Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1195.1 – Positron Emission Tomography (PET) for the diagnosis of Alzheimer disease

Applicant: Department of Molecular Imaging and Therapy, Austin Health

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

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

1. Purpose of application

An application requesting re-consideration of Medicare Benefits Schedule (MBS) listing for the use of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) to establish a diagnosis of Alzheimer disease (AD) where other diagnostic methods are inconclusive, was received from Austin Health by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for fluorodeoxyglucose (FDG) PET for the diagnosis of Alzheimer disease (AD) where clinical evaluation is inconclusive. MSAC accepted that FDG PET was more sensitive than its comparator, single-photon emission computed tomography (SPECT), which would largely be replaced. MSAC supported the proposed fee being the same as the comparator, but advised that utilisation and out-of-pocket payments should be monitored for 12 months after listing.

The MSAC-supported MBS item is as follows:

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS [item number] ^{18}F-FDG PET study of the brain that includes quantitative comparison to a normal database, performed for the diagnosis of Alzheimer disease where: • clinical evaluation by a specialist, or in consultation with a specialist is equivocal; AND • ^{18}F-FDG PET would assist in the differentiation of Alzheimer disease from other aetiologies; AND • differentiating Alzheimer disease from an alternative aetiology would alter the management of the patient. **Fee: $605.05 (as per MBS item 61402)**. Limit of three scans per patient per lifetime, which are performed no more frequently than once per year, and not applicable if a cerebral perfusion SPECT study has been performed within the previous 12 months.

Consumer summary

Austin Health applied for public funding via the Medicare Benefits Schedule (MBS) for fluorodeoxyglucose (FDG) positron emission tomography (PET) to diagnose Alzheimer disease where other diagnostic methods do not provide a definite answer.

People with Alzheimer disease lose activity in certain areas of their brain, which causes brain cells in these areas to use less glucose (a type of sugar). This produces a characteristic pattern that can be seen with an FDG PET scan of the brain. FDG is a slightly radioactive form of glucose that can be safely injected into a patient. By showing areas of brain malfunction, the scan may help doctors make a diagnosis.

The Medical Services Advisory Committee (MSAC) had considered this application in 2015, but did not support public funding at that time because the clinical evidence was weak and MSAC was not sure that FDG PET would provide value for money. This reapplication provided more clinical data and a revised economic analysis. MSAC concluded that the new data showed that FDG PET was a better test than the one it was being compared to (single-photon emission computed tomography, or SPECT), and recognised that replacing SPECT with FDG PET would align with international clinical guidelines. MSAC advised that FDG PET should be limited to three scans per lifetime and not more often than once per year, to ensure that it would be used only for diagnosis and not for monitoring (using FDG PET for monitoring was not requested by the applicant, and no evidence was provided to support its use for this purpose). MSAC noted the proposal to list FDG PET on the MBS at the same fee as SPECT, but considered that there may be out-of-pocket consumer costs if providers decide to charge more for the service.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported MBS funding for FDG PET to diagnose Alzheimer disease. MSAC concluded that FDG PET was acceptably effective, safe and cost-effective compared with SPECT. MSAC also recommended that the new item be reviewed after 12 months to monitor any out-of-pocket costs and access issues for patients in rural and remote areas.

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

MSAC noted that this was a reapplication for the MBS listing of FDG PET to establish a diagnosis of AD where other diagnostic methods are inconclusive. The initial application for FDG PET for the diagnosis of AD (Application No. 1195) was considered by MSAC at its April 2015 meeting. MSAC did not support public funding at that time because of uncertain cost-effectiveness compared with SPECT due to weak clinical comparative data and unclear translation of imaging performance to improved health outcomes.

MSAC noted that the reapplication focused on MSAC's concerns and advice from April 2015 (see Background in Section 4 below). MSAC considered that the applