of South Australia, and the Department of Health and Ageing in October 2012. An initial review of AChEIs listed on the PBS had been conducted by the Drug Utilisation Sub-Committee (DUSC) of PBAC in 2009 as part of a post-market surveillance program to ensure the safe and cost-effective use of these medicines. The review indicated these medicines were being prescribed to a larger population for longer periods of time than originally expected. This additional use, while not necessarily inappropriate, is not cost-effective use as originally assessed by PBAC.

The 2012 PBS Review of anti-dementia medicines is comprised of six parts, of which one in particular is relevant to Section B of the current Assessment Report: an update of the efficacy and safety of AChEIs and memantine. A systematic literature review was conducted to determine if any additional evidence on safety and efficacy had been

⁴ Summary and PBAC Minutes available on the PBS website; full report available by request to the PBAC Secretariat.

published since the PBS listing of these medicines that could inform PBAC on both short and longer term outcomes (beyond six months) when used individually and in combination.

Bond et al (2012) conducted a systematic review and economic evaluation for the National Institute for Health and Clinical Excellence (NICE) to update guidance to the National Health Service (NHS) in England and Wales on the clinical effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD, which was issued in November 2006 (updated September 2007 and August 2009). In the previous NICE review in 2004, there was evidence for the effectiveness of donepezil, galantamine and rivastigmine on improving cognition, function, behaviour and global impact over the short term whereas the evidence on the effectiveness of memantine was much more uncertain. Important gaps in the evidence were identified concerning long-term outcomes, impact on quality of life (QoL), carers and time to institutionalisation.

The PBS Review (2012) and HTA for NICE (Bond et al, 2012) will be discussed briefly in Section B.3 and then the findings from these reviews will be discussed in Section B.6. Only the studies of diagnostic accuracy are discussed in Section B.4 and Section B.5.

B.3. Assessment of the measures taken by investigators to minimise bias

B.3.1. Diagnostic accuracy

Primary studies assessing diagnostic accuracy were graded according to a pre-specified quality and applicability criteria (MSAC, 2005), as shown in Table B.3-1. Quality assessment was based on the QUADAS-2 tool (Whiting et al, 2011).

Table B.3-1 Grading system used to rank included studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on pre-defined key quality criteria. Medium quality = some potential for bias in areas other than those pre-specified as key criteria. Poor quality = poor reference standard and/or potential for bias based on key pre-specified criteria.	Q1 high quality Q2 medium Q3 poor reference standard, poor quality or insufficient information

Abbreviations: C, comparison; P, population; Q, quality.

As the focus of the research question is the *comparative* safety and effectiveness of FDG-PET and SPECT, the quality assessment was undertaken for comparative diagnostic studies only (i.e. primary studies listed in Table B.2 1). The indirect evidence serves as supplementary information only, as there is a high risk of bias introduced by comparing diagnostic techniques in different populations and settings.

Table B.3-2 Grading of included comparative studies

Study ID	Validity criteria results ^a
Döbert (2005)	<p>C1: FDG-PET vs HMPAO-SPECT.</p> <p>P1: All patients had suspected early dementia (no cases had severe MMSE score – lowest 14; median 24).</p> <p>Q3: Small sample size. Reference standard was longitudinal clinical follow-up (mean 16 months), which may not represent an accurate diagnosis.</p>
Herholz (2002)	<p>C1: FDG-PET vs HMPAO-SPECT.</p> <p>P2: Patients had a clinical diagnosis of probable AD, most of which were associated with mild cognitive impairment (MMSE 22.5). Patients had undergone CT or MRI to exclude structural brain lesions (e.g. brain infarcts, tumours). Controls with no cognitive impairment are unlikely to be representative of non-AD patients who undergo FDG-PET or SPECT in practice.</p> <p>Q3: Small sample size. Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up. Sample of healthy volunteers (n=6) was too small to provide an estimate of the diagnostic accuracy (sensitivity/specificity) of the two techniques.</p>
Ishii (1999)	<p>C1: FDG-PET vs ECD-SPECT.</p> <p>P2: Patients with probable AD. 9 patients (90%) had mild to moderate cognitive impairment and one patient (10%) had severe cognitive impairment, according to MMSE. Unable to determine whether they were patients with difficult-to-diagnose AD.</p> <p>Q3: Very small sample size. Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up.</p>
Ito (2014)	<p>C1: FDG-PET vs ECD-SPECT.</p> <p>P2: Patients had a cognitive disorder (AD, MCI, DLB or FTD). Mean MMSE score in those ultimately diagnosed with AD was 19.3 (i.e. applicable population was not severe cognitive impairment). Patients had not necessarily undergone CT and/or MRI to exclude structural brain lesions (e.g. brain infarcts, tumours) and therefore may not truly be mild/difficult-to-diagnose cases.</p> <p>Q3: Relatively small sample size. Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up. Final diagnosis was provided according to NIA-AA criteria by a team of certified dementia specialists. While the study provided a direct comparison of PET and SPECT, all results were interpreted using visual assessment only (i.e. not semi-quantitative).</p>
Kuwabara (1990)	<p>C1: FDG and ¹⁵OH₂O-PET vs I-123 IMP and HMPAO-SPECT.</p> <p>P2: Patients already had a diagnosis of AD. More severe AD than clinical indication of interest (all patients were classified as moderate or severe AD and were showing mild or moderate atrophy on CT and/or MRI). Relatively young AD patient population (mean age: 58 years).</p> <p>Q3: Small sample size. Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up. Different control groups were used for PET and SPECT – the PET controls were normal volunteers, whereas the SPECT controls had mild neurological symptoms.</p>
Messa (1994)	<p>C1: FDG-PET vs HMPAO-SPECT.</p> <p>P2: Patients with probable AD who had undergone clinical examination and MRI. 90% had mild or moderate cognitive impairment according to MMSE score (10% normal, 0% severe). However, controls with no cognitive impairment are unlikely to be representative of non-AD patients who undergo FDG-PET or SPECT in practice.</p> <p>Q3: Small sample size. Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up. Different control groups used for PET and SPECT (however all were free from known neurological diseases, as assessed by clinical history, standard clinical and neurological examinations and neuropsychological testing (MMSE)).</p>
Mielke (1994)	<p>C1: FDG-PET vs HMPAO-SPECT.</p> <p>P2: Overall, probable AD patients had mild cognitive impairment according to mean MMSE score (20.9); controls had no cognitive impairment (mean MMSE: 28.8). Controls with no cognitive impairment are unlikely to be representative of non-AD patients who undergo FDG-PET or SPECT in practice.</p> <p>Q3: Small sample size. Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up.</p>

Study ID	Validity criteria results ^a
Nihashi (2007)	C1: FDG-PET vs IMP-SPECT. P2: Patients with probable moderate AD (likely to be a more severe AD population than the disease stage of interest). Q2: Very small sample size. Different control groups used for PET and SPECT (however all were free from known neurological diseases). Poor reference standard – no histopathologic diagnosis or long-term clinical follow-up.

Abbreviations: AD, Alzheimer's disease; C, comparison; CT, computed tomography; DLB, Dementia with Lewy bodies; ECD, ethyl cysteinat dimer; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; HMPAO, hexamethylpropylene amine oxime; IMP, iodoamphetamine; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging and the Alzheimer's Association Workshop; P, population; PET, positron emission tomography; Q, quality; SPECT, single-photon emission computed tomography.

^a Grading system based on Table B.3-1.

Overall, the major limitations were very low sample sizes and variable control groups in which PET and SPECT results were assessed against different sets of controls. In addition, many studies concluded that one technique was superior on the basis of an extra one or two cases correctly diagnosed (Davison et al, 2014).

Most of the studies included insufficient reference standards, for example, validation of AD was against clinical diagnostic criteria (and without longitudinal follow-up). Therefore, the evidence base of comparative FDG-PET and SPECT studies is limited and, as highlighted by Davison et al (2014), “inadequate to make very broad generalisations about the superiority of one technique over another”.

B.3.2. Change in patient management

The study by Laforce et al (2010) reviewed the files of all patients who had been referred to a specialised memory clinic in Canada between January 2006 and June 2008 (i.e. 1,498 files including 554 new consultations). Patients were eligible if they had a clinical diagnosis of MCI, typical dementia or atypical/unclear dementia and had FDG-PET within two months of the clinical diagnosis. Patients were re-evaluated within three months of the FDG-PET scan (to limit the confounding impact of disease progression on diagnostic change) and again on average 18 months after the initial clinical diagnosis. The study was based on clinical diagnoses; no postmortem confirmatory analyses with histologically proven material were obtained.

All of the initial clinical diagnoses were made by two experienced cognitive neurologists and an experienced geriatric psychologist. All diagnoses were made using standard criteria based on clinical interview, functional assessment, neurological examinations, neuropsychological screening, MRI, and laboratory studies. Atypical/unclear dementias included cases where the initial clinical diagnosis was uncertain, unclassified, or the clinician listed several possible hypothetical diagnoses.

Images were evaluated by a unique rater who was not blind to the clinician's diagnostic hypotheses. The rater had extensive experience in reading FDG-PET scans in research and clinical settings. Scans were initially analysed visually but in the latter half of the study, software was introduced to compare each scan with a group of 18 normal elderly controls.

B.3.3. Change in patient outcomes

Bond et al (2012) HTA for NICE

A good-quality systematic review of clinical and economic evidence was undertaken to update NICE guidance on the use of AChEIs and memantine for the treatment of AD. The literature searches (conducted in November 2009 and again in March 2010) aimed to identify systematic reviews and/or meta-analyses, RCTs and ongoing research published since the previous literature search in 2004. Trials that included participants with mixed dementia were included if the predominant dementia was AD.

A total of four systematic reviews and 17 RCTs were identified that had been published since 2004. There were 12 pair-wise comparisons with placebo: five for donepezil (N = 234); three for galantamine (N = 1386); three for rivastigmine (N = 1995); and one for memantine (N = 350). The search also identified four head-to-head studies and one combination therapy study (memantine added to AChEIs). Taken as a whole, the quality of the trials was considered by the authors to be “disappointing”.

PBS Review of anti-dementia medicines to treat AD (2012)

The PBS Review of anti-dementia medicines to treat AD (October 2012) was undertaken for the PBAC by the Centre for Health Economics at Monash University, the Veterans’ Medicines Advice and Therapeutics Education Services at the University of South Australia, and the Pharmaceutical Policy Branch of the Department of Health and Ageing. As such, it is assumed that the assessment of the effectiveness and safety of the AChEIs and memantine is of high-quality. The literature search (conducted in May 2012) was intended to identify all systematic reviews and RCTs assessing donepezil, rivastigmine, galantamine and memantine, either alone or in combination in patients with AD, compared with placebo or another AChEI or memantine. Table B.3-3 summarises the number of trials identified from the literature search. The authors of the PBS Review undertook quality assessment of the included studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, reporting very low to high quality ratings for the AChEI studies and low quality ratings for all memantine studies. Some of the information in the report was redacted due to commercial confidentiality.

Table B.3-3 Trials of AChEIs and memantine identified in the PBS Review (October 2012)

Drug	Total number of clinical trials	Total number of patients
donepezil	24	5,493
rivastigmine	11	5,268
galantamine	8	4,631
memantine	4	1,475

B.4. Characteristics of the included studies

B.4.1. Diagnostic accuracy

Direct evidence

Of the three systematic reviews, Davison et al (2014) was the most recent and comprehensive. It included seven of the eight studies that directly compared the diagnostic accuracy of FDG-PET and SPECT. Davison et al (2014) also included studies that assessed either FDG-PET or SPECT alone.

Similarly, the systematic review by Bloudek et al (2001) included an array of studies that directly compared the diagnostic accuracy of FDG-PET with SPECT, and studies that reported the diagnostic accuracy of FDG-PET or SPECT. A variety of meta-analyses were conducted encompassing 33 PET studies, 19 SPECT studies and various subsets of those studies according to the comparison groups (e.g. normal controls, demented controls, MCI).

The third systematic review (Frisoni et al, 2013) identified two of the eight included comparative studies along with many other studies of FDG-PET or SPECT with a variety of reference standards. Primary studies were excluded from the systematic review if they reported the diagnostic accuracy of AD versus other types of dementia, as the focus was on separating AD from healthy controls. As such, this review has limited applicability to 'real-world' use of FDG-PET and SPECT, as proposed in the MBS item descriptor.

All of the comparative studies included in the Assessment Report had small sample sizes (ranging from 10 to 55 participants) and were relatively old, with four of the eight studies published prior to the year 2000. Four studies were conducted in Japan, three were from Germany, and one was from Italy. There were no studies of FDG-PET versus SPECT from Australia.

Döbert et al (2005) assessed the diagnostic accuracy of FDG-PET and HMPAO-SPECT according to a consensus clinical diagnosis at follow-up. While clinical follow-up was undertaken at an average of only 16 months (± 12 months), this study was the only one of the eight comparative studies that partly fulfilled the reference standard as per the Final Protocol (Table 4, p.15).

A recent Japanese study by Ito et al (2014) examined the concordance of diagnostic abilities and interobserver agreement between FDG-PET and ECD-SPECT in 55 patients with cognitive disorders. A team of dementia specialists diagnosed AD according to the NIA-AA research criteria, which included neuronal injury markers such as MRI, functional imaging and, importantly, an amyloid-binding radiotracer (^{11}C -PIB PET). DLB and FTD were also diagnosed according to established criteria. The findings of FDG-PET and SPECT scans were evaluated by three radiologists/nuclear medicine physicians and compared with the consensus clinical diagnosis.

The main similarity between Döbert et al (2005) and Ito et al (2014) is that both studies included a broad population of patients with suspected MCI or dementia (including DLB, FTD, vascular dementia (VD) and mixed-type dementia (MIX)).

In contrast, the remaining six studies all recruited patients with clinically suspected or diagnosed AD. The six studies adopted similar methodology, assessing patterns of

glucose metabolism (FDG-PET) or perfusion (SPECT) in certain brain regions of interest (ROIs).⁵ Diagnostic accuracy was evaluated by comparing the ability of FDG-PET and SPECT to detect differences in metabolism/perfusion between AD patients and cognitively normal controls (see Table B.4 1). In that respect, those studies were inherently different from Döbert et al (2005) and Ito et al (2014), which used the test to discriminate between people who were all cognitively impaired due to different sub-types of dementia.

Importantly, most of the included studies listed in Table B.4-1 did not precisely match the population relevant to the proposed MBS listing. Specifically, very few of the papers stated that FDG-PET or SPECT were used in difficult cases, where the diagnosis remained uncertain after clinical evaluation and structural imaging. As such, the diagnostic accuracy of FDG-PET and SPECT may have been evaluated in a patient population with more easily recognised and diagnosable AD. It is unclear whether this would have a differential effect on the results of FDG-PET versus SPECT.

⁵ In general, functional patterns (CMRgl in FDG-PET and CBF in SPECT) were condensed into a ratio of regional values of associative areas/ROIs (e.g. temporoparietal and frontal regions) divided by regional values in brain regions that are typically spared in AD (e.g. primary cortical areas, basal ganglia and cerebellum). The ratios were obtained in suspected AD patients and normal controls. Brain regions with ratios below the mean -2 SD for normal controls were regarded as significantly abnormal, and suggestive of AD.

Table B.4-1 Direct evidence of the comparative diagnostic accuracy of FDG-PET and SPECT

Study ID	Study population	Intervention	Comparator	Semi-quantitative analysis	Reference standard	Comments
Dementia	-	-	-	-	-	-
Ito (2014)	Cases: 55 patients with cognitive disorders (mean age: 73 years; mean MMSE: 19.3 ^a).	FDG-PET	ECD-SPECT	No	Clinical diagnosis according to NIA-AA research criteria, using neuronal injury markers such as MRI, functional imaging, and ¹¹ C-PiB PET ^b . DLB and FTD were diagnosed according to established criteria.	The diagnosis was made by a team of board-certified dementia specialists. Patients were categorised into four groups (AD, MCI, DLB, and FTD). To evaluate diagnostic accuracy, the four categories were condensed into two categories, "AD and MCI" and "non-AD".
Döbert (2005)	Cases: 24 patients with suspected early dementia (mean age: 69 years; mean MMSE: 22.9). 12 patients fulfilled criteria for mild dementia (defined as CDR of 1 and MMSE <23); the other 12 patients had MCI (defined as CDR of 0.5 and MMSE ≥23)	FDG-PET	HMPAO-SPECT	No ^c	Final diagnosis at follow-up (mean 16 ± 12 months) based on clinical judgement by a multiprofessional team (i.e. consensus diagnosis).	FDG-PET and HMPAO-SPECT scans were read blinded to clinical examination results by two experienced nuclear medicine physicians who reached a consensus diagnosis.
AD	-	-	-	-	-	-
Nihashi (2007)	Cases: 14 patients with probable moderate AD (NINCDS-ADRDA criteria; mean age: 70 years; mean MMSE: 18.8) <u>PET controls:</u> 7 normal controls (mean age 61 years) <u>SPECT controls:</u> 9 normal controls (mean age 70 years)	FDG-PET	IMP-SPECT	Yes	No reference standard.	Study compared the ability to discriminate an AD pattern of metabolism from normal metabolism in posterior cingulate gyri-precuneus and parietotemporal regions using a 3D-SSP analysis of FDG-PET and IMP-SPECT. Interpreted by four expert physicians.

Study ID	Study population	Intervention	Comparator	Semi-quantitative analysis	Reference standard	Comments
Herholz (2002)	<p><u>Cases:</u> 26 patients with probable AD (NINCDS-ADRDA criteria; mean age: 66 years; mean MMSE 22.5)</p> <p><u>Controls:</u> 6 healthy volunteers with normal results from neurologic and psychiatric examination and from neuropsychologic testing (mean age: 63; mean MMSE: NR)</p>	FDG-PET	HMPAO-SPECT	Yes	No reference standard.	<p>Patients had undergone CT or MRI to exclude structural brain lesions (e.g. tumours or hematomas).</p> <p>Statistical parametric mapping was used to compare abnormal brain areas objectively and quantitatively.</p>
Ishii (1999)	<p><u>Cases:</u> 10 patients with suspected mild to moderate AD (NINCDS-ADRDA criteria; mean age: 71 years; mean MMSE 19.2)</p>	FDG-PET	ECD-SPECT	Yes	No reference standard.	<p>Images were interpreted by one reader who was blinded to the patients' clinical data.</p> <p>During the ECD-SPECT scan the patients' eyes were open, whereas in FDG-PET, the patient's eyes were closed. This may have caused the high rCBF in the occipital lobe and may limit reliability of results.</p>
Messa (1994)	<p><u>Cases:</u> 21 patients with probable AD (NINCDS-ADRDA criteria; mean age: 63 years; mean MMSE: 19.9)</p> <p><u>PET controls:</u> 10 normal controls (mean age: 47 years)</p> <p><u>SPECT controls:</u> 10 normal controls (mean age: 53 years)</p>	FDG-PET	HMPAO-SPECT	Yes	No reference standard.	3 cases were normal on MRI; 1 had small lesions of the white matter; 17 showed atrophy.

Study ID	Study population	Intervention	Comparator	Semi-quantitative analysis	Reference standard	Comments
Mielke (1994)	<p><u>Cases:</u> 20 patients with probable AD (NINCDS-ADRDA criteria; mean age: 69 years; mean MMSE: 20.9); and 12 patients with probable VD (NINDS-AIREN criteria; mean age: 69 years; mean MMSE: 23.3)</p> <p><u>Controls:</u> 13 normal controls (mean age: 60 years; mean MMSE: 28.8)</p>	FDG-PET	HMPAO-SPECT	Yes	No reference standard.	Regional HMPAO uptake relative to whole brain uptake was used to assess regional perfusion differences (rCBF). Relative CMRgl was calculated as mean regional value relative to global value. Regional data were also evaluated with regional to cerebellar ratios.
Kuwabara (1990)	<p><u>Cases:</u> 9 patients diagnosed with AD (mean age: 58 years), 3 patients with Pick's disease; and 5 patients with multi-infarct dementia. AD diagnosed clinically (DSM-III criteria) as well as by CT and/or MRI.</p> <p><u>PET controls:</u> Normal volunteers (n=NR)</p> <p><u>SPECT controls:</u> Patients with mild neurological symptoms who were finally diagnosed by CT, MRI and PET as not having organic lesions (n=NR)</p>	FDG and ¹⁵ O-H ₂ O-PET	I-123 IMP and HMPAO-SPECT	Yes	No reference standard.	All AD patients had initial diagnosis of moderate or severe AD. All showed mild or moderate atrophy on CT and/or MRI.

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CT, computed tomography; DLB, Dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECD, ethyl cysteinyl dimer; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; HMPAO, hexamethylpropylene amine oxime; IMP, iodoamphetamine; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging and the Alzheimer's Association Workshop; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and of the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NR, not reported; PET, positron emission tomography; rCBF, regional cerebral blood flow; SPECT, single-photon emission computed tomography; VD, vascular dementia; 3D-SSP, three-dimensional stereotactic surface projections.

^a Mean MMSE only in patients with a final diagnosis of AD (according to NIA-AA).

^b Before the study, the 11C-PiB PET scans were interpreted by an independent nuclear medicine physician in accordance with the NIA-AA research criteria.

^c This aspect of the methodology was unclear. A quantitative analysis was conducted; however, it appeared that visual assessment was used for diagnosis and the quantitative results were used in a separate analysis.

Indirect evidence

The clinical evaluation includes additional diagnostic accuracy evidence from four FDG-PET studies and eight SPECT studies. Overall, the studies that provide indirect evidence of the diagnostic accuracy of FDG-PET or SPECT were heterogeneous, with a range of different methods of assessment. Only one of the FDG-PET studies (Foster et al, 2007) used semi-quantitative analysis; however, the study did not report relevant data (i.e. TP, FP, FN, TN) and its value is therefore limited.

All four FDG-PET studies were conducted in the United States and had sample sizes ranging from 22 to 138 patients. Five of the SPECT studies were also from the United States, two were from the United Kingdom and one was from the Czech Republic. The smallest SPECT study (Rusina et al, 2010) had 27 participants, of which 17 had pathologically confirmed AD and 10 had amyotrophic lateral sclerosis (ALS) without cognitive dysfunction. The largest SPECT study (Jobst et al, 1998) had 223 participants, including 80 AD patients, 24 patients with non-AD dementias and 119 normal controls.

Upon close inspection of the included studies it was apparent that some patients were reported in multiple publications. For example, a cohort of patients reported in Jobst et al (1998) later made up part of the patient population in Jagust et al (2001). Similarly, Bonte et al (2006) stated that 11 out of the 49 patients in their study had previously been reported in Bonte et al (1993) and Bonte et al (1997), and Silverman et al (2001) included some patients that had been included in Hoffman et al (2000).

While all of the studies included pathological confirmation of AD diagnoses, some did not have pathological confirmation for all non-demented controls. As discussed above, Rusina et al (2010) included 10 patients with ALS, of which five underwent autopsies confirming the absence of AD. Jobst et al (1998) included 105 living controls and only 14 controls with a postmortem diagnosis. Similarly, Jagust et al (2001) included 14 autopsied controls (possibly the same cohort) and 71 controls without a pathological diagnosis. In reporting diagnostic accuracy, the authors of the three aforementioned studies assumed that normal controls without autopsies were truly negative for AD pathology (i.e. they were true negatives or false positives), see Table B.4-2.

The only other study without autopsy confirmation of all cases was Bonte et al (2004), which evaluated the ability of SPECT to differentiate between AD and FTD. Autopsies were available for 17 out of 40 patients and for the purpose of analysis, the initial clinical diagnosis of either AD or FTD was assumed to be correct in the other 23 patients.

Table B.4-2 Indirect evidence of the diagnostic accuracy of FDG-PET and SPECT

Study ID	Study population	Intervention	Method of evaluation	Reference standard
FDG-PET	-	-	-	-
Foster (2007)	<u>Cases:</u> 31 patients with pathologically confirmed AD (mean age: 66 years; mean MMSE score: 14); and 14 patients with pathologically confirmed FTD (mean age: 66 years; mean MMSE: 16)	FDG-PET	Consensus diagnosis by six neurologists (some were recognised experts in FDG-PET imaging, others were novices). Neurologists were shown two different displays of PET data – transaxial and stereotactic surface projection ^a	Autopsy confirmation using NIA-Reagan Institute criteria
Jagust (2007)	<u>Cases:</u> 44 patients with dementia, cognitive impairment, or normal cognitive function (mean age: 75; mean MMSE: 23, both inclusive of 9 normal controls)	FDG-PET	Visual evaluation by two expert raters with extensive experience reading FDG-PET scans in research settings	Follow-up to autopsy at average 5 years. CERAD diagnostic criteria for AD were used for all cases ^b ; some patients also received a final diagnosis according to the NIA-Reagan Institute criteria
Silverman (2001)	<u>Cases:</u> 138 patients undergoing evaluation for dementia (mean age: 66 years; MMSE: 24)	FDG-PET	Visual evaluation by a medical physician	Follow-up to autopsy at average 2.9 years (pathologic criteria varied across sites)
Hoffman (2000)	<u>Cases:</u> 22 patients (mean age: 65 years) with difficult-to-characterise memory loss or dementia based on NINCDS-ADRDA criteria.	FDG-PET	Visual evaluation by an experienced medical physician	Follow-up to autopsy in 20 cases; biopsy in 2 cases (CERAD criteria)
SPECT	-	-	-	-
Rusina (2010)	<u>Cases:</u> 17 patients with pathologically confirmed AD (mean age: 79 years; mean MMSE: 18.7) <u>Controls:</u> 10 patients with ALS without signs of cognitive dysfunction (mean age: 56 years; mean MMSE: 30)	HMPAO-SPECT	3D SPECT ^c	AD confirmed by autopsy, as defined by NIA-Reagan Institute criteria (neocortical tangles score Braak V-VI) and the CERAD criteria (CERAD plaque score frequent)
McNeill (2007)	<u>Cases:</u> 31 patients with pathologically confirmed AD (mean age: 61; mean MMSE: 16) <u>Controls:</u> 25 patients with pathologically confirmed FTD (mean age: 58; mean MMSE: 20)	HMPAO-SPECT	Scans interpreted by a single, nuclear medicine expert, blinded to clinical status of the patient	Pathological diagnosis according to CERAD criteria
Bonte (2006)	<u>Cases:</u> 49 patients with suspected dementia. Mean age of those patients who had pathologically confirmed AD (n=26) was 73 years; mean MMSE was 19.	HMPAO-SPECT	Visual assessment by a single, experienced physician, blinded to clinical status of the patient. A random subset were assessed by a second consultant	Pathology confirmation by autopsy in all cases

Study ID	Study population	Intervention	Method of evaluation	Reference standard
Bonte (2004)	<u>Cases:</u> 20 patients with clinically confirmed (n=10) or autopsy-proven (n=10) AD (mean age: NR) <u>Controls:</u> 20 patients with clinically confirmed (n=13) or autopsy-proven (n=7) FTD (mean age: NR).	HMPAO-SPECT	Comparison with consolidated control image using statistical parametric mapping	Autopsy according to commonly used standards including NIA-Reagan Institute and CERAD criteria
Jagust (2001)	<u>Cases:</u> 70 patients with dementia followed to autopsy (mean MMSE: 13; mean age: 77 years) <u>Controls:</u> 14 controls followed to autopsy (mean age: 80 years; mean MMSE: 28); and 71 non-autopsied controls (mean age: 73 years; mean MMSE: 29)	HMPAO-SPECT (low resolution)	Visual evaluation by three experienced raters	Follow-up to autopsy (CERAD criteria)
Jobst (1998)	<u>Cases:</u> 80 ^d patients with pathologically confirmed AD (mean age: 77 years); and 24 patients with pathologically confirmed non-Alzheimer dementias (mean age: 75 years) ^e <u>Controls:</u> 105 normal, living controls (NINCDS-ADRDA/DSM-III-R criteria; mean age: 69 years); and 14 normal controls with pathological confirmation (mean age: 74 years)	HMPAO-SPECT ^f	Visual evaluation (consensus diagnosis)	Pathological diagnosis of AD (CERAD criteria) ^b
Bonte (1997)	<u>Cases:</u> 54 patients with suspected dementia (mean age: 70 years)	133Xe and/or HMPAO-SPECT	133Xe assessed by visual interpretation and semi-quantitative ROI ratio method; most HMPAO-SPECT results assessed visually only	Pathology confirmation on autopsy in 51 cases; biopsy 3 cases
Bonte (1993)	<u>Cases:</u> 73 patients with dementia or suspected dementia, 18 of which had histopathologic diagnosis (mean age: 70 years)	133Xe or HMPAO-SPECT	Visual interpretation or ROI ratio method	Histopathologic diagnosis (n=18)

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CERAD, Consortium to Establish a Registry for Alzheimer's disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; HMPAO, hexamethylpropylene amine oxime; MMSE, Mini-Mental State Examination; NIA, National Institute on Aging; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and of the Alzheimer's Disease and Related Disorders Association; NR, not reported; PET, positron emission tomography; ROI, region of interest; SPECT, single-photon emission computed tomography; Xe, Xenon.

^a All raters were informed that study subjects had an autopsy-confirmed diagnosis of either FTD or AD, but they did not know the proportion of subjects with each diagnosis.

^b Cases with CERAD pathological assessments of "definite-AD" or "probable-AD" were classified as having confirmed AD, and those regarded as "possible-AD" or "negative" were classified as "non-AD" cases.

^c 3D fuzzy edge detection and 3D watershed transformation.

^d 73 of the 80 AD patients underwent assessment by HMPAO-SPECT.

^e As diagnosed at pathological assessment.

^f All patients underwent CT prior to SPECT to exclude identifiable intracerebral pathology.

B.4.2. Change in patient management

In the study by Laforce et al (2010), a total of 96 files were retrospectively selected and two were excluded because functional imaging was performed over a year after the initial clinical diagnosis. Of the included patients, 56.4% were women, mean age at initial diagnosis was 64.7 years (SD 9.8), and the mean MMSE score was 23.5 (SD 5.0).

At the initial clinical diagnosis, 39.4% of patients were diagnosed with an atypical/unclear dementia, which reflects the complexity of the cases that are referred to the memory clinic. Functional neuroimaging is often ordered in these patients rather than those with typical dementia. Typical dementias made up 35.1% of patients (16 with AD, 12 with FTD, and five with other types). There were 17 patients (18.1%) with a clinical diagnosis of MCI and 7 (7.4%) with a purely psychiatric condition.

B.5. Outcome measures and analysis

B.5.1. Diagnostic accuracy

To assess the diagnostic accuracy of FDG-PET versus SPECT for the diagnosis of AD, the following outcomes were considered relevant, as per the PPICO criteria: sensitivity, specificity, number of true positives, false positives, false negatives, and true negatives.

Test sensitivity is calculated as the proportion of people with AD (as determined by histopathologic diagnosis or long-term clinical follow-up) who had a positive test result after FDG-PET or SPECT:

$$\text{Sensitivity (true positive rate)} = \text{number with true positive result} / \text{total with AD}$$

Test specificity is calculated as the proportion of people without AD (as determined by histopathologic diagnosis or long-term clinical follow-up) who had a negative test result after FDG-PET or SPECT:

$$\text{Specificity (true negative rate)} = \text{number with true negative result} / \text{total without AD}$$

According to the PPICO criteria, the appropriate reference standard for the diagnosis of AD is histopathologic diagnosis via autopsy or long-term clinical follow-up.

As discussed in Section B.4.1, four FDG-PET and eight SPECT studies were identified that used histopathologic diagnosis as the reference standard. One study assessed the sensitivity and specificity of SPECT in distinguishing between patients with suspected AD and cognitively normal (non-demented) controls (Rusina et al, 2010). In one study of FDG-PET (Jagust et al, 2007) and one of SPECT (Jobst et al 1998), diagnostic accuracy was examined in a cohort of patients that contained suspected AD patients, other demented patients, and cognitively normal controls. In those studies, the sensitivity and specificity of FDG-PET and SPECT could be calculated separately for the differentiation of AD patients versus non-demented patients; AD patients versus other demented patients (e.g. FTD, DLB, VD); and AD versus all controls (demented and non-demented).

The remaining three FDG-PET studies and six SPECT studies reported the sensitivity and specificity of the relevant test, where all patients included in the study had suspected dementia. The results of those studies are, therefore, thought to best represent the

patient population who would undergo FDG-PET or SPECT for the diagnosis of suspected AD in practice.

Section B.4.1 highlighted four studies that were included in the Assessment Report, despite not having pathological confirmation for all participants within the study (Bonte et al, 2004; Jagust et al, 2007; Jobst et al, 1998; Rusina et al, 2010). The publications reported diagnostic accuracy results that were inclusive of those patients without autopsy/biopsy results (often large, living control groups). As outlined in Section B.2.2, indirect evidence from studies that examined only FDG-PET or SPECT was included on the basis that true diagnoses were confirmed using the reference standard; however, the existing systematic reviews generally presented the results of those studies inclusive of participants without pathological control. For the purposes of the Assessment Report, information presented in the primary publications has been used to recalculate diagnostic accuracy results for the subset of patients with pathological confirmation only. As such, the results presented in Section B.6.1 do not necessarily match those in the published literature, which tended to include the entire patient population from within those studies.

Of the eight comparative studies, only one small study included long-term clinical follow-up (Döbert et al, 2005). Results from Ito et al (2014) – the only other study that assessed diagnostic accuracy results for FDG-PET versus SPECT in a broad dementia population – were combined with those from Döbert et al (2005). The combined results are shown in a 2 x 2 table, in which the results of the index diagnostic tests were cross-classified against the results showing true disease state (see Section B.6.1).

The remaining comparative studies adopted other, less accepted, measures of diagnostic accuracy. Due to limitations in study design (i.e. lack of reference standard) it was usually not possible to accurately estimate sensitivity or specificity. As such, the diagnostic abilities of FDG-PET and SPECT were assessed using qualitative or relatively crude quantitative outcomes. For example, three studies simply reported the number of patients in which FDG-PET detected hypometabolism in AD-associated ROIs (e.g. temporoparietal or frontal regions) compared to the number of patients in which hypometabolism was detected in the same ROIs using SPECT (Ishii et al, 1999; Kuwabara et al, 1990; Messa et al, 1994).

B.5.2. Safety

Section A.8 states the relevant safety outcomes agreed by PASC. These included adverse events and radiation exposure. Limited evidence is available to address the safety of FDG-PET in patients with AD or dementia and no comparative evidence was available comparing FDG-PET with SPECT in the target population.

B.5.3. Change in management

Section A.8 states the relevant patient management outcomes that were agreed by PASC: treatment instigated, treatment avoided, and other changes occurring in at least 10% of patients.

In the one study that reported change in patient management (Laforce et al, 2010), the impact of FDG-PET on diagnosis was scored retrospectively using two general categories:

- PET contribution including: ‘none’ (i.e. when PET results were entirely incompatible with the clinical presentation and did not contribute at all to the clinical diagnosis); ‘helps, clarifies, orients’ (i.e. when FDG-PET imaging contributed in some way to the clinical diagnosis); and ‘confirms clinical impressions’ (i.e. when FDG-PET and clinical diagnosis were identical).
- Diagnostic change following FDG-PET, scored as ‘yes’ or ‘no’.

The impact of FDG-PET on the prescription of AChEIs was also analysed.

In patients with an initial clinical diagnosis of MCI, FDG-PET was used to assess whether there was a pattern of hypometabolism that was at risk of conversion into AD (i.e. prognostic value of FDG-PET).

Due to the retrospective nature of the study, sensitivity and specificity values could not be generated.

B.5.4. Change in patient outcomes

A diagnostic test that assists with the diagnosis of AD has limited utility if treatment is ineffective. Section A.8 states the relevant patient outcomes agreed by PASC. These are related to downstream treatment, and include disease-specific mortality, disease progression (cognitive function, global outcome, activities of daily living) and quality of life.

Section B.6 addresses patient outcomes qualitatively, presenting a high-level summary of the findings of two recent systematic reviews undertaken for the PBAC (PBS Review, 2012) and NICE (Bond et al. 2012).

B.6. Systematic overview of the results

B.6.1. Diagnostic accuracy

Direct evidence

The diagnostic accuracy results of the two comparative studies examining FDG-PET and SPECT in patients with cognitive impairment or dementia are shown in Table B.6-1. In Ito et al (2014), the diagnostic tests were interpreted by three readers and these results are presented separately.

Döbert et al (2005) reported diagnostic accuracy using two different approaches. First, AD and mixed-type dementia were recognised as separate entities, which generally resulted in comparatively lower sensitivity and specificity results. Second, AD and mixed-type dementia were combined, with the authors noting that the differentiation of those two conditions is of limited clinical importance. The results of both approaches are shown in Table B.6-1.

Table B.6-1 Test results and performance characteristics of studies comparing FDG-PET and SPECT in patients with cognitive impairment or dementia

Study ID	TP	FP	FN	TN	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	Source
FDG-PET	-	-	-	-	-	-	-	-	-
Ito (2014)									
Reader 1	31	9	9	6	78% [62%-89%]	40% [16%-68]	78% [62%-89%]	40% [16%-68%]	Ito (2014), p.1084, Table 4
Reader 2	33	12	7	3	82% [67%-93%]	20% [4%-48%] ^a	73% [58%-85%]	30% [7%-65%]	Ito (2014), p.1084, Table 4
Reader 3	30	11	10	4	75% [59%-87%]	27% [8%-55%]	73% [57%-86%]	29% [9%-58%]	Ito (2014), p.1084, Table 4
Döbert (2005)									
AD only ^b	4	3	5	12	44% [14%-79%]	80% [52%-95%]	57% [19%-90%]	71% [44%-90%]	Döbert (2005), p.67, Table 4
AD/MIX combined ^c	16	1	0	7	100% [79%-100%]	88% [47%-98%]	94% [71%-99%]	100% [59%-100%]	Döbert (2005), p.67, Table 4
SPECT	-	-	-	-	-	-	-	-	-
Ito (2014)									
Reader 1	33	10	7	5	82% [67%-93%]	33% [12%-62%]	77% [61%-88%]	42% [15%-72%]	Ito (2014), p.1084, Table 4
Reader 2	33	13	7	2	82% [67%-93%]	13% [2%-40%]	72% [57%-84%]	22% [3%-60%]	Ito (2014), p.1084, Table 4
Reader 3	35	12	5	3	88% [73%-96%]	20% [4%-48%]	75% [60%-86%]	38% [9%-75%]	Ito (2014), p.1084, Table 4
Döbert (2005)									
AD only ^b	1	3	8	12	11% [2%-48%]	80% [52%-95%]	25% [4%-80%]	60% [36%-81%]	Döbert (2005), p.67, Table 4
AD/MIX combined ^c	6	3	10	5	38% [15%-65%]	63% [25%-91%]	67% [30%-92%]	33% [12%-62%]	Döbert (2005), p.67, Table 4

Note: Reader 1 was an expert with >20 years' experience as a neurological nuclear medicine physician; Reader 2 was a nuclear medicine physician trainee; and Reader 3 was a neuroradiologist with 10 years' experience, mainly in MRI.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; FDG, fluorodeoxyglucose; FN, false negative; FP, false positive; MIX, mixed-type dementia; NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

^a Table 4 (p.29) reported a specificity of 13% which did not match the TP, TN, FP, FN rates shown in the same table. The specificity was recalculated.

^b Table 1 (p.65) presented sensitivity, specificity, PPV, NPV; however the calculations were slightly discrepant from those that were calculated using TP, TN, FP, FN rates presented in Table 4. The table above shows the results which were calculated using data in Table 4 (p.67), assuming that a diagnosis of 'mixed dementia' does not include AD.

^c Calculated from Table 4 (p.67), assuming that a diagnosis of 'mixed dementia' includes AD. Note that there are discrepancies between the data reported in Table 4 and Table 1.

Due to the similarities between the patient populations, and the lack of any alternative evidence, it was thought to be appropriate to combine the results of the two studies, as shown in the 2 x 2 tables below (Table B.6-2 and Table B.6-3). The combined results are those of Döbert et al (2005) and Reader 1 from Ito et al (2014). Reader 1 was an expert neurological nuclear medicine physician with over 20 years' experience (i.e. best case diagnostic accuracy).

Table B.6-2 Test results and true disease state in patients with AD versus other dementias

	AD present	AD absent
FDG-PET	-	-
Test positive	35	12
Test negative	14	18
Sensitivity [95% CI]	71% [57%-83%]	-
Specificity [95% CI]	-	60% [41%-77%]
SPECT	-	-
Test positive	34	13
Test negative	15	17
Sensitivity [95% CI]	69% [55%-82%]	-
Specificity [95% CI]	-	57% [37%-75%]

Source: Table B.6-1 using data from Ito (2014; Reader 1) and Döbert (2005; AD only).

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; FDG, fluorodeoxyglucose; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Table B.6-3 Test results and true disease state in patients with AD or MIX versus other dementias

	AD present	AD absent
FDG-PET	-	-
Test positive	47	10
Test negative	9	13
Sensitivity [95% CI]	84% [72%-92%]	-
Specificity [95% CI]	-	57% [35%-77%]
SPECT	-	-
Test positive	39	13
Test negative	17	10
Sensitivity [95% CI]	70% [56%-81%]	-
Specificity [95% CI]	-	43% [23%-65%]

Source: Table B.6-1 using data from Ito (2014; Reader 1) and Döbert (2005; AD/MIX combined).

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; FDG, fluorodeoxyglucose; MIX, mixed-type dementia; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

The results shown in the 2 x 2 tables above represent the findings of only two of the eight included studies that compared FDG-PET with SPECT. All additional results and conclusions are presented in Table B.6-4.

In general, the studies reported relatively good overall accuracy results for both diagnostic tests, but found a greater magnitude of hypometabolism with FDG-PET than hypoperfusion with SPECT. Furthermore, FDG-PET was thought to be a superior test in terms of identifying mild forms of AD.

As a result of the many different approaches of reporting diagnostic accuracy and the various types of SPECT used, it is difficult to compare the results across multiple studies.

Table B.6-4 Results and conclusions presented in studies with direct evidence of the diagnostic accuracy of FDG-PET and SPECT

Study ID	Results	Conclusions
Ito (2014)	<ul style="list-style-type: none"> • Results were presented separately for each of the three readers (an expert with >20 years' experience as a neurological nuclear medicine physician; a nuclear medicine physician trainee; and a neuroradiologist with 10 years' experience, mainly in MRI). • FDG-PET sensitivity ranged from 75%-82% between the three readers; ECD-SPECT sensitivity ranged from 82%-88%. • FDG-PET specificity ranged from 20%-40%; ECD-SPECT specificity ranged from 13%-33%. • Among the three readers (expert, trainee, neuroradiologist), no marked differences were observed with regard to diagnostic ability, although the experienced reader demonstrated slightly better specificity. 	<ul style="list-style-type: none"> • The diagnostic abilities of FDG-PET and SPECT for "AD and MCI" when diagnosed according to the National Institute of Aging-Alzheimer's Association Workshop criteria, were nearly identical. • "Non-AD" patients tended to be difficult to diagnose with FDG-PET and ECD-SPECT. • Both tests had relatively good sensitivity and accuracy, although the specificity and negative predictive value did not yield sufficient diagnostic ability.
Nihashi (2007)	<ul style="list-style-type: none"> • FDG-PET results showed a sensitivity of detecting AD of 86% and specificity of 97%. • IMP-SPECT showed a sensitivity of 70% and specificity of 100%. 	<ul style="list-style-type: none"> • FDG-PET was superior in evaluating the posterior cingulate and precune regions, but FDG-PET and IMP-SPECT show no significant difference in diagnosing AD with 3D-SSP. • The poorly matched control groups impair ability to accurately compare the diagnostic differences between the two groups.
Döbert (2005)	<ul style="list-style-type: none"> • FDG-PET showed higher accuracy in identifying the type of dementia, detecting AD with sensitivity of 44.4% and specificity of 83.3% as compared with SPECT with sensitivity of 11.1% and specificity of 78.9%^a. • The clinical differential diagnosis of MIX from AD is difficult and of limited diagnostic reliability and validity. Thus, when AD and MIX groups were combined, these two types of dementia were diagnosed with a sensitivity and specificity of 92% and 89% by FDG-PET and of 64% and 84%^a by SPECT. 	<ul style="list-style-type: none"> • PET is significantly superior in identifying dementia sub-types, although the results are based on very small numbers. • In early stages of AD, the diagnostic value of SPECT is associated with low sensitivity.
Herholz (2002)	<ul style="list-style-type: none"> • Tracer uptake reduction was more pronounced with PET. • Correspondence between PET and SPECT was closest in areas known to be affected in most AD patients: the temporolateral, parietal, and posterior cingulate cortices. • Both PET and SPECT were able to separate all controls from AD cases when looking at abnormal voxels. • PET voxels in the volume of best correspondence was greater in all patients than in healthy volunteers for z thresholds ranging from -3.5 to -1.5. Thus, complete separation was achieved for this range of thresholds. • Complete separation was achieved by counts of abnormal SPECT voxels in the whole brain, but only at a more narrow range of z thresholds, from -3.0 to -2.75. • By visual inspection, most scans showed a reasonable correspondence between PET and SPECT, but in some cases distinct discordance of findings was apparent. 	<ul style="list-style-type: none"> • FDG-PET and HMPAO-SPECT provide comparable results for the main finding of temporoparietal and posterior cingulate functional impairment in mild and moderate AD. • The distinction between healthy volunteers and patients is less sensitive to z threshold selection with PET than with SPECT, and findings in the frontal, temporobasal, and temporomesial cortices and in the cerebellum may differ between the two techniques. • The sample of healthy volunteers in this study was too small to provide an estimate of the diagnostic accuracy (sensitivity and specificity) of the two diagnostic tests.

Study ID	Results	Conclusions
Ishii (1999)	<ul style="list-style-type: none"> • Temporoparietal changes were seen in 8/10 SPECT scans and 9/10 PET scans. • The contrast between radiotracer uptake in the sensorimotor area and that in the parietotemporal region was not as great in the ECD images as it was in the FDG images. 	<ul style="list-style-type: none"> • Good accuracy with both techniques. • Although ECD-SPECT is inferior to FDG-PET in spatial resolution and quantification, in routine clinical examinations, ECD-SPECT is good enough to detect parietotemporal reduction in patients with AD. • The study authors concluded that overall SPECT was superior because of convenience of clinical use.
Messa (1994)	<ul style="list-style-type: none"> • Temporoparietal changes typical of AD (i.e. abnormal metabolism/perfusion)^b were seen in all 21 AD subjects using PET and 19 out of 21 (90%) subjects using SPECT. • The difference between probable AD patients and controls in the frontal cortex was only statistically significant on PET ($p < 0.0001$). • Both PET and SPECT showed significant differences between controls and dementia subjects. 	<ul style="list-style-type: none"> • The study authors concluded that although both imaging techniques could detect characteristic temporoparietal changes with high accuracy in AD, PET was superior for detecting changes in other associated areas. • Davison et al (2014) stated that it is unclear whether this is of clinical benefit in improving diagnostic accuracy.
Mielke (1994)	<ul style="list-style-type: none"> • ROC curves demonstrated the differences in the diagnostic sensitivity and specificity between the metabolic and perfusion ratio. • For discrimination between AD patients and controls there was a marginally significant advantage for PET over SPECT ($p = 0.05$). FDG-PET reached 80% sensitivity at 100% specificity; SPECT reached 80% sensitivity at only 65% specificity. • The false negatives in PET were all mildly demented, whereas in SPECT they were scattered over the whole range of dementia severity. • For discrimination between AD and VD, FDG-PET was superior to SPECT ($p = 0.0001$). 	<ul style="list-style-type: none"> • SPECT and PET are both able to identify the typical temporoparietal changes found in AD but found PET to be significantly more accurate. • HMPAO-SPECT was only marginally inferior to FDG-PET for differentiation of AD patients from normal, since the typical temporoparietal functional impairment was detected with both methods. However, for differentiation between AD and VD, FDG-PET was clearly superior. • The study authors hypothesise that FDG-PET might be more sensitive for imaging small functional pathological changes.
Kuwabara (1990)	<ul style="list-style-type: none"> • Decreased bilateral hypoperfusion or metabolism was evident in parietal regions in 9/9 AD subjects using FDG-PET; 7/9 with IMP-SPECT; and 4/5 with HMPAO-SPECT. 	<ul style="list-style-type: none"> • FDG-PET was superior in identifying more mildly affected areas of change for both AD and Pick's disease; however, both SPECT tracers were able to effectively identify the more significant parietal and frontal changes. • FDG-PET showed the highest degree of detection of abnormal regions, and IMP and HMPAO-SPECT could not detect mildly affected areas efficiently (e.g. the frontal regions in AD). • Cannot draw conclusions on the differing ability of SPECT and PET to separate cases from controls due to different control selection criteria^c.

Abbreviations: AD, Alzheimer's disease; ECD, ethyl cysteinyl dimer; FDG, fluorodeoxyglucose; HMPAO, hexamethylpropylene amine oxime; IMP, iodoamphetamine; MCI, mild cognitive impairment; PET, positron emission tomography; SPECT, single-photon emission computed tomography; VD, vascular dementia; 3D-SSP, three-dimensional stereotactic surface projections.

^a Sensitivity and specificity as reported in Döbert (2005), Table 1 (p.65). Slightly different specificity values were calculated using information in Table 4 (p.67), as shown in Table B.6-1.

^b Metabolism or perfusion were considered abnormal when the regional values (either of the right or left hemisphere or both) were out of the mean ± 2 standard deviations of the control group.

^c Normal volunteers were used as controls for PET, while those with mild neurological symptoms were used as controls for SPECT.

Indirect evidence

As discussed in Section B.2.2, the Assessment Report includes evidence from a number of studies that only assess the diagnostic accuracy of either FDG-PET *or* SPECT. While the studies did not explicitly meet the eligibility criteria, they were included in order to supplement the limited body of comparative evidence regarding diagnostic accuracy (see Section B.2.1).

This indirect evidence is categorised into three different groups according to control population(s):

- (1) Cognitively normal ('normal' or non-demented) controls;
- (2) Demented controls excluding MCI; or
- (3) Various controls (including both cognitively normal and demented subjects).

As discussed in Section B.5.1, several of the primary studies reported diagnostic accuracy results that included some participants without pathological confirmation of diagnosis. The results, as reported in the publications, are presented in Appendix 3. Similar results are presented in Table B.6-5, however patients without confirmation of diagnosis using autopsy or brain biopsy have been removed from the analysis.

Table B.6-5 Test results and performance characteristics of FDG-PET and SPECT in patients with autopsy confirmation only

Study ID	Index test	TP	FP	FN	TN	Sensitivity [95% CI]	Specificity [95% CI]	Source
Non-demented controls	-	-	-	-	-	-	-	-
Rusina (2010) ^a	SPECT	16	0	1	5	94% [71%-99%]	100% [48%-100%]	Calculated: Rusina (2010), p.5 (in text)
Jobst (1998) ^b	SPECT	65	4	8	10	89% [80%-95%]	71% [42%-91%]	Calculated: Jobst (1998), p.296, Table 5
Demented controls	-	-	-	-	-	-	-	-
Foster (2007)	FDG-PET ^c FDG-PET ^d	NR NR	NR NR	NR NR	NR NR	96% [NR] 98% [NR]	59% [NR] 73% [NR]	Foster (2007), p.2623, Table 5
Jagust (2001) ^e	FDG-PET	29	7	17	31	63% [48%-77%]	82% [66%-92%]	Calculated: Jagust (2001), pp.953-4, Table 2-3
Silverman (2001)	FDG-PET	91	11	6	30	94% [87%-98%]	73% [57%-86%]	Silverman (2001), p.2123, Table 2
Hoffman (2000)	FDG-PET ^f FDG-PET ^g	13 14	3 2	1 2	5 4	93% [66%-99%] 88% [62%-98%]	63% [25%-91%] 67% [23%-95%]	Hoffman (2000), p.1922-3, Tables 1,3
McNeill (2007)	SPECT	NR	NR	NR	NR	65% [45%-81%]	72% [51%-88%]	Bloudek (2011), p.634, Figure 6
Bonte (2006)	SPECT	26	2	4	17	87% [69%-96%]	89% [67%-98%]	Bonte (2006), p.377, Tables 1-2
Bonte (2004)	SPECT	6	0	4	7	60% [26%-88%]	100% [59%-100%]	Calculated: Bonte (2004), p.772, Table 1
Jobst (1998) ^b	SPECT	65	11	8	13	89% [80%-95%]	54% [33%-74%]	Calculated: Jobst (1998), p.296, Table 5
Bonte (1997)	SPECT	37	3	6	8	86% [72%-95%]	73% [39%-94%]	Bonte (1997), p.795-6, Table 1-2
Bonte (1993)	SPECT ^d SPECT ^e	11 13	2 0	3 0	2 3	79% [49%-95%] 100% [75%-100%]	50% [8%-92%] 100% [30%-100%]	Calculated: Bonte (1993), p.364, Table 4
Various controls ^h	-	-	-	-	-	-	-	-
Jagust (2007)	FDG-PET	21	5	4	14	84% [64%-95%]	74% [49%-91%]	Cure (2014), p.175, Figure 2
Jobst (1998) ^b	SPECT	65	15	8	23	89% [80%-95%]	61% [43%-76%]	Calculated: Jobst (1998), p.296, Table 5

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; FDG, fluorodeoxyglucose; FN, false negative; FP, false positive; MIX, mixed-type dementia; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

^aExcludes five normal controls without autopsy confirmation – all AD cases and 5/10 non-demented controls underwent autopsy.

^bExcludes 105 living controls.

^cTransaxial assessment.

^dVoxel-wise method (SSP).

^eExcludes 71 non-autopsied controls.

^fVisual assessment (n=18).

^gRatio ROI/WBF (whole-brain cross-sectional flow) (n=16).

^hIncludes both demented and cognitively normal controls.

As highlighted in the literature, the highest diagnostic values tend to come from studies investigating the ability of diagnostic tests to differentiate between dementia and cognitively normal controls (Panegyres et al, 2009). In contrast, studies that focus on differentiating between various types of dementia generally lead to lower sensitivity and specificity results. Therefore, studies that compare the ability of FDG-PET and SPECT to differentiate between dementia and cognitively normal controls have low generalisability to clinical practice, as cognitively normal patients would rarely be referred for such tests.

Table B.6-6 presents similar test results and performance characteristics to Table B.6-5; however, only studies (or subsets of studies) that examined FDG-PET and SPECT in dementia or suspected dementia patients were included. Therefore, the study by Rusina et al (2010), which included cognitively normal ALS patients as controls, is not shown in the results from Table B.6-6 onwards.

The combined results, including overall sensitivity and specificity, are shown for FDG-PET and SPECT in Table B.6-7. It should be noted that Foster et al (2007) and McNeill et al (2007) are not included in the overall results because the relevant information (i.e. number of TP, FP, FN, TN) was not presented in the publications, nor could it be calculated using available information.

Table B.6-6 Test results and performance characteristics of FDG-PET and SPECT in patients with autopsy confirmation (demented controls only)

Study ID	Index test	TP	FP	FN	TN	Sensitivity [95% CI]	Specificity [95% CI]	Source
Foster (2007)	FDG-PET ^a	NR	NR	NR	NR	96% [NR]	59% [NR]	Foster (2007), p.2623, Table 5
	FDG-PET ^b	NR	NR	NR	NR	98% [NR]	73% [NR]	
Jagust (2007)	FDG-PET	19	4	3	9	86% [65%-97%]	69% [39%-91%]	Calculated: Jagust (2007), p.874 (in text)
Jagust (2001)	FDG-PET	29	6	17	18	63% [48%-77%]	75% [53%-90%]	Calculated: Jagust (2001), p.953
Silverman (2001)	FDG-PET	91	11	6	30	94% [87%-98%]	73% [57%-86%]	Silverman (2001), p.2123, Table 2
Hoffman (2000)	FDG-PET ^c	13	3	1	5	93% [66%-99%]	63% [25%-91%]	Hoffman (2000), p.1922-3, Tables 1,3
	FDG-PET ^d	14	2	2	4	88% [62%-98%]	67% [23%-95%]	
McNeill (2007)	SPECT	NR	NR	NR	NR	65% [45%-81%]	72% [51%-88%]	Bloudek (2011), p.634, Figure 6
Bonte (2006)	SPECT	26	2	4	17	87% [69%-96%]	89% [67%-98%]	Bonte (2006), p.377, Tables 1-2
Bonte (2004)	SPECT	6	0	4	7	60% [26%-88%]	100% [59%-100%]	Calculated: Bonte (2004), p.772, Table 1
Jobst (1998)	SPECT	65	11	8	13	89% [80%-95%]	54% [33%-74%]	Calculated: Jobst (1998), p.296, Table 5
Bonte (1997)	SPECT	37	3	6	8	86% [72%-95%]	73% [39%-94%]	Bonte (1997), p.795-6, Table 1-2
Bonte (1993)	SPECT ^e	11	2	3	2	79% [49%-95%]	50% [8%-92%]	Calculated: Bonte (1993), p.364, Table 4
	SPECT ^f	13	0	0	3	100% [75%-100%]	100% [30%-100%]	

Abbreviations: CI, confidence interval; FDG, fluorodeoxyglucose; FN, false negative; FP, false positive; NR, not reported; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

^a Transaxial assessment

^b Voxel-wise method (SSP).

^c Diagnostic accuracy results when only a single pathology was present.

^d Diagnostic accuracy results when two pathologic diagnoses were present (AD + other).

^e Visual assessment.

^f Ratio ROI/WBF.

Table B.6-7 Test results and true disease state in patients with AD versus other dementias

	AD present	AD absent
FDG-PET	-	-
Test positive	155	25
Test negative	29	79
Sensitivity [95% CI]	84% [78%-89%]	-
Specificity [95% CI]	-	76% [67%-83%]
SPECT	-	-
Test positive	145	18
Test negative	25	47
Sensitivity [95% CI]	85% [79% to 90%]	-
Specificity [95% CI]	-	72% [60% to 83%]

Source: Table B.6-6.

Note: Table B.6-6 presents two sets of results for the studies by Hoffman (2000) and Bonte (1993). For the purpose of the combined results shown in Table B.6-7, one set of results was chosen for each study. The results from Hoffman (2000) were those which included cases where two pathologic diagnoses were present. The results from Bonte (1993) were those that were assessed visually.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; FDG, fluorodeoxyglucose; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Finally, Table B.6-8 shows the results from two recent meta-analyses (Bloudek et al, 2011; Cure et al, 2014). Bloudek et al (2011) included studies with a variety of reference standards, while Cure et al (2014) only included studies with autopsy confirmation of diagnosis. Importantly, one study (Fazekas et al, 1989) without pathologically confirmed diagnoses was inadvertently included in the meta-analysis of five FDG-PET studies in Cure et al (2014). Nonetheless, it has not been removed from the meta-analysis shown in Table B.6-8, which shows all results as presented in the published literature.

Table B.6-8 Published meta-analyses of FDG-PET and SPECT for the diagnosis of AD versus all controls (normal and demented), normal controls only, and demented controls only

Study ID	Index test	No. of studies	TP	FP	FN	TN	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]
All controls	-	-	-	-	-	-	-	-	-	-
Cure (2014)	FDG-PET	5	182	29	13	78	93% [89%-97%]	73% [63%-83%]	86% [81%-91%]	86% [77%-92%]
Cure (2014)	SPECT	6	207	30	35	163	86% [81%-91%]	85% [79%-90%]	87% [82%-91%]	82% [76%-87%]
Bloudek (2011)	FDG-PET	33 ^a	NR	NR	NR	NR	91% [86%-94%]	86% [79%-91%]	NR	NR
Bloudek (2011)	SPECT	19	NR	NR	NR	NR	79% [72%-85%]	84% [78%-88%]	NR	NR
Normal controls	-	-	-	-	-	-	-	-	-	-
Bloudek (2011)	FDG-PET	20	NR	NR	NR	NR	90% [84%-94%]	89% [81%-94%]	NR	NR
Bloudek (2011)	SPECT	11	NR	NR	NR	NR	80% [71%-87%]	85% [79%-90%]	NR	NR
Demented controls	-	-	-	-	-	-	-	-	-	-
Bloudek (2011)	FDG-PET	13 ^b	NR	NR	NR	NR	92% [84%-96%]	78% [69%-85%]	NR	NR
Bloudek (2011)	FDG-PET	10	NR	NR	NR	NR	93% [85%-97%]	70% [64%-76%]	NR	NR
Bloudek (2011)	SPECT	8	NR	NR	NR	NR	79% [65%-88%]	81% [72%-87%]	NR	NR

Note: PPV and NPV results were calculated using information available in the systematic reviews.

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; FDG, fluorodeoxyglucose; FN, false negative; FP, false positive; MIX, mixed-type dementia; NPV, negative predictive value; NR, not reported; PET, positron emission tomography; PPV, positive predictive value; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

^a 27 reported in text (p.634); 33 shown in meta-analysis (fig.5).

^b Three studies had a control group of patients with MCI.

B.6.2. Safety

The literature search identified no primary studies that reported on the safety of FDG-PET versus SPECT for the diagnosis of AD. None of the studies included in the assessment of diagnostic accuracy reported any adverse events associated with FDG-PET or SPECT. A systematic review by Bohnen et al (2012) examined the effectiveness and safety of FDG-PET in the evaluation of dementia and noted that no safety issues were raised in the multitude of papers that have studied the application of FDG-PET in AD, AD-related dementia or other neurodegenerative disorders. One reference specifically mentioned the absence of any adverse effects related to the administration of the radiopharmaceutical (Lowe et al, 2009).

Patients undergoing a FDG-PET scan will be exposed to a certain amount of ionising radiation. The American College of Radiology ACR Appropriateness Criteria for Dementia and Movement Disorders (2014)⁶ acknowledges that potential health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Due to the wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication is reported for each imaging examination, including those for probable and possible AD. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Both FDG-PET/CT and Tc-99m HMPAO-SPECT of the head are listed for use as problem-solving techniques in differentiating dementias, and have been assigned the same RRL rating: adult effective dose estimate range 10-30 mSv. In comparison, CT and amyloid PET/CT of the head has an RRL of 1-10 mSv.

Although there is limited published information available on the safety of PET, it is generally accepted that PET is a non-invasive and safe diagnostic procedure. Safety issues would primarily relate to the positron emitting radiopharmaceutical rather than the safety of the procedure as a whole (Silberstein, 1998). As radiotracers are generally used in very small quantities, the incidence of adverse reactions to non-pharmacologic amounts of labelled molecules are likely to be low.

B.6.3. Change in patient management

The Laforce et al (2010) publication presents the percentage of cases that were diagnosed as either atypical/unclear, MCI, AD or FTD according to initial clinical diagnosis, Nuclear Medicine Physician's diagnosis (using FDG-PET) and the most recent diagnosis for each clinical subgroup (at an average follow-up of 1.5 years). These results are shown in Table B.6-9.

Table B.6-9 Difference between initial, FDG-PET and most recent diagnoses

Clinical subgroup	Initial clinical diagnosis	Diagnosis using FDG-PET	Most recent diagnosis
Atypical/unclear	39.4%	6.4%	16.0%
MCI	18.1%	3.2%	19.1%
AD	17.0%	33.0%	31.9%
FTD	12.8%	18.1%	16.0%

Source: Laforce et al (2010)

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; FTD, frontotemporal dementia; MCI, mild cognitive impairment

⁶ Available on the ACR website

Among the atypical/unclear cases at the initial clinical evaluation, 29.7% showed typical AD patterns of hypometabolism on FDG-PET, 21.6% were normal, 16.2% showed patterns of VD and 13.5% were compatible with FTD. At the end of the study, a total of 16% of the 94 cases remained atypical/unclear despite clinical evolution of the disease and extensive investigation, which in some cases included serial functional imaging studies.

Among the 18.1% of MCI cases at risk of conversion according to clinicians, only 11.8% were identified as MCIs at risk of conversion on FDG-PET. The remainder of the sample was composed of 52.9% with a normal PET, 29.4% with a typical pattern of AD, and 5.9% with a pattern of FTD.

Among patients with AD at the initial clinical evaluation, 68.8% showed an AD pattern on FDG-PET; the remainder included 12.5% with a typical FTD pattern, 6.3% with a typical DLB pattern, 6.3% with MCI, and 6.3% with normal brain metabolism. At the end of the study, 31.9% of all cases remained with a diagnosis of AD, which was consistent with the diagnosis based on FDG-PET.

Clinicians' impression of the contribution of FDG-PET to the diagnosis is shown in Table B.6-10. In patients with typical AD, PET's contribution was in confirming clinical impressions rather than generating a diagnostic change. However, in atypical/unclear cases, FDG-PET imaging was very helpful in 81.1% of cases, resulting in a diagnostic change in 59.5% of cases. In MCI, FDG-PET was very helpful in 88.2% of cases, presumably due to clarification of the risk of conversion to AD or in indicating that a primary neurodegenerative disease was less likely, both without requiring diagnostic change (which only occurred in 17.6% of MCI cases).

Table B.6-10 Clinician impression of the contribution of FDG-PET to diagnosis

Clinical subgroup	None	Helps	Confirms initial clinical diagnosis	Diagnostic change
Atypical/unclear	18.9%	81.1%	<10%	59.5%
MCI	<10%	88.2%	<10%	17.6%
AD	18.8%	12.5%	68.8%	<10%
FTD	<10%	16.7%	75.0%	<10%

Source: Laforce et al (2010)

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; FTD, frontotemporal dementia; MCI, mild cognitive impairment

FDG-PET findings were associated with a change in diagnosis in 29% of patients. Use of AChEIs increased from 13.8% before FDG-PET to 38.3% after FDG-PET, partly reflecting the impact on atypical/unclear cases that turned out to be potentially treatable patients with AD.

The findings from the Laforce et al (2010) study are supported by a prospective management impact study from a multidisciplinary memory disorders clinic in Melbourne, Australia. Elias et al (2014) examined the impact of FDG-PET in patients referred at the discretion of the treating specialist upon completion of an initial clinical evaluation. Of 194 patients referred from November 2003 to November 2007, a neurodegenerative disease was diagnosed in 75.2% of patients using FDG-PET compared with 82.9% after initial clinical diagnosis. The study did not follow patients over time and therefore the accuracy of the PET diagnosis could not be confirmed. Nonetheless, FDG-PET had a clinically relevant impact in 44% of patients by changing

the diagnosis and/or treatment. In 14% of the cohort a pre-scan diagnosis of dementia changed to a non-neurodegenerative condition post-PET, whereas in 6.1% of the cohort a pre-scan diagnosis of non-dementia (e.g. depression or anxiety disorder) changed to a diagnosis of a neurodegenerative disorder (such as AD) post-scan. Although the total proportion of patients prescribed AChEIs did not differ pre and post scan (38% vs 41%, respectively), treatment changed in 17% of patients (14 patients had AChEIs removed from their management plan while 19 patients had AChEIs added).

B.6.4. Change in patient outcomes

The sections below summarise the findings of the two systematic reviews listed in Section B.2 that were undertaken to inform decision-making in Australia and the UK relating to the safety, effectiveness and cost-effectiveness of AChEIs and memantine.

Bond et al (2012) HTA for NICE

This update of a 2004 NICE Review included RCTs of donepezil, galantamine, rivastigmine or memantine that were published after 2004. The following is a summary of the key findings.

Five small, poor-quality donepezil studies were added to the evidence base. All studies measured cognitive outcomes and a dose-related beneficial effect was found at 10 mg/day.

An additional three variable-quality RCTs of galantamine versus placebo were added to the six studies included in the 2004 review for NICE. The new studies all found significant benefit on cognitive outcomes; the results for functional and global outcomes were inconclusive, and no significantly positive gain was found for behavioural outcomes. However, when the results from these studies were pooled with evidence identified in the 2004 review for NICE, significant gains for people taking galantamine were found for cognitive, functional and global outcomes.

Three new studies of rivastigmine were identified, one of which was of reasonable size and quality. Positive benefits from rivastigmine were found on cognitive, functional and global outcomes, but, as in 2004, not on behavioural ones. The lower dose transdermal patch (9.5 mg/day) was shown to be as effective as the capsule (12 mg/day), but with fewer side effects.

One new, poorer-quality study of memantine failed to show any benefit from memantine on any outcome measure. When the data were pooled with evidence from the 2004 NICE review, a significant benefit from memantine was found from global outcomes. However, these results are based on two moderate-to-poor-quality trials and the authors warned that the results may be untrustworthy.

Three new head-to-head comparisons were found. Only one of the new studies – comparing donepezil to rivastigmine – was large and of reasonable quality. It measured cognitive, functional, behavioural and global outcomes, but found statistically significant differences only on functional and global outcomes, both favouring rivastigmine. One new study and one previous study (neither of good quality) compared donepezil with galantamine. The new study only looked at global outcomes and found no difference between the treatments. Finally, one very poor-quality study looking at behavioural outcomes compared all three AChEIs and found that rivastigmine was significantly

better than donepezil or galantamine. Overall, there was insufficient evidence to suggest that one treatment is better than another.

The review identified one new, reasonably good-quality study comparing combined memantine with an AChEI against AChEI and placebo. This showed no significant advantage to combining these treatments (in contrast to results from the previous review).

In terms of safety, the review found that the main AEs for the AChEIs were gastrointestinal, and agitation and hypertension for memantine. However, the source of this evidence was limited to the included RCTs; the trial populations and their experience of AEs may not reflect those of people with AD in clinical practice.

Overall, the authors noted that although more evidence had accumulated between 2004 and 2010, its impact on conclusions about effectiveness appears small. The evidence on effectiveness of galantamine and rivastigmine relative to placebo was consolidated but evidence on the effectiveness of memantine was not greatly strengthened. None of the gaps in evidence noted in the previous assessment were closed by the new RCTs and no new evidence emerged on differential effectiveness by subgroup, particularly disease severity. Furthermore, there is no evidence that the treatments increase longevity.

The review team noted a number of limitations that affect the interpretation of the clinical evidence:

- The length of follow-up of the trials was a maximum of 6 months, which makes it very difficult to reliably extrapolate findings years ahead.
- There is a lack of evidence from the trials on key outcomes, such as mortality, institutionalisation, the impact on carer's time and the prescription of antipsychotics.
- None of the trials conducted subgroup analyses based on disease severity, therefore no comment could be made on the effectiveness of treatments for mild, moderate or severe AD separately.
- Overall, the quality of the trials was medium to poor, with a lack of reporting of key measures of trial quality, thus adding to the uncertainty of the results.
- The use of last observation carried forward (LOCF) and observed case (OC) methods for accounting for missing data are inappropriate in a condition that naturally declines to death and may lead to an overestimation of the treatment benefit from the drugs.
- Some of the measures used in the trials are insensitive to change in AD (AD Assessment Scale – Cognitive Subscale, MMSE). Therefore, the effects of treatment may have been underestimated in some cases.

The authors noted that there continue to be many uncertainties and it is likely that the nature and extent of these uncertainties is similar to those operating when the last review was compiled. The most influential of these are:

- effect of anti-AD drugs in the longer term on any outcome, especially beyond one year;
- effect of anti-AD drugs on outcomes beyond cognition, function, behaviour and global impact, particularly QoL, impact on carers, effect on admission to full-time care and impact on resource use; and

- whether or not the effects vary substantially by subgroup, particularly severity of AD.

PBS Review of anti-dementia medicines to treat AD (2012)

The PBAC recommended the subsidy of AChEIs and memantine for AD in late 2000. At the time, the PBAC recognised the clinical need for an effective treatment for people with AD, but that the evidence supporting the effect of these medicines on patients' QoL and on the benefits of treatment, particularly beyond six months, was very limited. For these reasons, PBAC initially recommended restricting the subsidy of these medicines beyond six months to only those patients who demonstrated an improvement in their symptoms (assessed using MMSE score) following treatment.

However, it is argued that there is benefit in continuing treatment with these medicines when there is stabilisation or a perceived slowing of symptom progression without necessarily an improvement in symptoms. The PBS Review therefore sought to identify new and differential evidence on the benefits of treatment, with the impact on QoL and rates of institutionalisation as the outcomes of most interest, as these generally form the basis of cost-effectiveness claims.

The details of the findings of the PBS Review of the effectiveness and safety of AChEIs and memantine for the treatment of AD are available in the main report prepared for the PBAC⁷. Below is a brief summary of the main findings, taken from the publically available summary.

Based on the available clinical trials, between 8.6% and 40% (mean 28%) of patients demonstrate a response or improvement in symptoms equivalent to a two-point increase in MMSE. The review concluded that patients given AChEIs and memantine showed, on average, small improvements in cognitive ability compared with patients given placebo or no drug treatment. The clinical relevance of these improvements measured using the MMSE and Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) remains unknown because linking these changes to patient-relevant outcomes such as changes in QoL has not been demonstrated in clinical trials. No convincing evidence was identified that reported an improvement over placebo in QoL outcomes or time to institutionalisation.

The results of trials measuring cognitive response in people given AChEIs beyond six months were inconsistent. Some studies demonstrated statistically significant differences in people given AChEIs for one or two years compared with those given placebo, whereas other studies showed that MMSE scores declined at a similar rate to those in the placebo group.

Trials that studied the effect on cognition when these medicines were ceased found that symptoms deteriorated more rapidly than those who stayed on donepezil, galantamine and memantine. No similar trials of the effect of stopping treatment for rivastigmine were found in this literature search.

Observational studies of galantamine have reported delaying death, higher MMSE scores and delayed time to institutionalisation for those treated beyond six months, however the quality of this data is considered to be low when compared to other trials. There is also

⁷ Available on request from the PBAC Secretariat

one small trial that has reported delayed admission to an aged care facility for some patients taking memantine relative to placebo.

Review of longer term safety data did not provide any new information on further harms associated with AChEIs or memantine than had been previously assessed by PBAC. There are significant reports of side effects such as nausea and diarrhoea, however titration at commencement has been shown to help reduce these symptoms.

Taking more than one of the AChEIs or memantine at the same time appears unlikely to provide any further benefit to patients.

Overall the results of this review of more recent comparative evidence on the effectiveness of AChEIs and memantine are consistent with previous evidence on safety and efficacy considered by the PBAC when the medicines were originally recommended for PBS subsidy.

Furthermore, the review did not identify any new or stronger evidence for cost-effectiveness than that considered originally by PBAC. That is, the trial evidence identified in this review does not provide any further evidence that can be valued from a payer or government perspective to support or inform on the cost-effectiveness of these medicines. However, there is significant evidence that these medicines are being used in a broader population than originally agreed as cost-effective by PBAC.

According to the ratified Minutes of the December 2012 Special PBAC meeting⁸, the PBAC reaffirmed the view that the population-based, average benefits associated with the anti-dementia medicines on the PBS were small and poorly supported by comparative trial evidence. The PBAC also considered that there was little to be gained by updated cost-effectiveness models of these medicines in the absence of more conclusive clinical data on health outcomes. They noted that previous economic models rely on the assumption that change in MMSE predicts change in QoL or time to institutionalisation, but there is still insufficient evidence to link small changes in MMSE to patient-relevant clinical outcomes. In addition, the PBAC noted that the economic models previously presented to the PBAC were difficult to assess as many assumptions were implicit in the model, and implausible results occurred when the models were tested with revised assumptions.

The PBAC considered that the evidence on the clinical effectiveness and safety of the anti-dementia medicines for AD supports previous PBAC decisions to list each on a cost-minimisation basis with each other. The PBAC did not recommend delisting any of the AChEIs or memantine.

B.7. Interpretation of the clinical evidence

Diagnostic accuracy

There are a limited number of comparative studies evaluating FDG-PET and SPECT for the diagnosis of AD. Both diagnostic tests are able to detect temporoparietal changes, typical of AD, with a relatively high degree of accuracy. However, the comparative studies generally found that FDG-PET was marginally superior at identifying very mildly affected brains or brain regions (e.g. the frontal cortex) when compared with SPECT. A major limitation of the direct evidence is that, in most cases, validation was against

⁸ Available on the PBS website

clinical diagnostic criteria rather than histopathologic diagnosis. In the two studies that compared FDG-PET with SPECT in differentiating AD from non-AD dementia, the sensitivity and specificity of FDG-PET (71% and 60%) and SPECT (69% and 57%) were similar.

A larger number of low quality studies have assessed the diagnostic accuracy of either FDG-PET or SPECT. The Assessment Report included such studies, but only those that sought pathological confirmation of diagnosis. Ultimately, the combined results 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%. However, the pooling and comparison of indirect evidence is prone to bias due to inevitable differences between the patient populations across the different studies, which compromises the reliability of the estimates.

Several published systematic reviews have presented meta-analyses indicating that FDG-PET may have marginally superior diagnostic abilities to SPECT (Bloudek et al, 2011; Davison et al, 2014). Rather than teasing out the best available evidence, the meta-analysis by Bloudek et al (2011) combined results from all available studies, irrespective of the differences in assessment techniques (e.g. visual examination versus quantitative computer-based methods), populations (e.g. early versus late onset AD) and reference standards.

In addition, diagnostic accuracy can be influenced by factors such as the spatial resolution and count sensitivity of detector configurations and by other instrumentation parameters, acquisition and processing techniques, methods and quality of image display, the interpretive criteria used, and the experience of the interpreters with each modality (Silverman et al, 2004). Furthermore, the systematic review by Davison et al (2014) concluded that “the evidence base on direct PET and SPECT comparison studies is...limited and inadequate to make very broad generalisations about the superiority of one technique over another for the diagnosis of dementia”.

Importantly, some studies assessed the ability of FDG-PET and SPECT to distinguish between AD patients and normal controls, while other studies assessed the extent to which the test could differentiate between various types of dementia (e.g. AD and FTD). The most applicable studies are those that include the full range of patients likely to be seen in clinical practice, which could include patients with very early signs of disease (e.g. MCI) through to patients with manifest disease (Panegyres et al, 2009). Assessing highly selected subsets of patients limits the clinical applicability of the results.

Safety

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

Change in patient management

There was limited evidence available regarding change in management brought about by FDG-PET. One study found that FDG-PET resulted in a change in diagnosis in 29% of patients, and increased the use of AChEIs after diagnosis (Laforte et al, 2010). These findings are supported by the only available Australian evidence, which reported a change in diagnosis in 35% of dementia patients who underwent FDG-PET (Elias et al, 2014).

Change in patient outcomes

Evidence regarding the efficacy of anti-AD drugs is relatively limited. In particular, the effect of anti-AD drugs on outcomes beyond cognition, function, behaviour and global impact remains fairly uncertain. Of relevance to this assessment, there is limited evidence for the impact of treatment on QoL, admission to full-time care and resource use, which underpin claims of cost-effectiveness. Furthermore, long-term follow-up (especially beyond one year) on the effect of anti-AD drugs on any outcome remains a major evidence gap.

Section C. Translating the clinical evaluation to the economic evaluation

C.1. Identification of issues to be addressed

This section presents each of the translation issues identified to move from the clinical evidence discussed above to the economic evaluation presented in Section D.

Applicability, extrapolation and transformation issues were considered to identify each of the issues presented in Table C.1-1. In each instance, a focused analytical plan is presented prior to presenting the results of the pre-modelling study and the relationship between these and the economic evaluation presented in Section D.

Table C.1-1 Translation issues identified in preparing the economic evaluation

Translation issue	Comments	Section C subsection
Applicability issues		
Population and circumstances of use	As discussed in Section B, existing clinical and economic evidence relating to FDG-PET for the diagnosis of AD is not well-matched in terms of the population of the requested listing. Nonetheless, the link between the population of the requested listing and the economic model presented in Section D is discussed.	Section C.2
Extrapolation issues		
Duration of AD treatment	Since AD treatment is claimed to result in a reduction in time to disease progression, it was necessary to include the duration of treatment in the economic model so as to ensure that the treatment effect is adequately modelled/estimated.	Section C.3
Transformation issues		
Modelling the natural history of AD	Although the focus of the analysis is on the cost-effectiveness of diagnostic testing, it is also necessary to understand the natural history of AD as it unfolds in individuals over time and model this accordingly.	Section C.4
Treatment effect of AD drugs	In conjunction with the natural history of AD, the effect of treatment was necessary to include in the model to ensure that any impact treatment may have on survival and QoL is adequately captured in the assessment of the cost-effectiveness of diagnostic testing.	Section C.5
Utility weights applied to the economic model	To undertake the cost-utility modelling presented in Section D, it was necessary to source utility weights to be applied to the health states included in the economic model. As discussed, these needed to account for disease severity and residential status (i.e. community or nursing home) of individuals with AD.	Section C.6
Healthcare resource use and associated costs	The economic model required AD drug treatment and other costs associated with AD-related care to be applied to a range of included health states. It was necessary to source and, in some cases, calculate these from published sources.	Section C.7 (drug costs); and Section C.8 (costs related to the residential status of individuals with AD and ongoing management for those in community care/on treatment)

Translation issue	Comments	Section C subsection
Diagnostic accuracy	The diagnostic accuracy of FDG-PET and SPECT play a key role in the incremental cost-effectiveness of FDG-PET. Although discussed comprehensively in Section B, key data are repeated here for transparency.	Section C.9

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single-photon emission tomography

C.2. Issue 1: Population and circumstances of use

As discussed in Section B, existing publications relating to the use of FDG-PET and SPECT for the diagnosis of AD are not well-matched in terms of the population of the requested MBS listing. Nonetheless, the link between the population of the requested listing and the economic model presented in Section D is discussed in the section below.

C.2.1. Focused analytical plan

To compare the population and the circumstances of use in the economic model presented in Section D with the requested listing described in Section A, the following factors were considered:

- age
- gender
- disease severity
- residential status of individuals receiving diagnostic testing
- exclusion criteria

C.2.2. Results of the pre-modelling study

Table C.2-1 compares the key features of the requested listing and the population/circumstances of use applied to the economic model presented in Section D.

Table C.2-1 Population and circumstances of use

Translation issue	Population targeted on the MBS	Section C population applied to the economic model	Comment
Age	No restriction applied	Baseline age of 72.4 years of age at the beginning of the model (Wood et al, 2010)	According to the AIHW (2012), in 2011 74% of Australians with dementia were aged 75 years or over. Information regarding age at diagnosis was not available, and so no data to inform the appropriate age for FDG-PET/SPECT testing was available. The impact of baseline age is tested in sensitivity analyses presented in Section D.6.
Gender	No restriction applied	Gender was distributed in the model such that 61.98% of the cohort were female (calculated from Table 2.2 of AIHW, 2012)	The AIHW data reflect the prevalent population, rather than the population seeking screening. Since females have higher life expectancy, there is the possibility that the data used overestimate the proportion of females undergoing diagnostic testing. As such, the impact of this is tested in sensitivity analyses.

Translation issue	Population targeted on the MBS	Section C population applied to the economic model	Comment
Disease severity	No restriction applied	The economic model assumed that individuals undergoing diagnostic testing have either no AD, mild AD or moderate AD; patients with severe AD were not considered in the model	Individuals with severe AD would be past the diagnosis stage or could be diagnosed using standard diagnostic tests rather than functional imaging. Severe AD was included in the model only after disease progression.
Residential status	No restriction applied	The model assumed that individuals undergoing diagnostic testing would be in the community setting	
Exclusion criteria	None of note. Diagnostic testing is available to eligible individuals on the basis of suspected AD and previous inconclusive tests.	None	Exclusion criteria were not explicitly considered in the economic evaluation.

Abbreviations: AD, Alzheimer's disease; AIHW, Australian Institute of Health and Welfare; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single-photon emission tomography

C.2.3. Relationship of the pre-modelling study to the economic evaluation

The economic evaluation presented in Section D was designed with the factors presented above in mind. This is further discussed in Section C and Section D below.

Where there was uncertainty around any of these issues (e.g. baseline age), sensitivity analyses presented in Section D.6 examined the impact that varying assumptions had on the estimated incremental cost-effectiveness.

C.3. Issue 2: Treatment duration of Alzheimer's disease drugs

PBS-listed treatment of AD is restricted to ensure drugs are used in a cost-effective manner. This applies to both acetylcholinesterase inhibitors (AChEIs) and memantine. In the first instance, AChEIs are restricted to those with 'mild to moderate' AD, which is established by meeting set criteria. Additionally, treatment can only be continued in patients who have demonstrated a clinically meaningful response to the initial treatment. This refers to QoL, independence, cognitive function and behavioural symptoms; a clinically meaningful response must be demonstrated and documented every six months.

Similar conditions apply to the use of memantine, which is restricted to individuals with more advanced disease.

Since AD treatment is associated with a reduction in time to disease progression, and there are measures in place to limit use of AD drugs to individuals who continue to respond, it was necessary for the economic model to consider duration of treatment so as to effectively model disease progression in those who are receiving AChEIs and memantine.

C.3.1. Focused analytical plan

A broad literature search was undertaken to identify Australian data. This search was used to source any potentially relevant data that could be used in the economic model (including treatment duration/discontinuation rates, utility weights, transition

probabilities, costs and treatment effect). The broad search was conducted in PubMed and supplemented with a search of the Cochrane Library. The search terms and eligibility criteria are outlined in Appendix 2.

In the search for data relevant to inform treatment duration assumptions, the publications identified in the literature search were examined for any data that could provide an understanding of the proportion of patients continuing therapy past the first six months and, in those continuing, if and when patients cease therapy from that point onwards. This was conducted with a view to identifying data relevant for either AChEIs or memantine, as it was necessary to establish an understanding of treatment patterns for each. This was motivated by the fact that they have different restrictions applied to them on the PBS, but also because the model assumes they are used at different stages of the natural history of AD, meaning it was possible to apply different data to the economic model if required.

C.3.2. Results of the pre-modelling study

A study by Le Couteur et al (2012) examined adherence, persistence and continuation beyond six months with AChEIs in 18,000 Australians with AD in 2004. Their analysis reported that 62.8% of individuals commencing AChEIs in 2004 continued with a seventh prescription (i.e. continued therapy after the first six months). At the end of the first year, 54.7% of initiating patients were still on therapy; at the end of two years, 43% remained on therapy; and by three years, 32.9% were still on therapy.

In addition to these data, the *Post-market Review of PBS Anti-Dementia Medicines for AD* (PBS Review, October 2012), which was prepared for consideration by the PBAC in December 2012, provides similar data from PBS/RPBS cohorts in 2009 and 2010. The results for the proportion of patients filling a seventh prescription of either an AChEI or memantine were 56-70% and 55-69% in 2009 and 2010, respectively. Persistence at 12 months was estimated to be 60% and 59% for 2009 and 2010, respectively.

In the case of memantine, a study by Jones et al (2010) reviewed the safety and tolerability of memantine with AChEIs. The study, however, did not focus on Australia; no Australia-specific studies were available. The study found that memantine displays a safety and tolerability profile that is distinct from AChEIs and found, through a meta-analysis of study data, that withdrawal rates for memantine are comparable to placebo. The authors refer to data from the European Medicines Agency (EMA) and other pooled analysis of study data to support this finding, although it is clear that this conclusion was not affected by the presence of continuation rules aimed at promoting cost-effective use of memantine.

While Jones et al (2010) was not useful in providing an estimate of treatment duration relevant to the Australian situation, it did show that all of the drugs are reasonably well tolerated. On that basis, exclusion of explicit consideration of AEs could be justified. This is especially so since the PBS Review of anti-dementia medications (October 2012) suggests that starting on a low dose and increasing slowly has been shown to help reduce problematic side effects, such as nausea and diarrhoea.

C.3.3. Relationship of the pre-modelling study to the economic evaluation

From Le Couteur et al (2012), discontinuation rates at six months, one year, two years and three years can be estimated and applied to the economic model. Although older than the data available from the PBS Review of anti-dementia medications (October

2012), the data from the Le Couteur publication provides more comprehensive data at different points in time as well as providing point estimates rather than ranges. The discontinuation rates are provided in Table C.3-1.

Table C.3-1 Discontinuation rates applied to the economic model

Point in time	Proportion of patients remaining on treatment	Discontinuation rate applied to those remaining on treatment
Six months	62.8%	37.2%
One year	54.7%	12.9%
Two years	43.0%	21.4%
Three years	32.9%	23.5%

Source: Calculated from Le Couteur et al (2012)

The discontinuation rates from Table C.3-1 were applied to AChEIs and to memantine in the economic model presented in Section D. Although the data specifically related to AChEIs, no specific data were available for memantine, particularly in the Australian context. This is supported by the rates generated for 2009 and 2010 data in the PBS Review of anti-dementia medications; these rates included memantine data and were similar to the Le Couteur et al (2012) data for the seventh prescription and for persistence at 12 months.

Assumptions regarding the application of Le Couteur et al (2012) data to AChEIs and to memantine in the economic model are tested in sensitivity analyses presented in Section D.6.

C.4. Issue 3: Natural history of Alzheimer’s disease

Although the focus of the analysis is on the cost-effectiveness of diagnostic testing, the model also included a natural history (and associated treatment) component. It is also necessary to understand the natural history of AD as it unfolds in individuals over time, and model this accordingly, since disease progression and the impact of treatment on this progression is an important component of the cost-effectiveness of diagnostic testing. It was necessary, therefore, to include natural history in the model presented in Section D.

C.4.1. Focused analytical plan

The PubMed and Cochrane library literature searches for utility weights (see Section C.6) identified a systematic review by Green et al (2011) that aimed to identify methods to model AD progression over time. A total of 42 studies were included, the vast majority of which were cost-effectiveness analyses of pharmacotherapies for AD (see Appendix 4). The literature search described in Section C.6 for utility weights identified an additional 19 cost-utility studies of pharmacotherapies for AD (also summarised in Appendix 4).

Each of the studies was reviewed with a view to sourcing transition probabilities applicable to the model structure presented in Section D. In particular, transition probabilities were sought which would enable modelling of AD by severity and institutional setting, thereby allowing sufficient differentiation of individuals with AD.

The broad literature search referred to in Section C.3 was also used to identify any potentially relevant Australian sources that may have been missed in the search described above. The search strategy is described in Appendix 2.

C.4.2. Results of the pre-modelling study

As discussed in Green et al (2011), the CERAD-CDR (Consortium to Establish a Registry in Alzheimer's Disease – Clinical Dementia Rating) model (Neumann et al, 1999) is one of the most widely used of all models to date, and is the most suitable for sourcing transition probabilities for the economic model presented in Section D.

Neumann et al (1999) presents a state-transition Markov model used to characterise AD progression through states of disease and residential settings. The model has been used to examine the effects of medications, behavioural interventions and screening technologies on disease progression in AD. It was based on annual transition probabilities derived from the CERAD database of 1,145 people with AD, followed up to eight years, with AD severity categorised as mild, moderate or severe based on the CDR scale. A survival analysis approach was used to derive transition probabilities between different stages of AD severity, for transition to a nursing home setting and for the probability of death. The transition probabilities derived from the CERAD data covered staging of AD severity independent of residential setting, but the probabilities for residential setting and death were conditional on disease severity, with higher probabilities as disease progressed. These transition probabilities were framed in a way that was appropriate for use in the economic model presented in Section D.

Note that the transition probability estimates published in Neumann et al (1999) were the focus of a later paper (Neumann et al, 2001), which provided additional details.

An Australian study by Brodaty et al (1993) examined the deterioration of 91 dementia patients and provided estimates of institutionalisation and death over a five-year period (76% and 42%, respectively). It was, however, not possible to calculate transition probabilities appropriate for application to the economic model from the data presented in the study.

A later study by Brodaty et al (2014) examined the predictors of institutionalisation of individuals with dementia over a three-year period. Over the three years of the study, 25.3% of patients with dementia were institutionalised. A number of predictors including cognitive ability, functional ability and neuropsychiatric symptoms were identified. Nonetheless, it was not possible to calculate transition probabilities appropriate for application to the economic model from the data presented in the study.

An additional Australia study reported by You et al (2014) sought to identify risk factors for time to death or hospital admission in a sample of community-dwelling elderly people living with dementia in Australia. The study, however, was not adequate to calculate relevant transition probabilities which could be applied to the economic model for either of these possibilities.

C.4.3. Relationship of the pre-modelling study to the economic evaluation

Transition probabilities from Neumann et al (1999) were applied to the economic model presented in Section D. In the interest of pragmatism, however, assumptions were superimposed on the available data to simplify the model structure. Neumann et al (1999), for example, included the possibility of 'backward' transition (i.e. transition to less severe disease) in the case of individuals with mild AD. Since AD is a progressive disease, however, these transitions were not applied to the economic evaluation. Although not discussed comprehensively in Neumann et al (1999), it is likely that their inclusion was due to variation in clinical assessment methods in the CERAD population.

Table C.4-1 Transition probabilities applied to the economic model

Transition	Annual transition probability	Reference
Mild AD to mild AD	0.615	Calculated
Mild AD to moderate AD	0.364	Neumann et al (1999) ^a
Mild AD to severe AD	0.000	Assumption
Mild AD to dead	0.021	Neumann et al (1999)
Community to nursing home (individuals with mild AD)	0.038	Neumann et al (1999)
Moderate AD to mild AD	0.000	Assumption
Moderate AD to moderate AD	0.608	Calculated ^b
Moderate AD to severe AD	0.339	Neumann et al (1999)
Moderate AD to dead	0.053	Neumann et al (1999)
Community to nursing home (individuals with moderate AD)	0.110	Neumann et al (1999)
Severe AD to mild AD	0.000	Neumann et al (1999)
Severe AD to moderate AD	0.000	Neumann et al (1999)
Severe AD to severe AD	0.847	Neumann et al (1999)
Severe AD to death	0.153	Neumann et al (1999)

Abbreviations: AD, Alzheimer's disease

Note: No transition probability for severe community-based treatment to severe nursing home treatment is presented due to the assumption that all severe AD patients are residents of nursing homes due to disease severity

^a Neumann et al (1999) included scope for individuals to 'skip' from mild to moderate disease. In light of the six-week cycle length of the model, this was deemed inappropriate. Instead, the sum of these probabilities was applied to the model (i.e. 0.322 + 0.042 = 0.364).

^b Calculated by assuming no backward disease severity transitions.

The transition probabilities presented in Table C.4-1 were applied to the economic model presented in Section D. Specifically, these data were applied to those individuals not on treatment for AD. They were, however, also used as a basis for the estimates of transition probabilities applied to those on AD drugs. This is discussed in Section C.5 below.

The impact of any uncertainty around the transition probabilities was examined in sensitivity analyses presented in Section D.6.

C.5. Issue 4: Treatment effect associated with drugs to treat Alzheimer's disease

While Section C.4 presented transition probabilities to be used in the economic model to transition untreated patients through the natural history of AD, the model also required estimates of treatment effect to ensure that the impact of treatment was accounted for in the calculation of cost-effectiveness. Although it is true that the assessment is focused on diagnostic testing, the cost-effectiveness of this is intrinsically linked with the effectiveness of downstream treatment options; if, for example, treatment were not effective, there would be no benefit associated with diagnosis. The impact of treatment with AChEIs and memantine was required for the modelling.

C.5.1. Focused analytical plan

The cost-effectiveness studies presented in Section C.4 were examined to source appropriate estimates of treatment effect in AD patients, or relevant transition probabilities that could be applied to such patients in the economic model presented in Section D. Any potential estimates were assessed in light of the model structure to ensure compatibility with a structure which differentiates individuals by disease severity and (if appropriate) residential status in accordance with the model structure. The process was approached by acknowledging that, where appropriate, more recent

estimates/transition probabilities should (other things being equal) be given priority over older estimates.

The broad literature search referred to in Section C.3 was also used to identify any potentially relevant Australian sources that may have been missed in the search described above. The search strategy is described in Appendix 2.

C.5.2. Results of the pre-modelling study

Neumann et al (1999), which was discussed previously, applied a 50% reduction in the probability of transition from mild to moderate AD (a risk ratio of 0.5) and a 2.36-fold increase in the probability of progression from moderate to mild AD in the presence of treatment with donepezil. The estimate was based on the author's own calculations of data from a 24-week double-blind, placebo controlled trial of donepezil in AD patients (Rogers et al, 1998). The effects were assumed to be constant throughout the duration of treatment, with no residual effect at discontinuation.

This approach has subsequently been applied in a number of cost-effectiveness models building upon the Neumann et al (1999) study (McMahon et al, 2000; Lopez-Bastida et al, 2009; Fuh and Wang, 2007; Kirbach et al, 2008; Marikainen et al, 2004; Ikeda et al, 2002; Kulasingam et al, 2003).

No other studies were identified that presented treatment effect estimates which could be applied to the model's natural history transition probabilities discussed above.

A NICE HTA (Hyde et al, 2013) was conducted to re-consider and update the evidence base used to inform the 2007 NICE decision. They noted that from 2004 to 2010 "there was no new clinical effectiveness evidence on the impact on rates of, or time to institutionalisation and the clinical importance of the small statistically significant observed changes in cognition, function and behaviour remained unconfirmed. Current estimates of time to institutionalisation and the benefits which flow from this in terms of improved QoL and reduced cost are based almost wholly on predictions made by models. Although this is an important source of uncertainty, it is highly likely that this will be resolved empirically, as it would almost certainly be deemed unethical to perform an RCT to establish the effect on time to institutionalisation when individual effects on cognition, function and behaviour and global impact are relatively well established [...]. Fortunately it is likely that the cost of the AChEIs will fall as generic preparations emerge, increasing the likelihood that drug costs are indeed offset by savings in the large costs associated with full time care". This may go some way to explain the absence of an appropriate estimate of treatment effect relevant to AChEIs since the publication of the estimate by Neumann et al (1999).

Jones et al (2004) reports memantine transition probabilities sourced from Reisberg et al (2003), from which a treatment effect could be estimated. In moderately severe patients (MMSE 10-14), 19 of 52 placebo patients progressed to severe AD in a six-month period. In the memantine arm, 9 of 57 individuals progressed. This gave a relative risk estimate of 0.8026 for moderately severe patients.

C.5.3. Relationship of the pre-modelling study to the economic evaluation

The estimate from Neumann et al (1999), though several years old, remains the best estimate of the AChEI treatment effect that could be applied to mild AD patients in the model presented in Section D. That is, the model applied a 50% reduction in the natural

history transition probabilities to mild patients on drug treatment (assumed to take the form of AChEI, as discussed in more detail in Section D). The uncertainty around this estimate is acknowledged, however, and the impact is accordingly tested in sensitivity analyses presented in Section D.6.

With regards to the estimate to be applied to individuals treated with memantine (assumed to be the treatment given to moderate patients in the model), the natural history estimate was adjusted by the treatment effect estimated from Jones et al (2004) – a 19.74% reduction in transition from moderate to severe AD. It is acknowledged that the estimate is specific to a subgroup of moderate patients only (i.e. moderately severe patients), although it remains the only appropriate estimate available. For this reason, and due to the uncertainty inherent in any estimate of this type, the sensitivity analyses presented in Section D.6 consider the impact this has on the base case result.

C.6. Issue 5: Utility weights to inform the QALY transformations of the economic model

The economic model presented in Section D relies on the transformation of the health-related quality of life (HRQoL) associated with AD into quality-adjusted life years (QALYs). In order to do so, the model requires utility weights differentiated by disease severity and institutional setting (i.e. whether patients are in the community or have been placed in nursing care).

The following section presents the pre-modelling study aimed at sourcing appropriate utility weights to apply to the economic model.

C.6.1. Focused analytical plan

The economic model presented in Section D considers not only the diagnostic testing of individuals with suspected AD, but also the downstream impact of identification of AD. Consequently, it is necessary for the model to include the natural history of AD and its progression over time as well as the impact of treatment. Since it is expected that HRQoL will worsen with AD severity, and as patients move to more intensive care (i.e. from the community to nursing care), utility values were required to represent the associated health states.

A literature review was conducted to source utility weights to appropriately represent the health states of the economic model. Specifically, the search was aimed at identifying published studies that derive utility weights from a multi-attribute utility instrument (MAUI). Electronic searches of PubMed and the Cochrane Library were conducted using the search terms and eligibility criteria outlined in Appendix 2.

The broad literature search referred to in Section C.3 was also used to identify any potentially relevant Australian sources that may have been missed in the search described above, although this did not yield any additional studies in this case. The search strategy is described in Appendix 2.

C.6.2. Results of the pre-modelling study

The process used to identify relevant studies from the search results is presented in Appendix 2. The literature search identified four published systematic reviews of utility weights in individuals with AD and/or dementia, although one study had a broader focus on mental disorders (Sonntag et al, 2013) and another had a focus on Japanese literature

(Kasai et al, 2013). In addition, the literature search identified two HTAs of pharmacotherapy for the treatment of AD that included a systematic review of utility weights for use in an economic model for NICE decision-making (Loveman et al, 2006; Bond et al, 2012). Nine original studies that derived utility weights for patients with AD were reviewed in full.

Citation details for the systematic reviews are shown in Table C.6-1, while the original studies are presented in Table C.6-2.

Table C.6-1 Citation details for systematic reviews of utility weights relevant to AD and dementia

Study ID	Citation
Published articles	
Hounsome 2011	Hounsome N, Orrell M, Edwards RT (2011) EQ-5D as a quality of life measure in people with dementia and their carers: evidence and key issues. <i>Value Health</i> 14(2):390-9.
Shearer 2012	Shearer J, Green C, Ritchie CW, Zajicek JP (2012) Health state values for use in the economic evaluation of treatments for Alzheimer's disease. <i>Drugs Aging</i> 29(1):31-43.
Kasai 2013	Kasai M, Meguro K (2013) Estimated quality-adjusted life-year associated with the degree of activities of daily living in patients with Alzheimer's disease. <i>Dement Geriatr Cogn Dis Extra</i> 3(1):482-8.
Sonntag 2013	Sonntag M, Konig HH, Konnopka A (2013) The estimation of utility weights in cost-utility analysis for mental disorders: a systematic review. <i>Pharmacoeconomics</i> 31(12):1131-54.
HTAs	
Loveman 2006	Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. <i>Health Technol Assess</i> 2006;10(1).
Bond 2012	Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. <i>Health Technol Assess</i> 2012;16(21).

Table C.6-2 Studies evaluated in full to source utility weights for the economic model

Study	Study description	Relevant results	Comments
Bell et al (2001)	The HUI2, the SF-36, a caregiver time questionnaire and a caregiver burden instrument were administered to 679 caregivers to people with AD in the United States. The aim was to examine the association between caregiver burden and caregiver HRQoL.	<p>HUI2, community patients: Mild AD = 0.87 Moderate AD = 0.86 Severe AD = 0.86</p> <p>HUI2, institutionalised patients: Mild AD = 0.89 Moderate AD = 0.89 Severe = 0.88</p> <p>SF-36 mental component, community patients: Mild AD = 49.9 Moderate AD = 46.8 Severe AD = 49.4</p> <p>SF-36 mental component, institutionalised patients: Mild AD = 49.4 Moderate AD = 51.7 Severe AD = 52.2</p>	The study was aimed at determining the HRQoL of caregivers themselves, rather than having caregivers provide proxy utility weights for the patients. As such, the results of the study are not relevant for use in the economic model
Gomez-Gallego et al (2012)	102 patients, their carers and 25 health professionals were recruited from day centres. Patients' QoL was rated by patients, carers and health professionals. The Health Utilities Index, Clinical Insight Rating Scale and MMSE were also administered.	<p>QoL-AD in patients: MMSE\geq18 = 35.12 MMSE<18 = 34.73</p> <p>QoL-AD in carers: MMSE\geq18 = 29.80 MMSE<18 = 29.73</p> <p>QoL-AD in professionals: MMSE\geq18 = 31.44 MMSE<18 = 28.50</p>	While the paper reported mean QoL-AD scores for a variety of participant subgroups, disease severity was captured only via MMSE \geq 18 versus MMSE<18

Study	Study description	Relevant results	Comments
Jonsson et al (2006)	272 patients and their primary caregivers in Sweden were enrolled in a prospective observational study and underwent three consecutive interviews, six months apart to determine HRQoL. The EQ-5D instrument was used for this assessment, as well as the QoL-AD. All patients were community-dwelling patients with a diagnosis of possible or probable AD. Cognitive function was assessed via the MMSE.	<p>Average carer-proxy EQ-5D, EQ-5D VAS and QoL-AD utilities:</p> <p>MMSE 26-30 = 0.69 MMSE 21-25 = 0.64 MMSE 15-20 = 0.50 MMSE 10-14 = 0.49 MMSE 0-9 = 0.33</p> <p>EQ-5D where both carer and patient ratings were available:</p> <p>MMSE 26-30 = 0.70 MMSE 21-25 = 0.65 MMSE 15-20 = 0.52 MMSE 10-14 = 0.51 MMSE 0-9 = 0.40</p> <p>EQ-5D where just carer ratings were available</p> <p>MMSE 26-30 = 0.50 MMSE 21-25 = 0.19 MMSE 15-20 = 0.21 MMSE 10-14 = 0.39 MMSE 0-9 = 0.22</p>	Note that the focus here is on the proxy-ratings of carers. The sample size was far greater for carers than for patients themselves (as few as 33.2% of patients completed instruments in some MMSE categories, compared to >70% in the cases of carers)
Lopez-Bastida et al (2006)	Economic impact and HRQoL were assessed in 237 AD patients and caregivers in the Canary Islands. The HRQoL was assessed, via the EQ-5D instrument, using primary caregivers as proxy respondents.	Mild AD = 0.52 Moderate AD = 0.30 Severe AD = 0.12	
Mesterton et al (2010)	233 patients in Sweden and their caregivers cross-sectional data on cognitive function (MMSE), ADL ability, behavioural disturbances, formal and informal resource use and HRQoL were collected by questionnaires to caregivers and to the treating physician. Patients were stratified into the disease stages mild, moderate and severe AD based on MMSE scores. These data were used to estimate the relationship between costs, QoL and disease severity.	Patient QoL: Mild AD = 0.64 Moderate AD = 0.39 Severe AD = 0.24	One inclusion criterion in the study was that patients living at home had to have an informal caregiver. There is a risk that this could have influenced the utility weights, particularly at the less severe end of the spectrum

Study	Study description	Relevant results	Comments
Neumann et al (1999)	Development of a cost-utility model to estimate the cost-effectiveness of donepezil compared with non-treatment in the treatment of mild to moderate AD.	Patient-rated QoL: Mild AD, community = 0.68 Mild AD, nursing home = 0.71 Moderate AD, community = 0.54 Moderate AD, nursing home = 0.48 Severe AD, community = 0.37 Severe AD, nursing home = 0.31	The utility weights reported here are from a previous study by the author. They were derived via the HUI2 instrument in a cross-sectional study of 528 caregivers of AD patients, stratified by CDR disease stage (201 mild, 175 moderate and 142 severe) and setting of care (354 community and 164 nursing home). Caregivers completed the HUI2 as proxy respondents and also completed the questionnaire to assess their own health (though this is not a consideration in the current case)
Neumann et al (2000)	Cross-sectional study of 679 patient/caregiver pairs, stratified by disease severity (questionable, mild, moderate/severe/profound/terminal) and setting (community/assisted living/nursing home). Caregivers completed the HUI2 and HUI3 assessments as proxy respondents for patients and themselves.	Proxy assessment for patients: Questionable (CDR=0.5) = 0.73 for HUI2 and 0.47 for HUI3 Mild (CDR=1) = 0.69 for HUI2 and 0.39 for HUI3 Moderate (CDR=2) = 0.53 for HUI2 and 0.19 for HUI3 Severe (CDR=3) = 0.38 for HUI2 and 0.06 for HUI3 Profound (CDR=4) = 0.27 for HUI3 and -0.08 for HUI3 Terminal (CDR=5) = 0.14 for HUI2 and -0.23 for HUI3 "Pits"-to-perfect health scale scores: Questionable/mild (CDR=0.5, 1) = 0.70 for HUI2 and 0.42 for HUI3 Moderate (CDR=2) = 0.54 for HUI2 and 0.41 for HUI3 Profound/severe/terminal (CDR=3, 4, 5) = 0.35 for HUI2 and 0.25 for HUI3	Following the development of the HUI3 tool, which was expected to be more sensitive to the high levels of impairment associated with AD, the study aimed to compare the results of HRQoL in patients with AD. The HUI3 scores were shown to be far worse than the HUI2 scores, falling to as low as -0.23 in terminal patients. Consequently, adjusted scores were also reported which omitted negative scores by setting them to zero (i.e. equivalent to death). These are reported as "Pits"-to-perfect health scale scores

Study	Study description	Relevant results	Comments
Włodarczyk et al (2004)	100 AD patients (with mild to moderate, possible or probable AD) participating in an open-label trial of donepezil were followed for six months to examine the relationship between patient/caregiver-rated HRQoL and cognition. QoL was assessed using the AqoL scale, rated separately by patients and their caregivers.	Carer-proxy: MMSE 0-10 = 0.4 MMSE 10-15 = 0.46 MMSE 15-20 = 0.475 MMSE 20-25 = 0.52 MMSE 25+ = 0.59 Patient-rated: MMSE 0-10 = 0.52 MMSE 10-15 = 0.54 MMSE 15-20 = 0.61 MMSE 20-25 = 0.68 MMSE 25+ = 0.71	AQoL data extracted from Figure 1 of the paper, as per Bond et al (2012). Authors note that the reliance on a sample from day care means that it may not be representative
Xie et al (2012)	Computer-assisted interviews were held with 100 participants from the general public, assigning each participant a vignette describing mild, moderate or severe AD. QoL was assessed via the EQ-5D and QoL-AD while imagining living in the health state described in the assigned vignette.	EQ-5D utilities: Mild AD = 0.7413 Moderate AD = 0.6159 Severe AD = 0.4456 QoL-AD scores: Mild AD = 32.5 Moderate AD = 24.0 Severe AD = 21.8	The results generated are heavily influenced by the vignettes provided to participants, as this is the only understanding of AD and AD severity a participant can be expected to have. As such, the results of this study should be treated with caution

Abbreviations: AD, Alzheimer's Disease; ADL, activities of daily living; AqoL; Assessment of Quality of Life; CDR, Clinical Dementia Rating; EQ-5D, EurQol Five Dimension questionnaire; HRQoL, health-related quality of life; HUI, Health Utilities Index; MMSE, Mini-Mental State Examination; NA, not applicable; QoL-AD, Quality of Life in Alzheimer's Disease; SF-36, Short Form 36 Health Survey; VAS, Visual Analogue Scale

Bell et al (2001) was aimed at determining the HRQoL of caregivers rather than patients. As such, it was excluded from further consideration at the point of the full text review.

Gomez-Gallego et al (2012) reported utility weights based on the HUI3 instrument. These were reported by disease severity by reporting scores for patients with $MMSE \geq 18$ and $MMSE < 18$. This level of differentiation, however, was insufficient for use in the economic model and so the study was excluded from further consideration.

The study reported in Jonsson et al (2006) provides utility weights by disease severity, segregated into five MMSE categories. HRQoL was assessed using the EQ-5D, the EQ-5D VAS and the QoL-AD instrument. The study reports results provided by both patients and their caregivers, although the sample of completed instruments was far greater for carers due to cognitive problems preventing patients from completing the instruments in some cases. The average carer-proxy utility weights generated using all three instruments ranged from 0.69 for patients with MMSE scores of between 26 and 30, to 0.33 for patients with $MMSE < 10$. The utility weights generated in this study have been subsequently used in a NICE assessment of the effectiveness and cost-effectiveness of a range of drugs used to treat AD (Bond et al, 2012), following a review of the literature for suitable data to populate the economic model used in that assessment.

Lopez-Bastida et al (2006) reports utility weights generated in a study conducted in the Canary Islands using the EQ-5D instrument. The utility weights are differentiated by disease severity (assessed via the Clinical Dementia Rating (CDR) scale) to generate a result of 0.52 for mild AD, 0.30 for moderate AD and 0.12 for severe AD. These weights are considerably lower than those reported in Jonsson et al (2006), implying far greater disutility as disease progresses.

Mesterton et al (2010) reports utility weights for mild, moderate and severe AD (based on the MMSE) using the EQ-5D questionnaire. The study provides results of 0.64 for mild AD, 0.39 for moderate AD, and 0.24 for severe AD. Again, the range is greater than that reported in Jonsson et al (2006). There was concern about the applicability of the utility weights generated due to an inclusion criterion that patients in the community must have had an informal caregiver. As this could mean the population is more severe than would otherwise be the case, this could be a source of bias.

Although Neumann et al (1999) is not an original study to determine utility weights, it does report utility weights generated in a previous study by the same author (Neumann et al, 1998). These utility weights were derived via the HUI2 instrument in a cross-sectional study of caregivers of AD patients. Patient stratification by disease severity (by CDR disease stage) and setting of care allowed results to be disaggregated accordingly. The estimated utility weights range from 0.68 for mild patients in community care to 0.31 for patients with severe AD being treated in nursing care. Despite the use of a different instrument (HUI2), the range is similar to that reported in Jonsson et al (2006).

A subsequent study reported in Neumann et al (2000) attempts to update the results by using the HUI3 instrument, which is more sensitive to the high levels of impairment associated with AD. This sensitivity is evident in the results, which are considerably lower than those reported in Neumann et al (1999). The range for mild to severe patients is 0.47 to 0.06 using the HUI3 instrument and falls further to -0.08 and -0.23 for patients with profound and terminal AD, respectively. If samples with negative utility weights are ignored by being set to zero, the utility weight for questionable/mild AD is 0.42 while

the weights for moderate and for profound/severe/terminal are 0.41 and 0.35, respectively.

Wlodarczyk et al (2004) reports carer-proxy and patient-rated utility weights derived using the Assessment of Quality of Life (AQoL) instrument, which are disaggregated by MMSE score to capture the impact of disease severity. Carer-proxy weights range from 0.59 to 0.4, while patient-rated weights range from 0.71 to 0.52. As discussed in Bond et al (2012), the reliance on a sample from day care means that these weights may not be representative, which could explain why the range is narrower than is reported in other studies.

Xie et al (2012) reports utility weights derived using the EQ-5D instrument as well as QoL-AD scores. Both were generated via computer-assisted interviews held with participants from the general public. EQ-5D weights range from 0.7413 to 0.4456. While this range is not dissimilar to that reported elsewhere (e.g. Jonsson et al, 2006, and Neumann et al, 1999), the utility weights themselves are somewhat higher, which may imply that participants failed to grasp the impact AD has on HRQoL. This is unsurprising given the study design and the reliance on vignettes to understand the impact of AD.

Of the studies discussed above, Jonsson et al (2006) appears to provide the strongest estimates of utility weights associated with AD which are suitable for inclusion in the economic model. This is supported by the use of these results by NICE in their assessment of the cost-effectiveness of AD treatment (Bond et al, 2012).

C.6.3. Relationship of the pre-modelling study to the economic evaluation

As discussed in Section D, the health states included in the economic model are not defined by MMSE, but rather by whether a patient has mild, moderate or severe AD (health states which correspond better with severity captured via the CDR scale). As discussed in Bond et al (2012), a previous study has mapped CDR to MMSE ranges for people with dementia (Pernecky et al, 2006), thereby enabling the utility weights presented in Table C.6-3 to be applied to the economic model in Section D.

Table C.6-3 Utility weights applied to the economic model

Disease severity	MMSE range	Utility weight
Mild (CDR = 1)	21-25	0.64
Moderate (CDR = 2)	11-20	0.495 ^a
Severe (CDR = 3)	0-10	0.33

Source: Jonsson et al (2006); Pernecky et al (2006)

Abbreviations: CDR, Clinical Dementia Rating scale; MMSE, Mini-Mental State Examination

^a Average of utility weights corresponding to MMSE 10-14 and MMSE 15-20

The mild and moderate utility weights presented in Table C.6-3 were applied to the economic model for mild and moderate patients in community care. The severe utility weight was applied to all patients with severe AD, since, as described in Section D, the model assumes that all patients with severe AD are in nursing care. As per the NICE assessment (Bond et al, 2012), the same utility weight for severe AD was applied to mild and moderate AD patients who are in nursing care. This assumption was based on the understanding that any need for nursing care would be more representative of compromised QoL than disease severity captured via MMSE or the CDR. That is, if a patient is institutionalised it is due to a need for care, which would have QoL implications.

These utility weights were applied to the base case analysis, with the impact of alternative sources tested in sensitivity analyses presented in Section D.6.

C.7. Issue 6: Estimating the drug costs associated with treating Alzheimer's disease

Although the economic evaluation presented in Section D is primarily concerned with assessing the cost-effectiveness of diagnosis of AD with FDG-PET relative to SPECT, a comprehensive assessment of this requires the downstream impact of AD to be considered. As a consequence, the economic model requires estimates of treatment costs associated with AD. An important component of such costs is PBS-listed treatment options. Estimation of these costs is the focus of this section.

C.7.1. Focused analytical plan

As discussed previously, the model accounts for disease severity, residential setting and whether individuals are receiving AD medication. Currently, the PBS includes both AChEIs and memantine. Memantine is listed on the PBS for use in individuals with MMSE (or SMMSE) scores of 10-14 only. It was appropriate, therefore, to assume that memantine would be used in moderate patients only (defined as MMSE 11-20 in the current model, as discussed in Section C.2; Pernecky et al, 2006, as reported in Bond et al, 2012).

It was further assumed, for simplicity, that memantine would be the only PBS treatment used in moderate AD patients, while AChEIs would be used in patients with mild AD.

The AChEIs currently available via the PBS for the treatment of AD include donepezil, rivastigmine and galantamine. It was assumed that these were used exclusively in individuals with mild AD, with the implicit assumption that patients would move off AChEIs and on to memantine at progression from mild to moderate disease.

To estimate the cost of each PBS medication, the daily doses were assumed on the basis of the Product Information (PI) for each drug. This was then used to calculate the average daily cost of each treatment for a patient using that drug/formulation. It was assumed that the recommended maintenance doses were used in all patients receiving treatment. The impact of titration doses, or reductions in average doses due to adverse drug reactions or other issues related to adherence was not accounted for (see discussion of Jones et al (2010) presented in Section C.3 in support of this approach); this had a negligible impact on the results of the model.

In the case of the AChEIs, the PIs recommended a dose of 5-10 mg per day for donepezil, 6-12 mg per day as two separate doses for rivastigmine, and 16 mg or 24 mg per day for galantamine. The calculations were undertaken by using the packs that best correspond to each of these dosing possibilities. For example, in the case of galantamine, the 16 mg and 24 mg capsules were used in the costings, while the 8 mg capsules were not included as they would be more likely to be used in the titration phase. In the case of rivastigmine, however, the 4.6 mg/24 hours and 9.5 mg/24 hours patches were also included. Table C.7-1 presents the calculations of the daily treatment cost of each treatment option.

Following the calculation of the average daily cost for each treatment option, PBS statistics were used to calculate a weighted average daily cost per patient. This is presented in Table C.7-2.

In the case of memantine, a similar approach was used. By using the PI, it was determined that the recommended maintenance dose is 20 mg per day. The corresponding pack was used to then calculate an average cost per day of treatment with memantine (see Table C.7-3). As it was assumed that individuals with moderate AD would only use memantine and not AChEIs, there was no need to consider the distribution of patients across various treatment options.

C.7.2. Results of the pre-modelling study

Table C.7-1 presents the daily treatment costs associated with each of the PBS-listed AChEIs, while Table C.7-2 presents the weighted average cost per patient on the basis of the data presented in Table C.7-1 and the PBS scripts data.

Table C.7-1 Calculated daily treatment cost of AChEIs

Drug	PBS Item number	mg per administration	Assumed dose per day	Max quantity	mg per pack	DPMQ	Price per mg	Cost per day
Donepezil	2532G	5	5	28	140	\$39.64	\$0.28	\$1.42
Donepezil	2479L	10	10	28	280	\$39.64	\$0.14	\$1.42
Rivastigmine (capsule)	2493F	3	6	56	168	\$96.18	\$0.57	\$3.44
Rivastigmine (capsule)	2526Y	6	12	56	336	\$96.18	\$0.29	\$3.44
Rivastigmine (patch)	2477J	4.6	4.6	30	138	\$102.56	\$0.74	\$3.42
Rivastigmine (patch)	2551G	9.5	9.5	30	285	\$102.56	\$0.36	\$3.42
Galantamine	2537M	16	16	28	448	\$51.20	\$0.11	\$1.83
Galantamine	2531F	24	24	28	672	\$59.12	\$0.09	\$2.11

Source: Pharmaceutical Benefits Schedule ([PBS website](#), accessed November 24, 2014)

Abbreviations: AChEIs, acetylcholinesterase inhibitors; DPMQ, dispensed price per maximum quantity; mg, milligram; PBS, Pharmaceutical Benefits Schedule

Table C.7-2 Calculated average treatment cost of patients using AChEIs

Drug	PBS Item number	Scripts	Proportion of total scripts	Cost per day	Weighted average cost per day
Donepezil	2532G	2526	0.0322	\$1.42	\$0.05
Donepezil	2479L	42,522	0.5419	\$1.42	\$0.77
Rivastigmine (capsule)	2493F	486	0.0062	\$3.44	\$0.02
Rivastigmine (capsule)	2526Y	262	0.0033	\$3.44	\$0.01
Rivastigmine (patch)	2477J	3747	0.0478	\$3.42	\$0.16
Rivastigmine (patch)	2551G	12,134	0.1546	\$3.42	\$0.53
Galantamine	2537M	11,548	0.1472	\$1.83	\$0.27
Galantamine	2531F	5245	0.0668	\$2.11	\$0.14
Total		78,470	1.0000		\$1.95

Source: Pharmaceutical Benefits Schedule ([PBS website](#), accessed November 24, 2014) and Medicare Australia PBS Item and Group reports ([Medicare Australia provider PBS Stats](#), accessed November 24, 2014)

Abbreviations: AChEIs, acetylcholinesterase inhibitors; mg, milligram; PBS, Pharmaceutical Benefits Schedule

The calculated average daily treatment cost of memantine use is presented in Table C.7-3.

Table C.7-3 Calculated daily treatment cost of memantine

Drug	PBS Item number	mg per administration	Assumed dose per day	Max quantity	mg per pack	DPMQ	Price per mg	Cost per day
Memantine	2513G	20	20	28	560	\$67.08	\$0.12	\$2.40

Source: Pharmaceutical Benefits Schedule (www.pbs.gov.au, accessed November 24, 2014)

Abbreviations: DPMQ, dispensed price per maximum quantity; mg, milligram; PBS, Pharmaceutical Benefits Schedule

C.7.3. Relationship of the pre-modelling study to the economic evaluation

The weighted average cost of \$1.93 per day for AChEIs from Table C.7-2 is applied to individuals with mild AD in the economic model who are receiving treatment. The cost per day of memantine presented in Table C.7-3 is applied to treated patients in the moderate AD health states, as described above. Individuals not receiving treatment are not subject to either of these costs.

The impact of these calculated costs is considered in the sensitivity analyses presented in Section D.6.

C.8. Issue 7: Costs associated with residential status of individuals with Alzheimer's disease

In addition to the drug treatment costs discussed in Section C.7, individuals with AD are expected to accrue other costs related to healthcare resources consumed due to their AD. Such costs are potentially large, particularly in later disease stages, and so reliable estimates were necessary to ensure the incremental cost-effectiveness of diagnostic testing was accurately assessed.

C.8.1. Focused analytical plan

The broad literature search referred to in Section C.3 was also used to identify any Australian sources that may be relevant. Note that non-Australian studies were deemed not relevant, as it is highly likely that resource use varies by health system. The literature search strategy is described in Appendix 2. Additionally, known government sources of appropriate costs were considered.

C.8.2. Results of the pre-modelling study

No studies were identified to inform assumptions regarding ongoing monitoring costs for those in the community. As it is reasonable to assume, however, that patients with AD (diagnosed or otherwise) will require regular contact with a medical professional to seek treatment for symptoms of AD or to undertake re-assessments of disease status required by PBS restrictions for AD drugs, the model applied assumptions regarding this. Specifically, it was assumed that all patients with AD would require GP consultations in excess of what individuals without AD would require. As in McMahon et al (2000), it was assumed that individuals with AD would require two additional consultations per year related to their AD. It was assumed that these consultations would be Level B consultations with their GP (MBS item 23; \$37.05 per consultation). Although it is possible that individuals may be seeing specialists for their care, this is not likely for all patients and would have a negligible impact on the estimated cost-effectiveness.

With regards to other costs associated with nursing care or increased care required in the community setting, the cost of care packages (2009 costs; Access Economics, 2010, Tables 6.1-6.3) were updated to current costs and applied to the model. Although it is acknowledged that there have been recent changes to the home care and residential aged care packages in Australia (introduced 01 July 2014), the costs reported in the Access Economics report are considered to be indicative of the cost of care for AD patients in community and residential care settings. The packages described in the Access Economics report are detailed below.

Residential (i.e. nursing) care is for people for whom community care is not desirable or feasible, often because health care requirements are high or access to informal care is limited. Residential care provides accommodation, living services (e.g. cleaning, laundry, meals) and assistance with personal tasks (e.g. dressing, eating and bathing). There are two classes of residential care:

- Low-level care (\$19,963 per place, per year; \$21,476.43 in 2013 prices) focuses on personal care services such as help with daily activities, accommodation, support services such as cleaning, laundry and meals, and some allied health services such as physiotherapy and occupational therapy. There is limited access to nursing staff.
- High-level care (\$56,658 per place, per year; \$59,528.43 in 2013 prices) is for those who require full-time supervised health care under the supervision of registered nurses. People also receive the same services as those under low care.

Community aged care refers to formal services usually provided in the recipients home. The Community Aged Care Package (CACP) targets older people living in the community with care needs equivalent to a low needs residential care (\$11,934 per package, per year; \$12,410.40 in 2013 prices). Extended Aged Care at Home (EACH) packages target older people living at home with care needs equivalent to high-level residential care (\$41,021 per package, per year; \$41,951.52 in 2013 prices). In addition to the services offered in CACP, EACH clients may be able to receive nursing care, allied health care and rehabilitation services. EACH-D extends the EACH package with service approaches and strategies to meet the specific care needs of care recipients with dementia.

C.8.3. Relationship of the pre-modelling study to the economic evaluation

In the case of ongoing costs associated with symptoms and re-assessment, the unit cost of a Level B GP consultation was applied twice per year to all community-based individuals with mild or moderate AD (\$74.10 per year). This was applied whether individuals were receiving AD treatment or otherwise.

In the case of more comprehensive care, the unit cost of low-level residential care was applied annually to all individuals in nursing care with mild or moderate AD, while the unit cost of high-level residential care was applied annually to all individuals in nursing care for severe AD. CACP was applied annually to all individuals with moderate AD who remain in the community. The model assumed that all individuals with severe AD are in residential care (see Section D), and so the EACH-D unit cost was not applied in the economic model at any stage.

The inherent uncertainty in these costs is addressed through sensitivity analyses presented in Section D.6.

C.9. Issue 7: Diagnostic accuracy of FDG-PET and SPECT

The diagnostic accuracy of FDG-PET and SPECT play a key role in the incremental cost-effectiveness of FDG-PET. Specifically, the model requires the probability of individuals receiving a correct or incorrect diagnosis with either FDG-PET or SPECT.

C.9.1. Focused analytical plan

Diagnostic accuracy of FDG-PET versus SPECT was evaluated in Section B of the Assessment Report. Direct evidence (i.e. studies in which imaging with FDG-PET and SPECT was undertaken in the same patients) is less prone to bias and is considered to more reliably capture differences in diagnostic accuracy between FDG-PET and SPECT.

The main similarity between the two included comparative studies (Döbert et al, 2005, and Ito et al, 2014) is that both studies included a broad population of patients with suspected MCI or dementia (including DLB, FTD, VD and MIX), which increases the clinical applicability of the findings. However, in both studies the reference standard was not pathological diagnosis; patients were diagnosed on clinical grounds, which introduces verification bias in the estimates of test performance.

As a consequence of the shortcomings in the comparative evidence, Section B also evaluated the diagnostic accuracy of FDG-PET and SPECT using indirect evidence (i.e. studies where either FDG-PET or SPECT was used in the diagnosis of patients with SD). These studies were heterogeneous and also suffered from a number of methodological limitations that make it difficult to assess the applicability of the reported diagnostic values to routine practice (discussed in Section B.3 and Section B.4). Of note, there were differences across the studies in terms of how participants were recruited (often retrospectively and non-consecutively from specialty clinics), models of medical machines used (due to advances in imaging technology over time), ways of assessing imaging data (visual examination and a wide range of quantitative or semi-quantitative computer-based methods), and the use of control populations (i.e. normal controls, FTD, VD, DLB, and non-AD dementia). These differences, together with a general lack of blinding of researchers, mean that the pooled results from the indirect evidence must be interpreted with caution.

C.9.2. Results of the pre-modelling study

Although discussed comprehensively in Section B, key data are repeated here for transparency (see Table C.9-1). These data are from the comparative studies of diagnostic accuracy of FDG-PET versus SPECT. Overall, it cannot be concluded that FDG-PET is superior to SPECT; however, the pooled results from two small studies marginally favours FDG-PET in terms of correctly diagnosing AD.

Table C.9-1 Diagnostic accuracy data applied to the base case economic model

Study ID	TP	FP	FN	TN
FDG-PET	-	-	-	-
Ito (2014) ^a	31	9	9	6
Döbert (2005)	4	3	5	12
Total	35	12	14	18
SPECT	-	-	-	-
Ito (2014)	33	10	7	5
Döbert (2005)	1	3	8	12
Total	34	13	15	17

Source: Section B, Table B.6-1.

^a Scans were read by an expert neurological nuclear medicine physician (Reader 1). Note that this study also reported separate sets of results for scans read by a trainee and by a neuroradiologist.

C.9.3. Relationship of the pre-modelling study to the economic evaluation

The data presented in Table C.9-1 were used to determine the probability of individuals receiving a correct or incorrect diagnosis with either FDG-PET or SPECT. These probabilities are calculated in Section D.4.2 and applied to the base case of the economic model. Sensitivity analyses relating to these estimates are shown in Section D.6

C.10. Summary of the translation issues considered and their relationship to the economic evaluation

Table C.10-1 below summarises all potential translation issues/pre-modelling studies considered in Section C above.

Table C.10-1 Summary of translation issues considered in Section C

Translation issue	Methods and data sources	Relationship with Section D
Applicability issues		
Population and circumstances of use	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 AD treatment	On the basis of published data, duration of treatment was estimated for mild AD patients treated with AChEIs and moderate 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 AD	Following a literature search, published transition probabilities that considered the impact of disease progression (according to mild AD, moderate AD and severe AD 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.

Translation issue	Methods and data sources	Relationship with Section D
Treatment effect of AD drugs	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 AD 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 AD.	Treatment effect was applied to the natural history estimates of an untreated population to slow progression in individuals treated for AD. The uncertainty around the estimates used, which is acknowledged to be considerable, was examined in sensitivity analyses.
Utility weights applied to the economic model	A literature search was undertaken to source utility weights for individuals with AD, 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 sensitivity analyses.
Healthcare resource use and associated costs	Using published data, costs associated with AD 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	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; AD, Alzheimer's disease; GPs, general practitioners

Section D. Economic evaluation for the main indication

D.1. Overview of the economic evaluation

Diagnosis of AD usually involves:

- clinical evaluation (history, examination, cognitive testing) for the assessment of cognitive function;
- routine blood test (routine biochemistry, haematology, thyroid function, vitamin B12, folate) to exclude potentially treatable causes of cognitive decline; and
- structural imaging (MRI or CT) to exclude potentially treatable causes of cognitive decline and/or identify findings specific for AD (brain atrophy).

Functional imaging (using FDG-PET and ^{99m}Tc-hexamethylpropylene (HMPAO) SPECT) is able to identify changes in brain metabolism that are characteristic of AD before widespread atrophy occurs. The clinical need for such diagnostic techniques may therefore be higher in patients with early signs of AD, who have not yet passed the optimal window for therapeutic intervention.

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. Nonetheless, a cost-utility analysis (CUA) has been undertaken, as suggested by PASC, assuming inferiority of SPECT but at a much lower cost.

D.2. Population and circumstances of use reflected in the economic evaluation

The population and circumstances of use were described previously in Section C.2 (Table C.2-1). No key differences were identified between the requested listing and the economic evaluation presented here.

Where uncertainty around key inputs or assumptions was identified, the impact of these is tested in sensitivity analyses presented in Section D.6.

D.3. Structure and rationale of the economic evaluation

There are a large number of CUAs relating to treatment of AD, many of which incorporate complex modelling approaches with microsimulation and probabilistic sensitivity analysis. The PBAC considered a CUA for AD at their December 2000 meeting when they recommended listing rivastigmine on the PBS. All other AD medications were recommended on a cost-minimisation basis.

As first discussed in Green et al (2011), and subsequently discussed in Bond et al (2012), there is a vast number of published studies undertaking economic evaluations of AD treatment using progressive models of AD's natural history, although it is noted that none of the available models have been able to present a comprehensive model of the natural history of AD (Green et al, 2011). There is evidence of 10 general modelling

frameworks to assess the cost-effectiveness of AD treatment (Green et al, 2011). These general models each present a different method to model the statistical relationship between risk factors and health states. One of the most widely used of all the models, and the model best able to differentiate patients by disease severity and residential setting, was first presented in the cost-effectiveness study by Neumann et al (1999).

The approach taken in support of the current Assessment Report was to construct a Markov model based on the treatment model by Neumann et al (1999), which characterises progression of AD through different disease stages and residential settings. In any time period, patients are classified into one of three disease stages – mild, moderate or severe AD. Conditional on disease stage, patients are also assigned a probability of being in one of two settings: in the community or institutionalised in a nursing home.

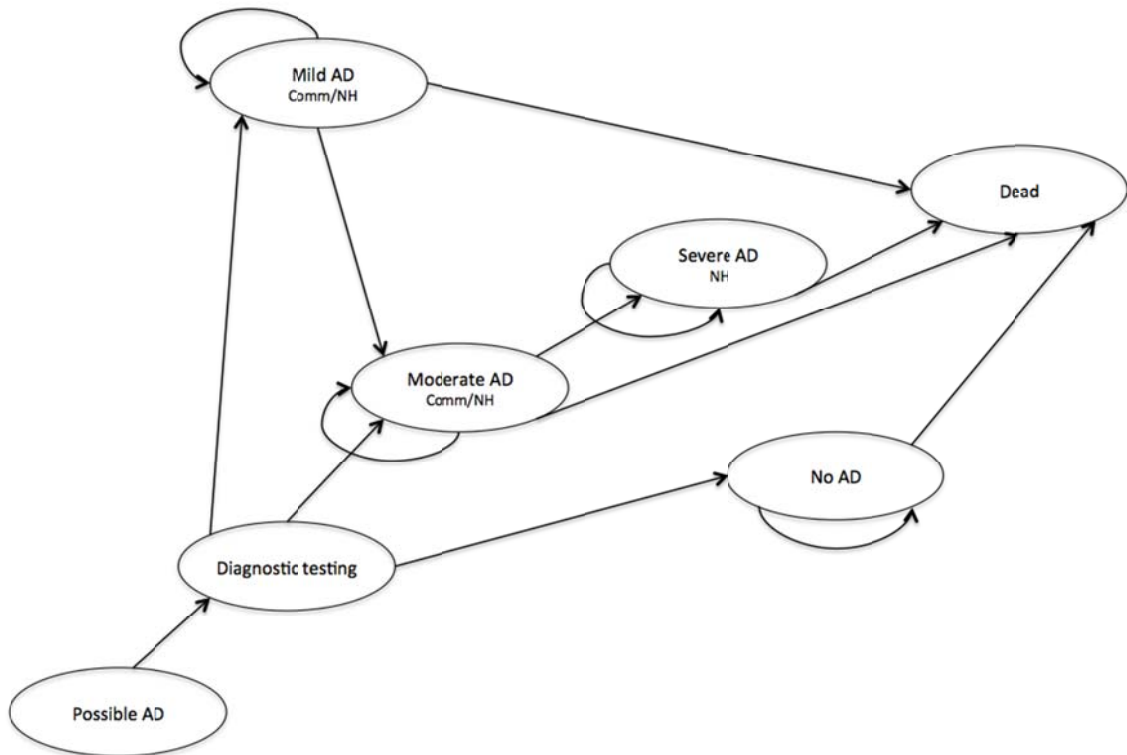
In the Neumann model, underlying disease progression was taken from a longitudinal database (CERAD) of 1,145 dementia patients in the USA. Different sets of transition probabilities were applied to cohorts receiving no treatment and drug treatment, based on RCT data for donepezil. Utility weights were derived from the HUI2 in a companion cross-sectional study of 528 caregivers of AD patients, stratified by severity and setting of care (discussed previously in Section C.6).

Although the Neumann model is quite old, the model has been one of the most widely used of all approaches taken in modelling cost-effectiveness of AD treatment (Green et al, 2011). Additionally, the PBS Review of anti-dementia medications concluded that there are only a small number of new trials assessing the efficacy and safety of AChEIs and memantine published since the listing of these medicines on the PBS. Overall, the review concluded this more recent evidence on the efficacy and safety of AChEIs and memantine to be consistent with the evidence previously considered by PBAC, with demonstration of a small average benefit relative to placebo. However, this average benefit more closely reflects stabilisation of symptoms, or relatively slower decline, as opposed to improvement.

The Neumann model did not, however, incorporate diagnostic testing. Although there are some diagnostic models available (e.g. McMahon et al, 2000; Silverman et al, 2002; McMahon et al, 2003; Biasutti et al, 2012), they do not adequately capture imaging test accuracy for a diagnostic model. Therefore, this Assessment Report presents a de novo model commencing with diagnostic testing in terms of true positive, true negative, false negative and false positive results.

A schematic of the model structure is provided in Figure D.3-1. The schematic is highly simplified, however, and a number of qualifications are noted in the description of the model structure below.

Figure D.3-1 Simplified schematic of the economic model



Abbreviations: AD, Alzheimer's disease; Comm, community-based care; NH, nursing home care

All individuals commence the model in the diagnostic testing state. Here, the model applies diagnostic testing with either FDG-PET or SPECT to a cohort of patients. It was assumed that individuals with severe AD at this stage were not included in the model, since such individuals would be past the diagnosis stage or could be diagnosed using standard diagnostic tests rather than functional imaging. Only individuals with mild AD, moderate AD and no AD (but suspected AD) were considered in the model. Severe AD was included as a health state only after disease progression.

It was assumed that 30% of individuals presenting for screening did not have AD. This is consistent with a multicentre prospective study by Silverman et al (2001) of 138 patients undergoing FDG-PET for evaluation of dementia, and a smaller study by Hoffman et al (2000) that included 22 individuals with memory loss that was considered “diagnostically challenging or difficult by clinical criteria”. Sensitivity analyses are shown in Section D.6 with the percentage of no AD cases ranging from 10% to 50%.

Of those with AD, two-thirds had mild AD and the remainder had moderate AD. McMahon et al (2000) applied a ratio of 1.5:1 for mild to moderate patients; the current analysis increased this slightly to reflect an understanding that FDG-PET may find greater use in individuals with mild AD than moderate AD. A sensitivity analysis shown in Section D.6 applied a ratio of 4:1 for mild to moderate patients.

The structure of the model differentiates patients according to three characteristics:

1. disease severity (i.e. mild AD, moderate AD, no AD and, in the later stages of the model, severe AD);
2. institutional setting (i.e. whether individuals are community-based or institutionalised in nursing homes); and
3. treatment status (i.e. whether individuals are receiving drug therapy for their AD or suspected AD).

The schematic presented in Figure D.3-1 doesn't illustrate discrete health states for each of these options, but rather condenses them where appropriate.

In the case of no disease, the model applied discrete health states for community-based individuals with no AD who receive no treatment and community-based individuals with no AD who, because of incorrect test results, mistakenly receive AD treatment. In the case of mild disease, the model considered discrete health states for community-based and nursing home-based individuals who are treated and who are untreated. Similar health states are included for individuals with moderate AD. In the case of severe AD, however, all individuals were assumed to be in nursing care and no longer receiving PBS medication for their AD. This is consistent with PBS restrictions. Additionally, data from the AIHW (2012) estimate that only 5% of all dementia cases are both severe and in the community, further justifying this assumption. The assumption of all severe cases of AD being based in nursing home care is consistent with the Neumann et al (1999) model.

The model was structured such that individuals are distributed according to their underlying disease state. Although individual's test results may influence this to some degree, the importance of the underlying disease status continues to play a crucial role. For example, an individual with moderate AD who has had a false negative test result was placed in a health state consistent with their moderate AD (i.e. not to 'no AD' despite their test result indicating this to be so). Specifically, their health state comprised their moderate AD, their being in the community (rather than nursing home), and remaining untreated.

Note that the model was structured so that all individuals are assumed to be community-based at the beginning of the model (i.e. diagnosis and treatment cannot commence in a nursing home setting). However, PBS data from a 2009 DUSC Secretariat report showed that 15-19% of patients starting treatment lived in an aged care facility (referenced in the PBS Review of anti-dementia medications, October 2012).

If an individual was community-based and then went on to disease progression, the model assumed he/she remained community-based at the time of progression. The exception was when a community-based moderate AD patient progressed to severe AD. As discussed above, it was assumed that this would include a transition to institutionalisation in a nursing home. Placement in institutionalised nursing care for mild and moderate AD is accounted for in the model, however, through a transition probability that was applied to community-based individuals at the end of each model cycle (six weeks).

The model assumed that individuals without AD remained so for the duration of the model. This was a simplifying assumption. In truth, these individuals may develop AD over time and will be eligible for repeat diagnostic testing after two-to-three years if symptoms persist. There is also the possibility that MCI may progress to AD; the

literature suggests the annual progression rate from MCI to AD may be around 10%, depending on clinical profile, setting and investigation for vascular disease (Mitchell et al, 2009).

Treatment-related adverse events were not explicitly captured in the model. The PBS Review of anti-dementia medications (October 2012) stated that there have been reports of significant side effects such as nausea and diarrhoea; however, starting on a low dose and increasing slowly has been shown to help reduce symptoms. As a pragmatic step, this period of risk of adverse events was not considered. Treatment discontinuations, however, were accounted for, as discussed in Section C.3. Note that the model assumed that a discontinuing patient would remain off treatment indefinitely.

Mortality risk was incorporated into the model, by considering both AD-related and non-AD-related mortality.

Finally, as implied by the structure of Figure D.3-1 (and discussed previously in Section C.4), AD is a progressive disease and the model, therefore, did not include 'backward' transitions. Although this was modelled by Neumann et al (1999), it was likely due to variations in clinical assessment from the CERAD database.

The model takes the form of a state-transition semi-Markov model with non-constant transition probabilities applied where appropriate (e.g. all-cause mortality, which is known to be age-dependent; discontinuations, which were related to time on therapy; etc.). The model was intentionally constructed in a way that would avoid the unnecessary technical complexity of previous models (e.g. Neumann et al, 1999) by avoiding microsimulation/Monte Carlo methods. Instead, 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 (Wood et al, 2010) and gender was distributed with 61.98% of the cohort female (calculated from Table 2.2 of AIHW, 2012).

Half-cycle correction was appropriately applied to the model, which was constructed using TreeAge Pro 2014. All costs and outcomes were discounted at an annual rate of 5%, in accordance with MSAC Guidelines.

D.4. Variables in the economic evaluation

The variables applied to the economic model, and the assumptions made in relation to these, are discussed in turn in the section below. The variables comprise healthcare resource use/unit costs applied as well as clinical variables. Due to the nature of the economic model, the clinical variables are comprehensive in that they include variables related to diagnostic accuracy as well as those related to downstream treatment and disease progression, and the impact of these on HRQoL and mortality.

Where variables were discussed comprehensively as part of Section C, the discussion below is brief and cross-references what was presented previously.

As discussed, the immediate need of the economic evaluation to place the primary focus on diagnostic testing rather than downstream treatment of AD means that the model has applied a number of simplifying assumptions to the downstream component. This approach was motivated by a wish to avoid unnecessary technical complexity in the modelling, while balancing the need to adequately inform the decision-making process.

Where simplifying assumptions were used, these are discussed and, where appropriate, tested in sensitivity analyses presented in Section D.6.

D.4.1. Healthcare resource use and unit costs

The model was structured such that individuals, at the beginning of the model, received diagnostic testing with either FDG-PET or with SPECT. It was assumed for the purposes of the model that this is a one-time test, with individuals receiving only one of these tests.

The unit cost of each of the diagnostic tests considered in the model is presented in Table D.4-1.

Table D.4-1 Unit costs of diagnostic tests included in the economic model

Diagnostic test	Unit cost	Reference
FDG-PET	\$918.00	Proposed MBS item fee; Section A.3.1
SPECT	\$605.05	MBS item 61402

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

The cost of diagnostic testing was applied to all individuals in the first cycle of the model. Appropriately, no half-cycle correction was applied to this unit cost.

All other resource use considered in the model was applied in subsequent cycles, and was related to disease severity and residential status of individuals. These resources comprise ongoing AD-related consultations, drug treatment for AD and other healthcare resources associated with AD. These were discussed previously in Section C.7 and Section C.8.

As discussed previously, the model assumed that all patients with AD would require GP consultations in excess of what individuals without AD would require. These consultations may be related to symptoms of AD or to re-assessments of disease status as required by PBS restrictions for AD drugs. As in McMahon et al (2000), it was assumed that individuals with AD would require two additional GP consultations per year related to their AD (totalling \$74.10 per year). Although it is possible that individuals may be seeing specialists for their care, this is not likely for all patients and would have a negligible impact on the estimated cost-effectiveness. The assumption of two consultations per year was applied to all individuals with AD (detected or otherwise); in those patients with no underlying AD, this cost was omitted from the analysis.

Additional to this, the model applied the cost of PBS medication to treated individuals, accounting for disease severity (and, therefore, drug type) and treatment duration. The costs, which were estimated in Section C.7, are presented in Table D.4-2, as are the costs associated with home and nursing home care for those requiring these (discussed in detail in Section C.8).

Table D.4-2 Unit costs of drug treatment and community-based and nursing home care

Resource description	Unit cost	Reference
Annual cost of consultations for community-based individuals with AD	\$74.10	MBS item 23, twice per year
Daily cost of drug treatment for mild AD (AChEIs)	\$1.95	Calculated in Section C.7
Daily cost of drug treatment for moderate AD (memantine)	\$2.40	Calculated in Section C.7
Annual cost of home-based care packages for moderate AD	\$12,410.40	Calculated in Section C.8
Annual cost of nursing home care for mild and moderate AD	\$21,476.43	Calculated in Section C.8
Annual cost of nursing home care for severe AD	\$59,528.43	Calculated in Section C.8

Abbreviations: AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; MBS, Medicare Benefits Schedule

D.4.2. Diagnostic accuracy

The diagnostic accuracy data described in Section B and again in Section C.9 were applied to the economic model. Specifically, these were used to determine the probability of individuals receiving a correct or incorrect diagnosis with either FDG-PET or SPECT.

As described above, the structure of the model required that these data were used to calculate the probability of correct and incorrect diagnoses. These are presented in Table D.4-3.

Table D.4-3 Probability of correct and incorrect diagnoses applied to the economic model

Parameter	Value	Reference
FDG-PET	-	-
Probability of a correct result in individuals with AD	0.71	TP / (TP + FN)
Probability of correct result in individuals with no AD	0.60	TN / (TN + FP)
SPECT	-	-
Probability of a correct result in individuals with AD	0.69	TP / (TP + FN)
Probability of correct result in individuals with no AD	0.56	TN / (TN + FP)

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; FN, false negative; FP, false positive; SPECT, single-photon emission tomography TN, true negative; TP, true positive

The uncertainty relating to the diagnostic accuracy data, and the impact these have on the probability described in Table D.4-3 is explored in Section D.6.

D.4.3. Transition probabilities

Transition probabilities relating to the natural history of AD were sourced from the published literature, as described previously in Section C.4, following a comprehensive search of the published literature.

Transition probabilities from Neumann et al (1999) were applied to the economic model. These included probabilities governing disease progression, progression from community-based care to institutionalisation in nursing home care and progression to death (dealt with separately in Section D.4.5 below), and so were deemed as being the most appropriate given the model structure and the need to differentiate individuals to this extent. As discussed previously, it was assumed that there were no 'backward' transitions possible for individuals with AD due to the progressive nature of AD.

Table D.4-4 Transition probabilities applied to the economic model

Transition	Annual transition probability	Reference
Mild AD to mild AD	0.615	Calculated
Mild AD to moderate AD	0.364	Neumann et al (1999) ^a
Mild AD to severe AD	0.000	Assumption
Community to nursing home (individuals with mild AD)	0.038	Neumann et al (1999)
Moderate AD to mild AD	0.000	Assumption
Moderate AD to moderate AD	0.608	Calculated ^b
Moderate AD to severe AD	0.339	Neumann et al (1999)
Community to nursing home (individuals with moderate AD)	0.110	Neumann et al (1999)
Severe AD to mild AD	0.000	Neumann et al (1999)
Severe AD to moderate AD	0.000	Neumann et al (1999)
Severe AD to severe AD	0.847	Neumann et al (1999)

Abbreviations: AD, Alzheimer's disease.

^a Neumann et al (1999) included scope for individuals to 'skip' from mild to moderate disease. In light of the six-week cycle length of the model, this was deemed inappropriate. Instead, the sum of these probabilities was applied to the model (i.e. 0.322 + 0.042 = 0.364).

^b Calculated by assuming no backward disease severity transitions.

Note: No transition probability for severe community-based treatment to severe nursing home treatment is presented due to the assumption that all severe AD patients are residents of nursing homes due to disease severity.

These data were applied to those individuals not on treatment for AD. They were, however, also used as a basis for the estimates of transition probabilities applied to those on AD drugs. This is discussed in Section C.5 and in Section D.4.5 below.

The inherent uncertainty of these transition probabilities is acknowledged; among the causes of this is the age of the source and the fact that they come from a non-Australian source. As a consequence, the effect of this uncertainty was examined in sensitivity analyses presented in Section D.6.

In addition to the natural history component, appropriate transition probabilities representative of drug discontinuations were calculated from the published literature. A detailed discussion of the search and estimation of these is presented in Section C.3.

From Le Couteur et al (2012), discontinuation rates at six months, one year, two years and three years were estimated. The discontinuation rates were applied as transition probabilities from treatment to no treatment, and are provided in Table C.3-1. They were applied as one-time transition probabilities at the associated time (e.g. at one year, a discontinuation rate of 12.9% was applied to all individuals on treatment, with no further discontinuations assumed until the cycle in which the second year begins).

As discussed previously, data limitations led to the rates presented in Table D.4-5 being applied to both individuals treated with AChEIs and to individuals treated with memantine.

Assumptions regarding the application of Le Couteur et al (2012) data to AChEIs and to memantine in the economic model are tested in sensitivity analyses presented in Section D.6

D.4.4. Treatment effect of AD drugs

In addition to the transition probabilities applicable to the natural history of AD, the model considered the impact that drug treatment has on disease progression (and associated costs and HRQoL). Although it is true that the assessment is focused on

diagnostic testing, the cost-effectiveness of this is intrinsically linked with the effectiveness of downstream treatment options.

A treatment effect of 0.5 was applied to individuals treated with AChEIs. This was sourced, via a literature search for relevant data, from Neumann et al (1999) (calculated from Rogers et al, 1998). The treatment effect was assumed to be constant throughout the duration of treatment, with no residual effect at discontinuation. As discussed in Section C.5, this estimate/approach has subsequently been applied in a number of cost-effectiveness models building upon the Neumann et al (1999) study.

In the case of individuals with moderate AD, who are treated with memantine, a treatment effect of 0.8026 was estimated from data presented in Jones et al (2004). As discussed previously in Section C.5, the estimate was derived from a population of patients with moderately severe (as opposed to moderate) AD and is, therefore, subject to considerable uncertainty.

The model applied these treatment effects such that they reduced the likelihood of disease progression. They were assumed not to impact on transitions from community care to nursing home care or to death, both of which were assumed to be unrelated to the possible impact of drug therapy. Given the high disutility associated with transition to nursing home care (particularly in mild and moderate AD), this assumption is appropriately conservative, eliminating any possibility of overstating the incremental QALY benefit arising from an effect of this type.

Table D.4-5 Treatment effects applied to the economic model

Risk of progression	Estimated treatment effect	Reference
Relative risk of progression from mild to moderate AD due to treatment with AChEIs	0.50	Neumann et al (1999)
Relative risk of progression from moderate to severe AD due to treatment with memantine	0.8026	Calculated from Jones et al (2005)

Abbreviations: AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease

The uncertainty around each of these estimates is examined in sensitivity analyses presented in Section D.6.

D.4.5. Mortality

Mortality was accounted for in the economic model in two ways: AD-related death and non-AD-related death.

The model structure required non-AD death to be accounted for in the case of individuals who went through the diagnostic testing process, but who did not in fact have AD. While it is true that individuals who have progressed this far through a diagnostic testing process are likely to be suffering from a non-AD condition that could have a profound on their survival (particularly if left untreated,) it is a highly complex process to model this and one that is fraught with uncertainty. This is out of scope. As such, a simplifying assumption was made that all-cause mortality rates would be applicable for this subgroup.

On the basis of published data, age- and gender-related mortality rates were applied to those with no AD. No adjustment was made to remove AD-related deaths from these data and the impact of this omission is negligible. Raw mortality data were sourced from

the Australian Bureau of Statistics (3302.0.55.001 - Life Tables, States, Territories and Australia, 2011-2013⁹). These were weighted by gender using data from AIHW (2012), as described in Section C.2. Age was accounted for in the model through the variable ‘Current_Age’, which was set to 72.4 years at baseline (according to Wood et al, 2010), as described in Section D.3) and increased by six weeks each cycle.

As discussed previously in Section C.4, estimates of AD-related mortality were sourced, via a literature search, from Neumann et al (1999), which provided mortality risks for those with AD, differentiated by disease severity. Specifically, annual mortality rates were provided for those with mild AD, those with moderate AD and those with severe AD.

Table D.4-6 AD-related mortality

Disease severity	Estimated treatment effect
Individuals with mild AD	0.021
Individuals with moderate AD	0.053
Individuals with severe AD	0.153

Source: Neumann et al (1999), calculated from the Consortium to Establish a Registry for Alzheimer's Disease data
Abbreviations: AD, Alzheimer's disease

The AD-related mortality risks were applied to all individuals with AD, regardless of treatment status. That is, as discussed above, treatment effect was assumed not to impact on this risk of death. This is examined as a possible source of uncertainty on the results in Section D.6.

D.4.6. Quality-adjusted life years

A comprehensive literature search to source utility weights applicable to the economic model was presented in Section C.6. As described previously, since it is expected that HRQoL will worsen with AD severity, and as patients move to more intensive care (i.e. from the community to nursing care), utility values play a crucial role in the estimation of the incremental cost-effectiveness of FDG-PET.

The literature search comprised two steps. Initially, a search was conducted to identify published studies that derive utility weights using a MAUI. Electronic searches of PubMed and the Cochrane Library were conducted using the approach discussed previously in Section C.6. Exclusion criteria were applied, leaving 15 studies (including systematic reviews). These were considered further for application to the model. Additionally, a broad literature search (see Section C.3) was also conducted to identify any potentially relevant Australian sources that may have been missed. This did not yield any results in this instance.

Of the identified studies, Jonsson et al (2006) provided the strongest estimates of utility weights associated with AD suitable for inclusion in the economic model. These were subsequently applied to the model, as described in Table D.4-7.

⁹ Downloaded from www.abs.gov.au on November 19, 2014

Table D.4-7 Utility weights applied to the economic model

Disease severity	Utility weight	Reference
No AD	1.000	Assumption
Mild AD, community-based	0.640	Jonsson et al (2006)
Moderate AD, community-based	0.495	Calculated from Jonsson et al (2006)
Mild or moderate AD, institutionalised in nursing home care	0.330	Bond et al (2012)
Severe AD ^a	0.330	Jonsson et al (2006)
Dead	0.000	Assumption

Source: Jonsson et al (2006)

Abbreviations: AD, Alzheimer's disease

^a As outlined previously, it was assumed that all severe AD cases were institutionalised in nursing home care

Bond et al (2012) – a NICE HTA that applied the utility weights from Jonsson et al (2006) – applied the mild and moderate utility weights from Jonsson et al (2006) to community-based individuals only. In the case of individuals with mild or moderate AD who are institutionalised in nursing home care, the same utility weight was applied as in the case of severe AD. A similar approach was taken in the current assessment. This was based on the reasoning that the need for institutionalisation in a nursing home would be more representative of substantially compromised QoL than any cognitive instrument capturing disease severity (such as the MMSE or CDR). That is, institutionalisation is a better indicator of HRQoL and thereby justified application of lower utility weights.

In the case of those with no AD, it was assumed that a utility weight of 1 (equivalent to perfect health) was applicable. This represents a simplifying assumption, similar to the mortality risk assumption discussed above. While it is true that individuals who have progressed this far through a diagnostic testing process are likely to be suffering from a non-AD condition that could have a profound impact on their HRQoL (particularly if left untreated), it is not possible to know the extent of this or for how long any disutility would apply. Modelling this would be subject to extreme uncertainty and out of scope of the current assessment. Consequently, it was conservatively assumed that any disutility would be temporary in nature and best captured by a value representative of perfect health. The impact of this is tested in sensitivity analyses, as is the impact of all utility weights applied.

D.5. Results of the economic evaluation

The results of the economic analysis of FDG-PET versus SPECT for diagnostic testing in individuals with suspected AD is presented below. Section D.5.1 presents the disaggregated average costs per patient, while Section D.5.2 presents the disaggregated health outcomes in terms of quality-adjusted life years. The base case incremental cost-effectiveness ratios are presented in Section D.5.3. Sensitivity analyses follow in Section D.6.

D.5.1. Disaggregated average costs

All costs, inclusive of downstream events and treatment, following on from diagnosis with either FDG-PET or SPECT are presented in Table D.5-1.

Table D.5-1 Disaggregated cost results of the economic evaluation, per patient

Health state	FDG-PET arm	SPECT arm	Incremental
Diagnostic testing	\$1088	\$775	\$313
No AD – community-based, untreated	\$0	\$0	\$0
Mild AD – community-based, untreated	\$6938	\$7148	-\$210
Mild AD – community-based, treated	\$6270	\$6091	\$179
Mild AD – nursing home care, untreated	\$853	\$869	-\$16
Mild AD – nursing home care, treated	\$558	\$542	\$16
Moderate AD – community-based, untreated	\$8420	\$8706	-\$286
Moderate AD – community-based, treated	\$4165	\$4046	\$119
Moderate AD – nursing home care, untreated	\$3064	\$3147	-\$83
Moderate AD – nursing home care, treated	\$1073	\$1043	\$30
Severe AD	\$65,994	\$67,219	-\$1225
Dead	\$0	\$0	\$0

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single-photon emission tomography

Over the five-year modelled period, diagnosis using FDG-PET is expected to cost \$1160 less per patient than diagnosis using SPECT. While there is an expected positive net cost associated with diagnostic testing and with increased use of AD medication due to better diagnostic accuracy, the cost difference is driven by larger downstream cost offsets associated with progression to severe AD. In particular, this is best understood as avoidance of the large nursing home care costs individuals incur in the severe AD health state. By avoiding/slowing progression to this health state (due to the effectiveness of AD drugs), there are large savings of \$1225 per patient (discounted), which more than fully offset the additional costs of FDG-PET and the drug treatment in those additional patients with AD detected.

If the analyses were confined to MBS costs only, FDG-PET would be associated with a positive incremental cost \$312 per patient. If only PBS costs were considered, FDG-PET would be associated with a positive incremental cost of \$21. The small positive cost differences here further serve to highlight the importance of the impact of downstream cost savings resulting from delayed progression to severe AD and the associated costs.

D.5.2. Disaggregated health outcomes

Total average QALYs, inclusive of those associated with downstream events and treatments, following on from diagnosis with either FDG-PET or SPECT are presented in Table D.5-2.

Table D.5-2 Disaggregated QALY results of the economic evaluation

Health state	FDG-PET arm	SPECT arm	Incremental
Diagnostic testing	0.04	0.04	0.00
No AD – community-based, untreated	0.78	0.74	0.04
Mild AD – community-based, untreated	0.36	0.37	-0.01
Mild AD – community-based, treated	0.30	0.29	0.01
Mild AD – nursing home care, untreated	0.01	0.01	0.00
Mild AD – nursing home care, treated	0.01	0.01	0.00
Moderate AD – community-based, untreated	0.33	0.35	-0.01
Moderate AD – community-based, treated	0.15	0.15	0.00
Moderate AD – nursing home care, untreated	0.05	0.05	0.00
Moderate AD – nursing home care, treated	0.02	0.02	0.00
Severe AD	0.37	0.37	-0.01
Dead	0.00	0.00	0.00

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single-photon emission tomography

Note: Rounding may impact on some figures

Over the five-year modelled period, diagnosis using FDG-PET is expected to accrue 0.03 QALYs more per patient than diagnosis using SPECT. The difference is driven by more accurate diagnosis of No AD (the probability of correct diagnosis of no AD is 0.60 with FDG-PET and 0.56 with SPECT). This is inherently linked with the assumption of perfect utility in these individuals (i.e. a utility weight of 1). This assumption, however, is uncertain since it hinges on the belief that these individuals do not have markedly compromised HRQoL and/or will receive adequate treatment for any other conditions they may have. This was discussed previously in Section C.6.

Since this assumption is responsible for such a large portion of the incremental QALY difference between FDG-PET and SPECT, the importance of testing this in sensitivity analyses in Section D.6 is highlighted.

In addition to the difference described above, there is a small positive QALY difference of 0.01 in the mild AD health state for those individuals who are treated in the community setting. This is the result of delayed progression due to treatment. Other observable differences in QALY results appear to favour SPECT, though this is perhaps misleading. In truth, delays in progression are responsible for these differences (e.g. less individuals progressing to severe AD means that, on average, there is a lower QALY in the FDG-PET arm for this health state).

Nonetheless, it is important to note that the incremental QALY difference of 0.03 per patient over a five-year period is small. This is particularly striking when considering how the assumption of perfect health in the No AD health state is intrinsically linked with the benefit that is observed. This is unsurprising given the small differences in diagnostic accuracy and the fact that treatment will slow progression rather than cure patients of AD altogether.

D.5.3. Incremental cost-effectiveness ratio

On the basis of the total costs and QALYs presented in Table D.5-1 and Table D.5-2, respectively, Table D.5-3 presents the base case ICER in terms of the QALY gain offered by FDG-PET.

Table D.5-3 Incremental cost-effectiveness ratio of FDG-PET versus SPECT

Parameter	FDG-PET arm	SPECT arm	Incremental
Cost	\$98,424	\$99,585	-\$1160
QALY	2.41	2.39	0.03
Incremental cost per QALY	-	-	-\$42,991

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single-photon emission tomography

Note: Rounding may impact on some figures

It was estimated that FDG-PET will save \$1160 per patient over a five-year period, while also delivering an incremental QALY gain of 0.03. While this renders the ICER itself somewhat difficult to interpret, the key conclusion to draw from this result is that FDG-PET is more effective and less costly than SPECT in the diagnosis of AD.

Consequently, if the assumptions of the base case analysis are to be accepted, the decision-making process is simple: FDG-PET is to be accepted as a cost-effective alternative to SPECT for the requested listing. Sensitivity analyses presented in Section D.6, however, explore the impact alternative assumptions have on the result.

In addition to the ICER, Table D.5-4 presents other health outcomes likely to be of interest to decision-makers in this instance. In particular, life years gained are considered, as is the number of deaths in each treatment arm.

Table D.5-4 Life years gained and number of deaths generated in the base case analysis

Parameter	FDG-PET arm	SPECT arm	Incremental
Cost	\$98,242	\$99,585	-\$1160
LYG	4.21	4.21	0.00
Incremental cost per LYG	-	-	-\$382,755

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; LYG, life year gained; SPECT, single-photon emission tomography

As in the base case cost per QALY analysis, FDG-PET appears to be cost-saving relative to SPECT (no difference to the QALY analysis) while potentially offering superior health outcomes (albeit, marginal enough to be undetectable at the level of two decimal places). The difference in LYG is, as expected, smaller than the difference in QALYs making the result very close to the margin. This renders the acceptability of the base case assumptions more sensitive when this perspective is adopted. Nonetheless, FDG-PET appears to remain a cost-effective alternative to SPECT in the case of an incremental cost per LYG analysis.

D.6. Sensitivity analyses

As discussed throughout Section C and D, many of the variables applied in the base case analysis are subject to considerable uncertainty. The possibility of uncertainty has been discussed several times previously, but its impact has not been presented thus far.

The sensitivity analyses are separated into two parts. In Section D.6.1, sensitivity analyses around the AD portion of the model will be performed, with baseline characteristics and model specifications being varied, as well as data around costs, treatment duration, utilities, treatment effect and transition probabilities. Section D.6.2 provides a detailed assessment of the effect of varying data around the comparative efficacy of FDG-PET and SPECT in the diagnostic accuracy portion of the model.

D.6.1. AD model

Table D.6 1 below presents a series of one-way sensitivity analyses aimed at better understanding the impact of the uncertainty around key variables and assumptions in the AD portion of the model. Where these are shown to have a meaningful impact on results, this is discussed below.

Table D.6-1 One-way sensitivity analyses

Analysis	Incremental cost	Incremental QALY	Result
<i>Base case</i>	-\$1160	0.03	<i>FDG-PET leads to cost savings while improving QALYs</i>
Baseline characteristics/model specifications			
Starting age set to 50 years (72.4 in base case)	-\$1160	0.03	FDG-PET leads to cost savings while improving QALYs
Starting age set to 65 years (72.4 in base case)	-\$1160	0.01	FDG-PET leads to cost savings while improving QALYs
Gender weighting set to 50% female (61.98% in the base case)	-\$1160	0.03	FDG-PET leads to cost savings while improving QALYs
Initial distribution of patients with no AD decreased to 10% (30% in the base case)	-\$290	0.01	FDG-PET leads to cost savings while improving QALYs
Initial distribution of patients with no AD increased to 50% (30% in the base case)	-\$2117	0.04	FDG-PET leads to cost savings while improving QALYs
Weighting of initial AD severity set to 80% mild and 20% moderate (67% mild and 33% moderate in base case)	-\$1125	0.03	FDG-PET leads to cost savings while improving QALYs
Weighting of initial AD severity set to 50% mild and 50% moderate (67% mild and 33% moderate in base case)	-\$1204	0.03	FDG-PET leads to cost savings while improving QALYs
Discount rate set to 0% for costs and outcomes (5% in the base case)	-\$1344	0.03	FDG-PET leads to cost savings while improving QALYs
Discount rate set to 3% for costs and outcomes (5% in the base case)	-\$1229	0.03	FDG-PET leads to cost savings while improving QALYs
Model duration reduced to 3 years (5 years in the base case)	-\$443	0.02	FDG-PET leads to cost savings while improving QALYs
Model duration increased to 10 years (5 years in the base case)	-\$2567	0.05	FDG-PET leads to cost savings while improving QALYs
Costs			
MBS item fee for FDG-PET increased by 10% to \$1009.80 (\$918.00 in the base case)	-\$1069	0.03	FDG-PET leads to cost savings while improving QALYs
MBS item fee for FDG-PET decreased by 10% to \$826.20 (\$918.00 in the base case)	-\$1252	0.03	FDG-PET leads to cost savings while improving QALYs
MBS item fee for FDG-PET set to Applicant's requested fee of \$1180.00	-\$898	0.03	FDG-PET leads to cost savings while improving QALYs

Analysis	Incremental cost	Incremental QALY	Result
Daily cost of AChEIs set to price of highest priced treatment option (\$3.42 per day instead of average of \$1.93 in the base case)	-\$1160	0.03	FDG-PET leads to cost savings while improving QALYs
Daily cost of AChEIs set to price of lowest priced treatment option (\$1.42 per day instead of average of \$1.93 in the base case)	-\$1160	0.03	FDG-PET leads to cost savings while improving QALYs
Daily treatment cost of moderate AD set to be 50% memantine and 50% AChEIs (100% memantine in the base case)	-\$1162	0.03	FDG-PET leads to cost savings while improving QALYs
Home-based care removed for moderate AD (\$12,410.40 per year in the base case)	-\$945	0.03	FDG-PET leads to cost savings while improving QALYs
Nursing home care set to \$21,476.43 per year to equal cost of low-level residential care (\$59,528.43 in the base case)	-\$377	0.03	FDG-PET leads to cost savings while improving QALYs
Treatment duration			
Discontinuations removed from the model	-\$1235	0.03	FDG-PET leads to cost savings while improving QALYs
Discontinuations set to 100% at the end of first six months (base case assumes discontinuation rate of 37.2% at the end of the first six months)	-\$1195	0.03	FDG-PET leads to cost savings while improving QALYs
Discontinuations set to 100% at the end of first year (base case assumes cumulative discontinuation rate of 45.3% at the end of the first year)	-\$1168	0.03	FDG-PET leads to cost savings while improving QALYs
Discontinuations set to 100% at the end of second year (base case assumes cumulative discontinuation rate of 57% at the end of the second year)	-\$1166	0.03	FDG-PET leads to cost savings while improving QALYs
Discontinuation rate of memantine set to zero (base case assumes cumulative rate of 67.1% over three years)	-\$1162	0.03	FDG-PET leads to cost savings while improving QALYs
Utilities			
Utility weight of no AD set to 0.7 (1 in the base case)	-\$1160	0.01	FDG-PET leads to cost savings while improving QALYs
Utility weight of nursing home for mild and moderate AD set equal to community-based AD (0.33 in the base case)	-\$1160	0.03	FDG-PET leads to cost savings while improving QALYs
Treatment effect			
Treatment effect of AChEIs reduced by 0.15 to 0.65 (0.5 in the base case)	-\$1128	0.03	FDG-PET leads to cost savings while improving QALYs
Treatment effect of AChEIs increased by 0.15 to 0.35 (0.5 in the base case)	-\$1197	0.03	FDG-PET leads to cost savings while improving QALYs
Treatment effect of AChEIs set at 0.8026 to equal the estimate for memantine (0.5 in the base case)	-\$1098	0.03	FDG-PET leads to cost savings while improving QALYs
Treatment effect of memantine reduced by 0.15 to 0.9526 (0.8026 in the base case)	-\$1062	0.03	FDG-PET leads to cost savings while improving QALYs
Treatment effect of memantine increased by 0.15 to 0.6526 (0.8026 in the base case)	-\$1207	0.03	FDG-PET leads to cost savings while improving QALYs

Analysis	Incremental cost	Incremental QALY	Result
Transition probabilities			
Annual transition probability from mild to moderate AD increased by 10% to 0.4004 (0.364 in the base case)	-\$1181	0.03	FDG-PET leads to cost savings while improving QALYs
Annual transition probability from mild to moderate AD decreased by 10% to 0.3276 (0.364 in the base case)	-\$1137	0.03	FDG-PET leads to cost savings while improving QALYs
Annual transition probability from moderate to severe AD increased by 10% to 0.3729 (0.339 in the base case)	-\$1219	0.03	FDG-PET leads to cost savings while improving QALYs
Annual transition probability from moderate to severe AD decreased by 10% to 0.3051 (0.339 in the base case)	-\$1097	0.03	FDG-PET leads to cost savings while improving QALYs
Probability of mild community-based care to mild nursing home care removed (0.038 per annum in the base case)	-\$1158	0.03	FDG-PET leads to cost savings while improving QALYs
Probability of mild AD to death set to age-related all-cause mortality (0.021 per annum in the base case)	-\$1162	0.03	FDG-PET leads to cost savings while improving QALYs

Abbreviations: AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

^a Neumann et al (1999) set backward transitions from severe to 0, thereby eliminating the need for a positive transition probability for backward transition from severe to be included in this analysis

A number of these one-way sensitivity analyses are worth further comment.

In the case of analyses involving modifications to baseline age and gender, the difference from the base case is negligible. While this may be surprising at first glance, it is due to age and gender having an isolated impact on non-AD mortality only. Further, since this is applied in such rare cases in the model (i.e. in only those cases of individuals with no AD), the impact is small. Mortality in the AD health states was set to be equal to estimates from the literature and was not related to either age or gender.

The proportion of the cohort with no AD has a notable impact on the results. As more individuals with no AD are tested with FDG-PET, the technology appears more cost-effective. This result is unsurprising given that the diagnostic power of FDG-PET is greater in these cases than with SPECT (probability of correct diagnosis is 0.60 versus 0.56). As this has the impact of leading to fewer individuals undergoing unnecessary PBS treatment, the result is intuitive. It is worth noting, however, that the estimate used in the base case was uncertain and that any change in assumptions relative to the base case could impact on the expected cost-effectiveness.

The distribution of individuals with AD between mild and moderate AD has only marginal impact on the results of the analysis.

The model duration, as expected, has a notable impact with a longer time horizon leading to an increase in cost savings. This result is intuitive as it allows for greater emphasis on the delayed progression due to effective treatment. As is always the case with longer extrapolation, however, this would also increase uncertainty and should be viewed in this light.

The results of the model are somewhat robust with regards to cost assumptions. The exception, however, is with regards to the more expensive home- and nursing care

resources that occur downstream as individual's conditions worsen. If these costs are eliminated or lessened, the cost savings offered by FDG-PET reduce markedly. Most notable is the analysis which reduces the cost of nursing care by 50%, which has the effect of reducing the incremental cost saving by 67.5%. If the assumptions regarding downstream treatment costs cannot be accepted, this could alter the conclusions drawn from the economic evaluation.

Treatment discontinuation assumptions have very little impact on the base case result. The same can be said for the utility weight sensitivity analyses reported in Table D.6-1, although utility weights as a potential source of uncertainty are explored further below.

Treatment effects similarly have only a modest impact on the results. This result is expected given the very small difference in the power of FDG-PET to correctly diagnose AD cases relative to SPECT. Since this difference would lead to correct drug treatment is just two additional individuals out of every 100 tested, reasonable variations the effect of treatment have little impact on the results of the cost-effectiveness analysis.

A similar logic applies to the analyses modifying transition probabilities. Small differences in the number of individuals correctly treated lessen the impact of the transition probabilities relating to the natural history of AD. These, while perhaps uncertain in themselves, are not expected to be a notable source of uncertainty in the modelled results.

In addition to the one-way sensitivity analyses presented in Table D.6-1, it was necessary to further explore the impact of the utility weight assumptions incorporated into the base case analysis. As discussed in Section C.6, Jonsson et al (2006) provided the best estimates of utility weights for use in the model. There were, however, a number of other sources which differentiated HRQoL by disease severity using MAUIs. The impact of using these alternative sources is presented in Table D.6-2.

Table D.6-2 Sensitivity analyses of utility weights used in the economic model

Analysis	Incremental cost	Incremental QALY	Result
<i>Base case</i> <i>Mild AD, community-based = 0.64</i> <i>Mild AD, nursing home = 0.33</i> <i>Moderate AD, community-based = 0.495</i> <i>Moderate AD, nursing home = 0.33</i> <i>Severe AD (all nursing home) = 0.33</i>	-	-\$1160	0.03
Utility weights from Neumann et al (1999) Mild AD, community-based = 0.68 Mild AD, nursing home = 0.71 Moderate AD, community-based = 0.54 Moderate AD, nursing home = 0.48 Severe AD (all nursing home) = 0.31	-\$1160	0.03	<i>FDG-PET leads to cost savings while improving QALYs</i>
Utility weights from Neumann et al (2000) ('Pits-to-perfect' adjustment, HUI3) Mild AD = 0.42 Moderate AD = 0.41 Severe AD = 0.25	-\$1160	0.03	<i>FDG-PET leads to cost savings while improving QALYs</i>
Utility weights from Neumann et al (2000) ('Pits-to-perfect' adjustment, HUI2) Mild AD = 0.70 Moderate AD = 0.54 Severe AD = 0.35	-\$1160	0.03	<i>FDG-PET leads to cost savings while improving QALYs</i>
Włodarczyk et al (2004) Mild AD = 0.68 Moderate AD = 0.575 Severe AD = 0.52	-\$1160	0.02	<i>FDG-PET leads to cost savings while improving QALYs</i>

Abbreviations: AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

The first of the utility weight sensitivity analyses was from the same source as the base case, but used the EQ-5D utility weight results for samples in which patient and carer results were available. The range of utility weights was tighter in this analysis than in the base case, with the most notable difference being the higher estimate for those with severe AD or in institutional care in a nursing home. It did not lead to a perceptible change in the incremental QALY, however, with the difference remaining at 0.03 at the level of two decimal places.

An analysis was also undertaken applying the HUI2 estimates used in the study by Neumann et al (1999). This source used a similar range (0.37, compared to 0.36 in the base case), but was distributed differently; the main difference being the markedly higher estimates for mild and moderate AD when treated in nursing homes. Again, no difference was perceptible at the level of two decimal places versus the base case.

Two analyses were also undertaken using updated estimates generated by Neumann et al (2000). These analyses used the estimates which excluded negative score results from the sample by setting these to zero, thereby avoiding the risk of overstating the value of FDG-PET by using heavily negative utility weights (which would appear unreasonable and perhaps related to issues with the use of the HUI2 and HUI3 in dementia/AD). Both HUI2 and HUI3 scores were used to generate these analyses. The range of scores was similar to the base case in the HUI3 example (0.35) but much tighter in the HUI2 case (0.17). In both, however, the distribution of utility weights by disease severity was very different, with the most notable difference that mild and moderate AD was not given a compromised utility weight if treated in nursing homes instead of the community.

Again, no difference was perceptible at the level of two decimal places versus the base case.

Finally, an analysis was undertaken using Australian utility weights from Wlodarczyk et al (2004). The range of these utility weights was much smaller than in the base case (0.16), and no compromised utility was applied on the basis of individuals being institutionalised in nursing homes. This was the only analysis that had an impact on the incremental QALY which could be observed at two decimal places. The difference, however, was small with a reduction from 0.03 to 0.02. The reason for this analysis having the only observable difference was the much narrower range in utility weights as an individual's AD progresses. The result of this is that treatment offers less benefit than it otherwise would.

The results of these analyses is unsurprising given the small difference in the diagnostic accuracy of FDG-PET compared with SPECT. With a larger difference, and more accurate diagnosis of AD, the impact of the utility weights would be greater. As it stands, however, it is clear that the utility weights selected for use in the model have a small impact on the results of the analysis.

D.6.2. Diagnostic accuracy model

A series of sensitivity analyses was undertaken to explore the impact of the diagnostic accuracy data used in the diagnostic accuracy portion of the economic model. Table D.6-3 presents alternative estimates of the diagnostic accuracy of FDG-PET and SPECT. Compared with the data presented in Section C.9.2, these apply a different set of values from the study by Döbert et al (2005), whereby AD and mixed-type dementia were combined, on the basis that differentiation of those two conditions may be of limited clinical importance. Using these led to a change in the probability of correct diagnosis of AD when using FDG-PET (0.71 to 0.83) and of no AD when using FDG-PET (0.60 to 0.56). Similarly, there was also a change in the probability of correct diagnosis of AD when using SPECT (0.69 to 0.70) and no AD when using SPECT (0.56 to 0.43).

Table D.6-3 Diagnostic accuracy data applied to the sensitivity analysis

Study ID	TP	FP	FN	TN
FDG-PET	-	-	-	-
Ito (2014) ^a	31	9	9	6
Döbert (2005)	16	1	0	7
Total	47	10	9	13
SPECT	-	-	-	-
Ito (2014) ^a	33	10	7	5
Döbert (2005)	6	3	10	5
Total	39	13	17	10

Source: Section B, Table B.6-3

Abbreviations: CI, confidence interval; FDG-PET, fluorodeoxyglucose positron emission tomography; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission tomography TN, true negative; TP, true positive
^a Scans were read by an expert neurological nuclear medicine physician. Note that this study also reported separate sets of results for scans read by a trainee and by a neuroradiologist.

As shown in Table D.6-4, the net impact of the alternative analysis was to increase the cost saving offered by FDG-PET by over \$4,700 per patient and to increase the incremental QALY gain considerably by 0.08. This is driven largely by the improved true positive rate of FDG-PET which, in turn, leads to the technology better identifying cases of individuals with AD positive status.

Table D.6-4 Sensitivity analyses of diagnostic accuracy

Analysis	Incremental cost	Incremental QALY	Result
Base case	-\$1160	0.03	FDG-PET leads to cost savings while improving QALYs
Alternative diagnostic accuracy rates from Table D.6-3	-\$5889	0.11	FDG-PET leads to cost savings while improving QALYs

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; QALY, quality-adjusted life year.

Additionally, indirect evidence regarding the diagnostic accuracy was available for application to the model. Although indirect evidence is not ideal due to underlying differences in the patient populations, indirect evidence was explored in Section B due to the very limited direct evidence available for FDG-PET versus SPECT in the diagnosis of AD. Table D.6-5 presents indirect evidence of studies in patients with dementia or suspected dementia, with pathological diagnosis as the reference standard; Table D.6-6 presents data from a published meta-analysis of FDG-PET and SPECT for the diagnosis of AD including normal controls and demented controls, with pathological diagnosis as the reference standard. The limitations of each of these studies is discussed in Section B.4. Of note, closer examination of primary studies within the published meta-analysis by Cure et al (2014) found that not all had pathologic diagnosis, despite this being a requirement for inclusion.

Table D.6-5 Diagnostic accuracy rates applied to the sensitivity analysis, indirect evidence

Study ID	TP	FP	FN	TN	Total
FDG-PET	-	-	-	-	-
Jagust (2007)	19	4	3	9	35
Jagust (2001)	29	6	17	18	70
Silverman (2001)	91	11	6	30	138
Hoffman (2000)	14	2	2	4	22
Total	153	23	28	61	265
SPECT	-	-	-	-	-
Bonte (2006)	26	2	4	17	49
Bonte (2004)	6	0	4	7	17
Jobst (1998)	65	11	8	13	97
Bonte (1997)	37	3	6	8	54
Bonte (1993)	11	2	3	2	18
Total	145	18	25	47	235

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; FN, false negative; FP, false positive; SPECT, single-photon emission tomography TN, true negative; TP, true positive.

Table D.6-6 Diagnostic accuracy rates applied to the sensitivity analysis, meta-analysis data

Study ID	Index test	No. of studies	TP	FP	FN	TN
Cure (2014)	FDG-PET	5	182	29	13	78
Cure (2014)	SPECT	6	207	30	35	163

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; FN, false negative; FP, false positive; SPECT, single-photon emission tomography TN, true negative; TP, true positive.

Table D.6-7 presents the results of these data being used in the model and highlight the model's sensitivity to different diagnostic accuracy data.

Table D.6-7 Sensitivity analyses of diagnostic accuracy

Analysis	Incremental cost	Incremental QALY	Result
<i>Base case</i>	-\$1160	0.03	<i>FDG-PET leads to cost savings while improving QALYs</i>
Diagnostic accuracy rates from Table D.6-5	\$242	>0.00	\$127,567
Diagnostic accuracy rates from Table D.6-6	\$4390	-0.08	FDG leads to additional costs but poorer QALY outcomes

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; QALY, quality-adjusted life year

In the case of the indirect evidence, the data markedly reduce the diagnostic benefit offered by FDG-PET relative to SPECT with the incremental probability of correctly diagnosing AD in disease positive patients reduced to just 0.008 and the incremental probability of a correct negative diagnosis falling to 0.014. The consequence is a watering down of the benefit in terms of both QALYs and downstream costs such that there is a positive net cost and an associated ICER of approximately \$128,000 per QALY.

In the case of the data taken from the meta-analysis reported in Table D.6-6, the data bring about a reversal in the results relative to the base case. The incremental cost becomes positive and the benefit negative, indicating that FDG-PET would be a poor choice if these data were to be accepted. This is driven by these data translating to significantly poorer ability for FDG-PET to correctly diagnose cases in which individuals do not have AD.

While the results shown here serve to highlight the complex relationship between diagnostic accuracy and cost-effectiveness, they also highlight the sensitivity of the base case results to the assumptions therein. If the data used in the base case can be accepted, it would appear that FDG-PET is a cost-effective alternative to SPECT in the diagnosis of AD. If, however, there is doubt regarding the acceptability of these data, it is clear that the conclusions of the base case may not be valid and particular caution should be taken to ensure that the impact of alternative data are well understood. In cases such as the present, where the incremental cost and QALY results are so close to zero, the conclusions are particularly sensitive and this should be accounted for in the decision-making process.

Section E. Estimated utilisation and financial implications

E.1. Justification of the selection of sources of data

The estimated financial implications of a successful listing of FDG-PET on the MBS would ideally rely on either robust 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 AD across Australia and how diagnosis is achieved using functional imaging.

Unfortunately, a scarcity of data of either type instead meant that the following analysis was undertaken using more general data derived from the incidence of dementia and associated estimates of how this is made up, in part, from individuals with AD.

That is, the following analysis follows an epidemiological approach that aimed to estimate the current use of SPECT in identifying AD from estimates of projected dementia incidence (Access Economics, 2009) and estimates of the proportion of dementia cases which are due to AD (Alzheimer's Disease International, 2014). These data were used in conjunction with assumptions regarding the rate at which SPECT is used to diagnose AD 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 an MBS listing for FDG-PET were also applied.

Note that, while SPECT was assumed to be the relevant comparator for this analysis, the MBS item fee for SPECT is shared with other diseases/indications. That is, while SPECT may be used under the MBS for diagnosing AD, it is also used for epilepsy, stroke, acute brain injury, etc. Consequently, it was not possible to derive estimates from MBS usage statistics, as there is no way to estimate what proportion of use relates to dementia/AD diagnosis.

In addition to these data and assumptions to estimate the use of FDG-PET for diagnosis of AD, the analysis also considered the possibility of increased expenditure on PBS-listed medications to treat AD. That is, with the increased use of FDG-PET, it is anticipated that more positive diagnoses would be made (both true positives and false positives). Since this will lead to greater use of PBS-listed medication, the financial impact of this has been accounted for. This part of the analysis relied on data considered in Section C (i.e. daily treatment costs and treatment duration estimates). These were described previously and are referred to again in detail below.

Table E.1-1 below summarises the data used in the analysis of the financial implications of an MBS listing for FDG-PET to diagnosis AD. It is acknowledged that the approach taken is inherently uncertain due to the lack of robust data. This, however, was considered insurmountable and sensitivity analyses were undertaken in recognition of this fact.

Table E.1-1 Data sources used for the financial estimates

Data retrieved	Reference	Justification
Dementia incidence	Access Economics, 2009 (Table 2.10)	Best available source of Australia-specific dementia incidence data, including projections for the years of interest in the analysis.
Proportion of dementia cases due to AD	Alzheimer's Disease International (2014); supported by Kukull (2003)	No Australia-specific estimate available. Best available source describing the proportion of dementia cases attributable to AD.
Proportion of AD diagnoses made in Australia using SPECT	Assumption	No data available.
Proportion of functional imaging in private hospitals	Assumption	No data available.
Substitution from SPECT to FDG-PET over five-year period	Assumption	No data available.
Additional use of FDG-PET over use of SPECT in the event of a successful MBS listing	Assumption	No data available.
Additional positive diagnoses made with FDG-PET relative to SPECT	Ito et al (2014) and Döbert et al (2005)	Best available source of data, as described previously.
Daily cost of AChEIs (PBS) and memantine	Calculated (see Section C.7)	Discussed in Section C.
Average duration of AChEI treatment and memantine treatment	Le Couteur (2011)	Only available source of Australia-specific data.

Abbreviations: AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; PBS, Pharmaceutical Benefits Schedule; SPECT, single-photon emission tomography

E.2. Estimation of use and costs of the proposed medical service

The estimated use of FDG-PET in the diagnosis of AD in the event of a successful listing on the MBS was estimated from the current use of SPECT for this purpose. Consequently, these are presented in turn below.

As discussed previously, SPECT is currently available for reimbursement via the MBS for the diagnosis of AD. The MBS listing, however, is not confined to AD diagnosis, but is rather unlimited in scope (see the listing for MBS item 61402 presented in Section A); it is used for diagnosis of AD but also for epilepsy, stroke, acute brain injury, etc. It was not possible, therefore, to estimate how many services are provided each year for the diagnosis of AD.

Nonetheless, the use of MBS item 61402 is known (presented in Table E.2-1). This number serves as an absolute upper limit for the number of AD diagnoses made using SPECT and is referred to later in the analysis to ensure estimates derived are not outside the range of possibility.

Table E.2-1 MBS SPECT use per calendar year

	2008	2009	2010	2011	2012	2013
Medicare items processed (MBS Item 61402)	2871	3898	3905	4043	4685	5090

Abbreviations: MBS, Medicare Benefits Schedule; SPECT, single-photon emission tomography
Source: [Medicare Australia statistics](#) (accessed December 6th, 2014)

Access Economics (2009) provides projected estimates of Australian dementia incidence from 2009 to 2050. Data were estimated on the basis of gender, with base case projections provided alongside both a ‘low case’ and ‘high case’ projection. The (all persons) estimates for the five years from 2015 are presented in Table E.2-2. The base case projection is applied in the present analysis.

Table E.2-2 Total Australian dementia incidence projections by scenario

	2015	2016	2017	2018	2019
Base case projection	94,453	99,107	103,932	108,044	112,896
Low case projection	93,319	97,683	102,294	106,185	110,795
High case projection	98,269	103,353	108,725	113,223	118,587

Source: Access Economics (2009), Table 2.10

The data in Table E.2-2, relate to dementia rather than AD specifically. No Australian data relevant to the population of interest could be sourced to estimate the appropriate incidence of AD. It has been suggested, however, that 50%-75% of dementia is attributable to AD globally (Alzheimer’s Disease International, 2014). Examination of incidence and prevalence data would suggest that this might vary with age (see Waite et al, 2001, which shows increasing AD incidence with age).

Despite this, it is not possible to know where the eligible population is likely to fit within this 50%-75% range, as it is not possible to know at this stage whether SPECT (or FDG-PET) is likely to be used in younger or older individuals. Considering, in conjunction with the low incidence in younger individuals, that the mean start age applied to the economic model was 72.4 years (on the basis of Wood et al, 2010), it would be reasonable to expect that both SPECT and FDG-PET are more likely to be used in an older population.

For this reason, the analysis applied an assumption that 70% of dementia cases are due to AD. This assumption was based on the proportion observed in a population of individuals aged 65 years and above in a US study (Kukull et al, 2002).

Additionally, it was acknowledged that the use of SPECT in diagnosis of AD is rare. As described previously, SPECT is used only in cases of suspected AD where other methods of diagnosis have been inconclusive (including basic screening, blood tests, clinical evaluations, MRI, etc.). While there are no data available to suggest what proportion of attempted AD diagnoses are made on the basis of SPECT, it was assumed that SPECT is used in only 5% of cases.

On the basis of the approach described above, the base case expected use of SPECT in diagnosing AD (in the event of no listing for FDG-PET) for the five years from 2015 is presented in Table E.2-3. Note that the 2015 estimate is well below the last available estimate from 2013 presented in Table E.2-1. Representing under one-third of all use of MBS item 61402, this would appear reasonable, given the availability of this MBS service for a broad range of use.

Table E.2-3 Expected use of SPECT to diagnose AD in the event of no listing for FDG-PET

	2015	2016	2017	2018	2019	Reference
Dementia incidence	94,453	99,107	103,932	108,044	112,896	Access Economics (2009)
Estimated AD incidence	66,180	69,375	72,752	75,631	79,027	Assume 70% of dementia on basis of ADI (2014) and Kukull et al (2002)
AD diagnoses attempted using SPECT	3309	3469	3638	3782	3951	Assume 5%
AD diagnoses attempted using SPECT in private hospital setting	1324	1387	1455	1513	1581	Assumption of 40% use in private hospital setting

Abbreviations: AD, Alzheimer's disease; ADI, Alzheimer's Disease International; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule; SPECT, single-photon emission tomography

The estimates presented in Table E.2-3 represent the use of SPECT in diagnosing AD if there is no change to the MBS to list FDG-PET for this purpose. In the event of a successful listing of FDG-PET, however, some substitution away from SPECT is anticipated.

It was assumed that over a five-year period, 75% of SPECT for AD diagnosis would be replaced with FDG-PET. It was assumed that this would start at 15% in the first year, increasing linearly over the five-year period. Some residual SPECT use would remain on the basis of FDG-PET being unavailable in some areas (e.g. regional areas without the facilities, even after a successful MBS listing). FDG-PET use to replace SPECT is summarised in Table E.2-4.

Table E.2-4 Expected use of FDG-PET to replace diagnosis of AD using SPECT, in the event of a successful MBS listing

	2015	2016	2017	2018	2019	Reference
AD diagnoses attempted using SPECT in private hospital setting	1324	1387	1455	1513	1581	Table E.2-3
Substitution from SPECT to FDG-PET	15%	30%	45%	60%	75%	Assumption
AD diagnoses attempted using FDG-PET in private hospital setting	199	416	655	908	1106	Calculated

Abbreviations: AD, Alzheimer's disease; ADI, Alzheimer's Disease International; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule; SPECT, single-photon emission tomography

On the basis of the estimates presented in Table E.2-3 and Table E.2-4, the associated MBS costs are provided in Table E.2-5. These were calculated on the basis of the current MBS fee for SPECT and the proposed fee for FDG-PET applied throughout this Assessment Report. Additionally, since both SPECT and FDG-PET are provided as an outpatient service, the 85% MBS benefit was applied.

Table E.2-5 Estimated cost of diagnosis with SPECT and FDG-PET

	2015	2016	2017	2018	2019	Reference
AD diagnoses attempted using SPECT in private hospital setting	1324	1387	1455	1513	1581	Table E.2-3
MBS cost per service	\$526.65	\$526.65	\$526.65	\$526.65	\$526.65	MBS item 61402 (85% benefit)
Cost to the MBS for SPECT in the event of no listing for FDG-PET	\$697,075	\$730,726	\$766,301	\$796,619	\$832,393	Calculated
AD diagnoses attempted using FDG-PET instead of SPECT in private hospital setting in the event of a successful listing on the MBS	199	416	655	908	1106	Table E.2-4
MBS cost per service ^a	\$839.60	\$839.60	\$839.60	\$839.60	\$839.60	On the basis of the listing applied to this Assessment Report
Cost to the MBS for FDG-PET instead of SPECT in private hospital setting in the event of a successful listing on the MBS ^b	\$166,694	\$349,483	\$549,746	\$61,995	\$928,917	Calculated

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule; SPECT, single-photon emission tomography

^a 85% MBS benefit

^b Calculated using non-rounded figures in financial impact model

E.3. Estimation of changes in use and cost of other medical services

In the event of a successful listing on the MBS for FDG-PET, the total cost of SPECT for the same use would decrease. Table E.2-4 describes how FDG-PET would be used in place of SPECT in the diagnosis of AD. A consequence of this is a reduction in the cost of SPECT to the MBS. In the first year of a listing for FDG-PET, it is anticipated that the use of SPECT would fall by 199 services per year, falling further to a reduction of 1,106 in the fifth year as diagnosis relies more heavily on FDG-PET. The impact of this is presented in Table E.3-1.

Table E.3-1 Estimated cost of diagnosis with SPECT in the event of a successful listing on the MBS for FDG-PET

	2015	2016	2017	2018	2019	Reference
AD diagnoses attempted using SPECT in private hospital setting, no MBS listing for FDG-PET	1324	1387	1455	1513	1581	Table E.2-3
SPECT services replaced with FDG-PET	199	416	655	908	1106	Table E.2-4
Net AD diagnoses attempted using SPECT in private hospital setting, with MBS listing for FDG-PET	1125	971	800	605	474	Calculated
MBS cost per service	\$526.65	\$526.65	\$526.65	\$526.65	\$526.65	MBS item 61402 (85% benefit)
Cost to the MBS for AD diagnosis with SPECT, with MBS listing for FDG-PET	\$592,514	\$511,508	\$421,466	\$318,648	\$249,718	Calculated

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule; SPECT, single-photon emission tomography

Note: Figures calculated using non-rounded figures in financial impact model

While Table E.2-5 shows that the cost to the MBS for diagnostic testing for AD is expected to increase in the event of a successful listing for FDG-PET, this represents a partial analysis. Specifically, it accounts for substitution only. It is expected, however, that there will be an increase in the use of functional imaging for this purpose if FDG-PET is listed on the MBS. Although this increase is expected to be small, omitting it from the analysis could understate the true cost to the MBS.

No data are currently available to inform any assumptions made in this regard. As such, the associated estimates are highly uncertain. It was assumed, however, that there would be a 10% increase in imaging for this purpose over a five-year period. A linear increase was assumed. The impact this has on the use of FDG-PET and the cost impact to the MBS is presented in Table E.3-2.

Table E.3-2 Estimated cost of diagnosis with FDG-PET, accounting for increased use in functional imaging in the event of a successful MBS listing

	2015	2016	2017	2018	2019	Reference
AD diagnoses attempted using FDG-PET in place of SPECT in private hospital setting	199	416	655	908	1106	Table E.2-4
Proportionate increase in FDG-PET due to successful listing on MBS ^a	0.0%	2.5%	5.0%	7.5%	10.0%	Assumption
Total AD diagnoses attempted using FDG-PET in private hospital setting	199	451	728	1021	1264	Calculated ^b
MBS cost per service ^a	\$839.60	\$839.60	\$839.60	\$839.60	\$839.60	On the basis of the listing applied to this Assessment Report
Total cost of FDG-PET to the MBS in the event of a successful listing	\$166,694	\$378,607	\$610,829	\$857,245	\$1,061,620	Calculated

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule; SPECT, single-photon emission tomography

Note: Figures calculated using non-rounded figures in financial impact model

^a Increase relative to SPECT in the case of no listing for FDG-PET on the MBS

^b Product of proportion in row above and the SPECT numbers presented in Table E.2-3, added to the FDG-PET estimates in the first row

In addition to the direct cost of diagnostic testing, both SPECT and FDG-PET will incur associated costs for consultations. In both cases, it was assumed that individuals undergoing diagnostic testing would require an initial specialist consultation to refer the individual (MBS item 110) for testing as well as a follow-up consultation (MBS item 116). The total cost associated with these is presented in Table E.3-3 (applying the 85% benefit).

Table E.3-3 Estimated cost of consultations associated with diagnostic testing

	2015	2016	2017	2018	2019	Reference
Unit cost of initial specialist consultation (85% benefit)	\$128.30	\$128.30	\$128.30	\$128.30	\$128.30	MBS item 110
Unit cost of follow-up specialist consultation (85% benefit)	\$64.20	\$64.20	\$64.20	\$64.20	\$64.20	MBS item 116
No MBS listing for FDG-PET						
Initial specialist consultations	1324	1387	1455	1513	1581	Table E.2-3 and assumption
Follow-up specialist consultations	1324	1387	1455	1513	1581	Table E.2-3 and assumption
Cost of initial specialist consultations	\$169,818	\$178,016	\$186,683	\$194,069	\$202,784	Calculated
Cost of follow-up specialist consultations	\$84,975	\$89,077	\$93,414	\$97,110	\$101,471	Calculated
Total cost of specialist consultations	\$254,793	\$267,093	\$280,097	\$291,179	\$304,255	Calculated
With MBS listing for FDG-PET						
Initial specialist consultations	1324	1422	1528	1626	1739	Calculated from Table E.3-1, Table E.3-2 and assumption ^a
Follow-up specialist consultations	1324	1422	1528	1626	1739	Calculated from Table E.3-1, Table E.3-2 and assumption ^a
Cost of initial specialist consultations	\$169,818	\$182,466	\$196,017	\$208,624	\$223,062	Calculated
Cost of follow-up specialist consultations	\$84,975	\$91,304	\$98,085	\$104,393	\$111,618	Calculated
Total cost of specialist consultations	\$254,793	\$273,771	\$294,102	\$313,017	\$334,680	Calculated

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule

^a FDG-PET services + remaining SPECT services x one consultation per service

Note: Figures calculated using non-rounded figures in financial impact model

The increase in the cost of consultations associated with functional imaging diagnoses presented in Table E.3-3 is a consequence of the shift toward greater use of functional imaging in the event of a successful FDG-PET listing on the MBS.

E.4. Estimated financial implications on the MBS

As shown in Table E.4-1, a listing for the use of FDG-PET in the diagnosis of AD will lead to an increase in costs to the MBS. This is a consequence of two factors: the higher fee relative to SPECT and the possible increase in the use of functional imaging if FDG-

PET is available to clinicians. The latter of these has an impact on the cost of the diagnostic test as well as the associated consultations required for diagnosis.

The cost to the MBS is expected to increase by \$62,133 in the first year of a listing for FDG-PET, increasing further to \$509,370 in the fifth year of the listing.

Table E.4-1 Total MBS costs with and without a successful FDG-PET listing on the MBS

	2015	2016	2017	2018	2019	Reference
No MBS listing for FDG-PET						
Total cost of SPECT for AD diagnosis	\$697,075	\$730,726	\$766,301	\$796,619	\$832,393	Table E.2-5
Total cost of FDG-PET for AD diagnosis	\$0	\$0	\$0	\$0	\$0	Assumption
Total cost of associated specialist consultations	\$254,793	\$267,093	\$280,097	\$291,179	\$304,255	Table E.3-3
Total cost to the MBS	\$951,868	\$997,819	\$1,046,398	\$1,087,798	\$1,136,648	Calculated
With MBS listing for FDG-PET						
Total cost of SPECT for AD diagnosis	\$592,514	\$511,508	\$421,466	\$318,648	\$249,718	Table E.3-1
Total cost of FDG-PET for AD diagnosis	\$166,694	\$378,607	\$610,829	\$857,245	\$1,061,620	Table E.3-2
Total cost of associated specialist consultations	\$254,793	\$273,771	\$294,102	\$313,017	\$334,680	Table E.3-3
Total cost to the MBS	\$1,014,002	\$1,163,885	\$1,326,396	\$1,488,910	\$1,646,018	Calculated
<i>Total net financial impact of a successful listing for FDG-PET on the MBS</i>	<i>\$62,133</i>	<i>\$166,066</i>	<i>\$279,999</i>	<i>\$401,112</i>	<i>\$509,370</i>	<i>Calculated</i>

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule
 Note: Figures calculated using non-rounded figures in financial impact model

E.5. Estimated financial implications for Government health budgets

As discussed in Section D.4.2, it is anticipated that FDG-PET will lead to more positive test results than in the case of SPECT. A consequence of this is a greater proportion of individuals moving on to PBS-listed therapies to treat AD. This has obvious cost implications, further increasing the total financial impact to the total Government health budget.

To estimate the increased cost to the PBS budget, it was necessary to account for the daily treatment cost associated with both AChEIs and memantine and the average duration of treatment of each of these. Additionally, it was necessary to account for the stage at which individuals are diagnosed with AD. This is an important consideration, as it impacts on whether patients receive memantine only (in the case of individuals diagnosed with moderate AD) or AChEIs followed by memantine (in the case of individuals diagnosed with mild AD). The values used in the analysis are presented in Table E.5-1.

Table E.5-1 Data used in the estimation of PBS costs associated with increased AD diagnosis

Parameter	Value	Reference
Daily cost of AChEIs	\$1.95	Section C.7
Average duration of AChEI use (days)	476	Le Couteur (2011) ^a
Daily cost of memantine	\$2.40	Section C.7
Average duration of memantine use (days)	476	Assumption
Proportion of individuals diagnosed with AD who are diagnosed with mild AD	0.33	Assumption building on from McMahon (2000)
Average PBS cost per positive test result	\$1449.38	Calculated

Abbreviations: AChEIs, acetylcholinesterase inhibitors AD, Alzheimer's disease; PBS, Pharmaceutical Benefits Schedule

^a Median treatment duration estimated as 17 months. Consistent with typical pack sizes, one month was assumed to be equivalent to 28 days of treatment (or 476 days)

Note that an absence of data relating to the average duration of treatment with memantine forced an assumption that this was the same as for patients treated with AChEIs. This is consistent with the approach applied in Section D (see justification in Section C).

From the diagnostic accuracy data described in Section C.9.2, it is expected that true positive diagnoses will increase with the use of FDG-PET, while false negative diagnoses will fall. The combined effect is an increase of 2% in positive diagnoses. Applying this to the number of FDG-PET services expected in the event of a positive listing on the PBS, the number of additional positive diagnoses was estimated.

Table E.5-2 Net cost to the PBS due to additional positive diagnoses with FDG-PET

	2015	2016	2017	2018	2019	Reference
Patients tested with FDG-PET in the event of MBS listing	199	451	728	1021	1264	Table E.3-2
Proportion of patients with AD	70%	70%	70%	70%	70%	McMahon (2000); Section D.3
Proportionate increase of positive diagnoses	2%	2%	2%	2%	2%	Calculated from Table D.4-3
Increase in correct positive diagnoses	2.8	6.4	10.4	14.6	18.1	Calculated
Average cost to PBS per positive diagnosis	\$1,449.38	\$1,449.38	\$1,449.38	\$1,449.38	\$1,449.38	Table E.5-1
Net increase in PBS cost	\$4,110.85	\$9,336.82	\$15,063.67	\$21,140.53	\$26,180.62	Calculated

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; FP, false positive; PBS, Pharmaceutical Benefits Schedule; TP, true positive

The net impact to the PBS shown in Table E.5-2 is modest. It is notable, however, that it may represent an overestimate as it does not explicitly account for the impact mortality may have on treatment duration. This is not expected to have a marked impact and this pragmatic approach is justified on that basis.

Furthermore, decreased false positive diagnoses with FDG-PET compared with SPECT could result in a reduction in the number of patients inappropriately placed on treatment. This has not been captured in the financial estimates in Table E.5-2, which could therefore represent an overestimate.

The net impact to the total Government health budget (i.e. the MBS and PBS budget) is presented in Table E.5-3. In the first year of a successful listing to the MBS, FDG-PET will be responsible for adding \$66,244 to the total budget. This will increase by 808% over five years to \$535,550, largely as a result of increased uptake over time leading to increases in the cost to the MBS for the diagnostic test itself. The impact of increased use of functional imaging is modest and the impact that different diagnostic accuracy has on the PBS budget is expected to be negligible.

Table E.5-3 Net financial impact to the Government health budget

	2015	2016	2017	2018	2019	Reference
Net impact to the MBS	\$62,133	\$166,066	\$279,999	\$401,112	\$509,370	Table E.4-1
Net impact to the PBS	\$4,111	\$9,337	\$15,064	\$21,141	\$26,181	Table E.5-2
Total net impact	\$66,244	\$175,403	\$295,062	\$422,252	\$535,550	Calculated

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

E.6. Identification, estimation and reduction of uncertainty

A series of one-way sensitivity analyses on the financial impact of a positive listing for FDG-PET in the detection of AD are reported in Table E.6-1. Note that since the additional cost to the PBS plays such a small role in the estimates of total Government costs due to a listing of FDG-PET on the MBS, the sensitivity analyses focused on the number of individuals tested in the event of a positive listing. This represents the greatest source of uncertainty and the most likely source of differences from that reported in the base case.

Table E.6-1 Sensitivity analyses of the net financial impact to the Government health budget

	2015	2016	2017	2018	2019
<i>Base case analysis</i>	\$66,244	\$175,403	\$295,062	\$422,252	\$535,550
Low case projection of dementia incidence data from Access Economics (2009)	\$65,386	\$172,883	\$290,412	\$414,987	\$525,584
High case projection of dementia incidence data from Access Economics (2009)	\$68,855	\$182,918	\$308,669	\$442,493	\$562,547
Proportion of dementia incidence due to AD set to 50% (70% in the base case)	\$46,478	\$123,382	\$207,684	\$297,294	\$377,193
Proportion of dementia incidence due to AD set to 75% (70% in the base case)	\$71,290	\$188,646	\$317,291	\$454,031	\$575,808
Proportion of current AD diagnoses attempted using SPECT set to 1% (5% in the base case)	\$13,249	\$35,081	\$59,012	\$84,450	\$107,110
Proportion of FDG-PET and SPECT attempts at diagnosis of AD made in private hospitals set to 100% (40% in the base case)	\$165,610	\$438,507	\$737,655	\$1,055,631	\$1,338,876
Substitution from SPECT to FDG-PET set to increase linearly from 10% in the first year to 50% in the fifth year (linear increase from 15% to 70% in the base case)	\$44,163	\$129,108	\$222,239	\$321,314	\$430,079
Substitution from SPECT to FDG-PET set to increase linearly from 20% in the first year to 100% in the fifth year (linear increase from 15% to 70% in the base case)	\$88,325	\$221,698	\$367,885	\$523,191	\$693,758
Additional use of FDG-PET relative to SPECT not included (linear increase from 0% in the first year to 10% in the fifth year in the base case)	\$66,244	\$138,884	\$218,468	\$302,815	\$369,150

Abbreviations: AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose positron emission tomography; SPECT, single-photon emission tomography

The greatest upside risk in the net financial impact of a positive listing on the MBS appears to be from the uncertainty around the proportion of diagnoses of this type attempted in the private hospital setting. In the base case, a proportion of 40% was assumed though, in truth, it is not possible to know an accurate figure for this. If it is the case that diagnoses of this type are rarely attempted in a public hospital setting, the net financial impact more than doubles by the fifth year of listing from approximately \$536,000 to approximately \$1.3m. While this remains a modest impact to the total health care budget, any improvements in certainty surrounding this proportion would minimise upside risk on the net financial impact.

It would appear that none of the remaining uncertainty is likely to have a notable effect on the net financial impact of a positive listing. Moreover, it is anticipated that the financial impact when considering the MBS and PBS in sum is expected to be marginal over the first five years of a listing.

Appendix 1. Assessment Group

Name	Organisation
Dr Suzanne Campbell	HealthConsult Pty Ltd
Ms Kate Applegarth	HealthConsult Pty Ltd
Dr Lisa Fodero	HealthConsult Pty Ltd
Mr Joe Scuteri	HealthConsult Pty Ltd
Mr Paul Mernagh	Subcontractor for HealthConsult Pty Ltd

Appendix 2. Search strategies

Literature searches to support the clinical evaluation

A literature search was conducted of EMBASE.com (which concurrently searches Medline and EMBASE) to identify studies of FDG-PET for the diagnosis of AD. The search terms are shown in Table A2.1.

Table A2.1 EMBASE.com search terms to identify clinical evidence for FDG-PET in AD

#	Query	No. of citations
#1	'alzheimer disease'/exp OR 'alzheimer disease'	130,577
#2	'dementia'/exp OR 'dementia'	251,208
#3	'mild cognitive impairment'/exp OR 'mild cognitive impairment' OR MCI	25,652
#4	alzheimer* OR dement*	235,921
#5	#1 OR #2 OR #3 OR #4	286,158
#6	'positron emission tomography'/exp OR 'positron emission tomography' OR PET	137,478
#7	#5 AND #6	11,017
#8	'glucose metabolism'/exp OR 'glucose metabolism'	120,210
#9	'fluorodeoxyglucose f 18'/exp	34,457
#10	'fluorodeoxyglucose'/exp	6,414
#11	fdg OR fludeoxyglucose OR '18f fdg' OR 18fdg OR fdg18 OR flurodeoxyglucose	31,819
#12	'cerebral metabolic rate' OR cmrgl OR rcmrglu	2,096
#13	#8 OR #9 OR #10 OR #11 OR #12	164,028
#14	#7 AND #13	4,006
#15	#14 AND [humans]/lim AND [english]/lim	3,347
#16	#15 AND 'case report'/de	346
#17	#15 NOT #16	3,001
#18	#17 AND 'conference abstract'/it	796
#19	#17 NOT #18	2,205

A literature search was also conducted of the Cochrane Library (Cochrane Reviews, Other Reviews, Technology Assessments, Economic Evaluations, Trials) to identify studies of FDG-PET for the diagnosis of AD. The search terms are shown in Table A2.2

Table A2.2 Cochrane Library search terms to identify clinical evidence for FDG-PET in AD

#	Query	No. of citations
#1	"Alzheimer's disease" or dementia or alzheimer or "mild cognitive impairment" or MCI	-
#2	PET or "positron emission tomography" or neuroimaging or "functional imaging" [Title/Abstract/Keyword]	-
#3	#1 AND #2	284

An additional literature search was conducted of the Cochrane Library (Cochrane Reviews, Other Reviews, Technology Assessments) on 17 November 2014 to identify published systematic reviews of the effectiveness and safety of donepezil, galantamine, rivastigmine or memantine for the treatment of AD. The literature search was limited to recent evidence (2010 to November 2014). The search terms are shown below.

Table A2.3 Cochrane Library search terms for treatment of AD

#	Query	No. of citations
#1	(cholinesterase or acetylcholinesterase or memantine or donepezil or galantamine or rivastigmine)	-
#2	dementia or Alzheimer's or Alzheimer <i>[Title/Abstract/Keyword]</i>	-
#3	#1 AND #2	92

Literature searches to support the economic evaluation

Literature search for Australian data

A literature search was conducted to identify Australian studies that could provide inputs for the economic model. The search strategy is shown below.

Table A2.4 Australian AD literature search terms and results

Database	Query	No. of citations
PubMed (searched 17 Nov 2014)	(Australia OR Australian) AND alzheimer[Title/Abstract] OR alzheimer's[Title/Abstract] OR dementia[Title/Abstract] Limit: English, Human	2772
Cochrane Library: Cochrane Reviews, Other Reviews, Technology Assessments, Trials, Economic evaluations (searched 17 Nov 2014)	(Australia or Australian) AND (Alzheimer or Alzheimer's or dementia) [Title/Abstract/Keyword]	145

To be eligible for inclusion, studies had to fulfil the requirements below:

- report on Australian patients with AD;
- report results in a form that is appropriate for the health states in the economic model (i.e. by disease severity mild/moderate/severe); and
- report any of the following:
 - costs;
 - utility weights;
 - patient distribution at diagnosis with FDG-PET;
 - disease progression rates;
 - hospitalisation rates;
 - treatment effect;
 - treatment continuation/discontinuation rates; or
 - treatment-related adverse events.

This search was utilised to identify potentially relevant data for a number of subsections of Section C.

The literature search yielded very few studies that fulfilled the requirements above. Citation details for those studies that were considered potentially appropriate for inclusion in the base case economic evaluation or a sensitivity analysis are shown below.

Table A2.5 Australian publications considered for use in the economic model

Citation	Potential use in economic model
Brodaty H, McGilchrist C, Harris L, Peters KE. Time until institutionalization and death in patients with dementia. Role of caregiver training and risk factors. Arch Neurol. 1993;50(6):643-650.	Transition probabilities
Brodaty H, Woodward M, Boundy K, Ames D, Balshaw R. Patients in Australian Memory Clinics: baseline characteristics and predictors of decline at six months. Int Psychogeriatr. 2011;23(7):1086-1096.	Transition probabilities
Brodaty H, Connors MH, Xu J, Woodward M, Ames D; PRIME study group. Predictors of institutionalization in dementia: a three year longitudinal study. J Alzheimers Dis. 2014;40(1):221-226.	Transition probabilities
Le Couteur DG, Robinson M, Leverton A, Creasey H, Waite L, Atkins K, McLachlan AJ. Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer's disease. Australas J Ageing. 2012;31(3):164-169.	Treatment duration
Nikmat AW, Hawthorne G, Al-Mashoor SH. Quality of life in dementia patients: nursing home versus home care. Int Psychogeriatr. 2011;23(10):1692-1700.	Utility weights
Włodarczyk JH, Brodaty H, Hawthorne G. The relationship between quality of life, Mini-Mental State Examination, and the Instrumental Activities of Daily Living in patients with Alzheimer's disease. Arch Gerontol Geriatr. 2004;39(1):25-33.	Utility weights
Wood MJ, Berlangieri SU, Rowe CC. Can brain SPECT be used to cost-effectively triage which patients require PET for the investigation of dementia? ANZ Nuclear Medicine. 2010;41:1-4.	Baseline characteristics
You E, Dunt DR, White V, Vander Hoorn S, Doyle C. Risk of death or hospital admission among community-dwelling older adults living with dementia in Australia. BMC Geriatrics. 2014;14:71.	Transition probabilities
Zilkens RR, Spilbury K, Bruce DG, Semmens JB. Linkage of hospital and death records increased identification of dementia cases and death rate estimates. Neuroepidemiology. 2009;32(1):61-69.	Mortality rates

Literature search for utility weights

A literature search was conducted to identify primary studies eliciting utility weights relevant to the health states in the economic model. The search strategy is shown below.

Table A2.6 Utility weight literature search terms and results (searched on 15 November 2014)

Database	Query	No. of citations
PubMed (searched 15 Nov 2014)	#1: "alzheimer's disease"[Title] OR "alzheimer disease"[Title] OR dementia[Title]	69508
-	#2: utility[Title/Abstract] OR utilities[Title/Abstract] OR HUI[Title/Abstract] OR AQOL[Title/Abstract] OR EuroQol[Title/Abstract] OR SF-6D[Title/Abstract] OR EQ-5D[Title/Abstract]	129799
-	#3: #1 AND #2	1029
Cochrane Library: Economic Evaluations (searched 16 Nov 2014)	(Alzheimer or Alzheimer's or dementia) [Title/Abstract/Keyword]	90
Cochrane Library: Cochrane Reviews, Other Reviews, Technology Assessments, Trials (searched 16 Nov 2014)	(Alzheimer or Alzheimer's or dementia) AND (utility or utilities or HUI or AQOL or EuroQOL or SF-6D or EQ-5D) [Title/Abstract/Keyword]	111

Following the identification of potentially useful citations, the abstracts for each publication was reviewed. Studies were excluded at this stage if:

- the study was not an original study aimed at generating utility weights (*exclusion criterion 1*)
- the patient population was incorrect (i.e. not in AD patients, or in a subpopulation that compromised the generalisability of the results) (*exclusion criterion 2*)
- the study did not disaggregate utility weights to all levels of disease severity considered in the model, or otherwise presented inadequate health states for consideration in the economic model (*exclusion criterion 3*)

Any studies not excluded at this stage were reviewed in full to determine the suitability, with the same exclusion criteria applied.

Of the 90 identified studies reviewed in full, 75 were excluded from further consideration on the basis of the full text review. Fifteen papers were subsequently considered further as potential sources of utility weights to be applied to the model.

Table A2.7 Summary of the process used to identify relevant utility studies

	Embase.com	Cochrane Library
Number of citations retrieved by search	1029	201
Number of citations excluded after title/abstract review:	-	-
• Wrong study type: not a systematic review or primary utility study	951	176
• Wrong indication: not AD	44	21
• Incorrect disease severity states/inadequate health states	17	0
Total excluded	1012	197
Number of citations screened by full text review	17	4
Duplicates removed	4	-
Number of citations excluded after full text review:	-	-
• Wrong study type: not a systematic review or primary utility study	0	-
• Wrong indication: not AD	0	-
• Incorrect disease severity states/inadequate health states	2	-
Total excluded	2	-
Total number of citations included for further consideration	15	-

Abbreviations: AD, Alzheimer's disease

Appendix 3. Indirect evidence – as presented in the literature

Table A3.1 Test results and performance characteristics of FDG-PET and SPECT alone in the diagnosis of AD, in studies which report having autopsy controls

Study ID	Index test	TP	TN	FP	FN	Sensitivity [95% CI]	Specificity [95% CI]	Source
Non-demented controls	-	-	-	-	-	-	-	-
Rusina (2010)	SPECT	16	8	2	1	94 [71%-100%]	80 [44%-97%]	Cure (2014), p.175, Figure 2
Jobst (1998)	SPECT	65	102	17	8	89% [80%-95%]	86% [78%-91%]	Cure (2014), p.175, Figure 2
Demented controls	-	-	-	-	-	-	-	-
Foster (2007)	FDG-PET ^a FDG-PET ^b	NR NR	NR NR	NR NR	NR NR	96% [NR] 98% [NR]	59% [NR] 73% [NR]	Foster (2007), p.2623, Table 5
Jagust (2001) ^c	FDG-PET	29	101	8	17	63% [48%-77%]	93% [86%-97%]	Jagust (2001), pp.953-4, Tables 2-3
Silverman (2001)	FDG-PET	91	30	11	6	94% [87%-98%]	73% [57%-86%]	Silverman (2001), p.2123, Table 2
Hoffman (2000)	FDG-PET ^e FDG-PET ^f	13 14	5 4	3 2	1 2	93% [66%-99%] 88% [62%-98%]	63% [24%-91%] 67% [23%-95%]	Hoffman (2000), p.1922-3, Tables 1,3
McNeill (2007)	SPECT	NR	NR	NR	NR	65% [45%-81%]	72% [51%-88%]	Bloudek (2011), p.634, Figure 6
Bonte (2006)	SPECT	26	17	2	4	87% [68%-96%]	89% [66%-98%]	Bonte (2006), p.377, Tables 1-2
Bonte (2004) ^g	SPECT	16	19	1	4	80% [56%-93%]	95% [73%-100%]	Bonte (2004), p.772, Table 1-2
Jobst (1998)	SPECT	65	13	11	8			Calculated: Jobst (1998), p.296, Table 5
Bonte (1997)	SPECT	37	8	3	6	86% [72%-95%]	73% [39%-94%]	Bonte (1997), p.795-6, Table 1-2
Bonte (1993) ^h	SPECT	50	9	5	9	85% [73%-93%]	64% [35%-87%]	Cure (2014), p.175, Figure 2
Various controls	-	-	-	-	-	-	-	-
Jagust (2007) ^c	FDG-PET	21	14	5	4	84% [64%-95%]	74% [49%-91%]	Cure (2014), p.175, Figure 2
Jobst (1998)	SPECT	65	115	28	8	89% [80%-95%]	80% [71%-87%]	Jobst (1998), p.2867, Table 5-6

Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; FDG, fluorodeoxyglucose; NR, not reported; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

^a Transaxial assessment.

^b Voxel-wise method (SSP).

^c Assuming that control subjects without autopsies (n=71) were truly negative for AD pathology.

^e Diagnostic accuracy results when only a single pathology was present.

^f Diagnostic accuracy results when two pathologic diagnoses were present (AD + other).

^g Includes 17 patient with and 23 patients without autopsy-confirmed diagnosis.

^h Only 18 patients had histopathologic diagnoses.

Appendix 4. Additional economic information

Table A4.1 Summary of CEAs for AD identified in Green et al (2011)

Author	Year	Country	Study type/Intervention objective	Model used	Evaluation framework
Weimer & Sager	2009	USA	CBA/ screening strategy	Study-specific	Cohort simulation
López-Bastida et al	2009	Spain	CEA / donepezil for mild-moderate AD	CERAD-CDR model	Markov cohort model
Kirbach et al	2008	USA	CEA / olanzapine for psychosis	CERAD-CDR model	Markov cohort model
Fuh & Wang	2008	Taiwan	CEA / donepezil for mild-moderate AD	CERAD-CDR model	Markov cohort model
Wattmo et al	2008	Sweden	Statistical / long-term donepezil for mild-moderate AD	Predictors ADAS-cog model	Regression-based analysis using cohort data
Teipel et al	2007	Germany	CEA / donepezil for mild-moderate AD	Kungsholmen-MMSE model	Markov cohort model
Getsios et al	2007	UK	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
Weyker et al	2007	USA	CEA / memantine/donepezil for moderate-severe AD	CERAD-SIB model	Microsimulation
Gagnon et al	2007	Canada	CEA / memantine for moderate-severe AD	Memantine model	Markov cohort model
Antonanzas et al	2006	Spain	CEA / memantine for moderate-severe	Memantine model	Markov cohort model
Small et al	2005	Multinational	Statistical / long-term rivastigmine for mild-moderate AD	CERAD-MMSE model	Regression-based analysis using cohort data
Green et al	2005	UK	CEA / ChEI for mild-moderate AD	AHEAD model	Markov cohort model
Jönsson et al	2005	Sweden	CEA / memantine for moderate-severe	Kungsholmen-MMSE model	Markov cohort model
Caro et al	2004	Multinational	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
Martikainen et al	2004	Finland	CEA / family CBT for mild-moderate	CERAD-CDR model	Markov cohort model
Francois et al	2004	Finland	CEA / memantine for moderate-severe AD	Memantine model	Markov cohort model
Jones et al	2004	UK	CEA / memantine for moderate-severe AD	Memantine model	Markov cohort model
Fagnani et al	2003	France	CMA / donepezil for mild-moderate	Predictors ADAS-cog model	Mathematical model, cohort data
Migliaccio et al	2003	USA	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
Ward et al	2003	UK	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
McMahon et al	2003	USA	CEA / PET screening for AD	CERAD-CDR model	Markov cohort model
Kulasingam et al	2003	USA	Decision analysis / screening	CERAD-CDR model	Markov cohort model
Caro et al	2002	Netherlands	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
Ikeda et al	2002	Japan	CEA / donepezil for mild-moderate	CERAD-CDR model	Markov cohort model
Garfield et al	2002	Sweden	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
McDonnell et al	2001	Netherlands	CEA / medications	McDonnell model	Regression-based analysis using cohort data
Neumann et al	2001	USA	Statistical / Progression in mild-moderate AD	CERAD-CDR model	Markov cohort model
Getsios et al	2001	Canada	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model

Author	Year	Country	Study type/Intervention objective	Model used	Evaluation framework
Caro et al	2001	USA	CEA / galantamine for mild-moderate AD	AHEAD model	Markov individual-based model
Mendiondo et al	2000	USA	Methods / Statistical model of progression in AD	CERAD-MMSE model	Regression-based analysis using cohort data
Hauber et al	2000a	Canada	Cost analysis / rivastigmine for mild-moderate AD	Fenn & Gray model	Statistical model, using individual-patient level data
Hauber et al	2000b	USA	Cost analysis / rivastigmine for mild-moderate AD	Fenn & Gray model	Statistical model, using individual-patient level data
McMahon et al	2000	USA	CEA / screening for AD (MRI/SPECT)	CERAD-CDR model	Markov cohort model
Kinosian et al	2000	USA	Methods / Statistical model of progression in AD	Kinosian model	Statistical analysis, using 'grade of membership' approach, using cohort data
Jönsson et al	1999	Sweden	CEA / donepezil in mild-moderate	Kungsholmen-MMSE model	Markov cohort model
O'Brien et al	1999	Canada	CEA / donepezil in mild-moderate AD	Study-specific	Markov cohort model
Neumann et al	1999	USA	CEA / donepezil in mild-moderate AD	CERAD-CDR model	Markov cohort model
Fenn & Gray	1999	UK	Cost analysis / rivastigmine for mild-moderate	Fenn & Gray model	Statistical model, using individual-patient level data
Stewart et al	1998	UK	CEA / donepezil in mild-moderate AD	Study-specific	Markov cohort model
Henke & Burchmore	1997	USA	Cost analysis / tacrine in mild-moderate AD	Study-specific	Decision Tree Analysis using cohort data
Wimo et al	1997	Sweden	Cost analysis / tacrine in mild-moderate AD	Kungsholmen-MMSE model	Cohort simulation
Stern et al	1994	USA	Methods / Statistical model of disease progression in mild-moderate AD	Predictors ADAS-cog model	Regression-based analysis using cohort data

Source: Green et al (2011), Appendix 2.

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; AHEAD, Assessment of Health Economics in Alzheimer's Disease model; CBA, cost benefit analysis; CBT, cognitive behavioural therapy; CEA, cost-effectiveness analysis; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry in Alzheimer's Disease; CMA, cost-minimisation analysis; MMSE, Mini-Mental State Examination; SIB, Severe Impairment Battery; UK, United Kingdom; USA, United States of America

Table A4.2 Summary of additional CEAs for AD/dementia identified in the literature search

Author	Year	Country	Intervention objective	Population treated	Utility weights	Model
Loveman et al	2006	UK	Update NHS model for treatment with donepezil, rivastigmine, galantamine and memantine	Mild to moderately severe AD; moderately severe to severe AD	Neumann 1999	Markov model for mild to moderately severe AD based on AHEAD model (Caro 2001) with a 5-year time horizon.
Fuh et al	2008	Taiwan	Donepezil relative to usual care	Mild to moderate AD	Based on a previous US study which used the HUI2 with a sample of 528 AD caregivers of patients cared for at home.	Markov model with 5-year time horizon.
Suh et al	2009	South Korea	Galantamine versus placebo	Mild to moderately severe AD	Neumann 1999	Used an adaptation of the AHEAD model with a 5-year time horizon and PSA.
Kasuya et al	2010	Japan	Donepezil relative to usual care	MCI with CDR of 0.5	Health state values for CDRs 1.0 to 3.0 were those reported in previous studies that used the HUI3 (Feeny 2002 and Ikeda 2002). The authors assumed two values, 0.34 and 1.0, for the CDR 0.5 health state.	Markov model simulations through CDR health states.
Getsios et al	2010	UK	Donepezil versus	Mild to moderate AD	Based on a published regression equation (Jonsson 2006)	Discrete event simulation, with a 10-year time horizon.
Rive et al	2010	UK	Memantine relative to standard care (established clinical practice of either no pharmacological treatment or background therapy with AChEIs)	Moderate to severe AD	Derived using a published predictive equation of time to full-time care. The predictive equation was derived using the London and South East Region (LASER-AD) UK epidemiological study.	Markov model with 5-year time horizon. Simplifying assumptions included the assumption that immediate benefits from treatment modified patients' time-related risk of progression from pre-full-time care to the full-time care health state were obtained and maintained for a five-year period.

Author	Year	Country	Intervention objective	Population treated	Utility weights	Model
Hoogveldt et al	2011	Netherlands	Memantine relative to standard care	Moderate to severe AD	Level of dependency and residential status utility values were from a UK study of 224 patients with AD.	Markov model with 5-year time horizon with PSA.
Lachaine et al	2011	Canada	Concomitant use of memantine and a AChEI, compared with a AChEI alone to delay institutionalisation	Mild to moderate AD	From a published study that elicited preferences from patients with AD. Derivation not fully described but authors stated that the weights were considered appropriate by NICE	Markov model with 7-year time horizon and PSA. Time to nursing home admission.
Nagy et al	2011	UK	Rivastigmine compared with best supportive care	Mild to moderate AD	Estimated using regression to convert the MMSE scores to utility values, based on published mapping functions for the HUI3.	Two models with 5-year time horizons and PSA, one based on MMSE scores and the other based on ADL.
Hartz et al	2012	Germany	Donepezil versus memantine or no treatment	Mild to moderate AD	Based on a published regression equation, which used data collected using the EQ-5D from 272 patients in Nordic countries. Carers' utilities from a donepezil trial where carers' QoL was assessed using the SF-36 and transformed to utilities based on a published study.	Discrete event model with 10-year time horizon and PSA, adapted from Getsios 2010
Bond et al	2012	UK	Update NHS model for treatment with donepezil, galantamine, rivastigmine and memantine versus each other and combinations and best supportive care	Mild, moderate, severe AD	Jonsson 2006 for patient utility weights. Neumann 1999 for carer utility weights. Appendix 17 of report has published utility values by severity from Kerner 1998, Miller 2008, Sano 1999, Ekman 2007, Naglie 2006, Anderson 2004, Włodarczyk 2004, Karlawish 2008, Neumann 1999, Jonsson 2006.	PenTAG Markov model based on time to institutionalisation, replaced previous SHTAC-AHEAD model used for NICE.
Pfeil et al	2012	Switzerland	Combination treatment of an AChEI and memantine compared with mono treatment (either an AChEI or memantine)	Mild to moderate AD	Neumann 1999 and Ward 2003	Markov state-transition model using French adaptation (Touchon 2010, abstract only) of Canadian model from Lachaine 2011, with 7-year time horizon.

Author	Year	Country	Intervention objective	Population treated	Utility weights	Model
Rive et al	2012	Norway	Memantine versus no pharmacological treatment or background therapy with AChEIs	Moderate and severe AD	Scandinavian Study of Cost and Quality of Life in Alzheimer's Disease (SQUAD) study by Jonsson 2006. Details provided of grouping by model state.	Markov model with 5-year time horizon.
Biasutti et al	2012	France	Screening with contrast agents for MRI compared with standard diagnosis (cognition tests and standard MRI), then treat with donepezil or memantine or a hypothetical higher-efficacy drug	MCI	Based on Neumann 1999	Markov model based on Neumann 1999, with diagnostic accuracy captured as per McMahon 2000
Getsios et al	2012	UK	Early assessment and treatment for AD compared with treatment after diagnosis or no treatment	Annual assessment of patients (aged 65-100) with subjective memory complaints and MMSE 10-26 (5% of cases have CT or MRI)	Patient utilities estimated on basis of published regression equation (Jonsson 2006). Caregiver utilities based on data from donepezil trials using SF-36 transformed to utilities.	Discrete event simulation based on Getsios 2010 for donepezil and adapted for effect of early assessment, with a 10-year time horizon.
Hyde et al	2013	UK	Update evidence used to inform NICE 2007 decision regarding treatment with donepezil, rivastigmine, galantamine and memantine	Commencement of treatment for AD	No change from Loveman 2006	Update of PenTAG model (Loveman 2006).
Skoldunger et al	2013	Sweden	Hypothetical model of disease modifying treatment compared with standard care	MCI and AD	Utility scores were from a Swedish study of utility for patients with MCI and dementia. These scores were assigned to each model state.	Markov model with 20-year time horizon. Assumed prolonged survival with disease modifying treatment.
Touchon et al	2014	France	Combination treatment of a AChEI and memantine on nursing home admission	Community-dwelling AD	Neumann 1999	Markov model with structure identical to Lachaine 2011

Author	Year	Country	Intervention objective	Population treated	Utility weights	Model
Bermingham et al	2014	Canada	Image all versus selective use of structural imaging (CT and MRI) then treatment with AChEIs. Four imaging strategies compared	Mild to moderate dementia	Utilities for the six health states, representing severity of illness (mild, moderate or severe) and institutional status (community or nursing home) were modified from the CERAD publication (Neumann 1999) to create three states for severity of illness.	Decision tree to determine positive and negative predictive values of disease. Diagnostic utility was estimated based on a clinical evidence-based analysis, conducted by Health Quality Ontario. Markov models, probabilistic, with lifetime time horizon. Cochrane review showed no higher adverse events with donepezil vs placebo (Birks & Harvey, 2006).

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; ADL, Activities of Daily Living; AHEAD, Assessment of Health Economics in Alzheimer's Disease model; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry in Alzheimer's Disease; CT, computed tomography; EQ-5D, EuroQol 5-Dimension; HUI, Health Utilities Index; LASER-AD, London and the South East Region Alzheimer's Disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NHS, National Health Service; NICE, National Institute of Clinical Excellence; PSA, probabilistic sensitivity analysis; QoL, quality of life; PenTAG, Peninsula Technology Assessment Group; PSA, probabilistic sensitivity analysis; SHTAC-AHEAD, Southampton Health Technology Assessment Centre-Assessment of Health Economics in Alzheimer's Disease model; SQUAD, Scandinavian Study of Cost and Quality of Life in Alzheimer's Disease; UK, United Kingdom

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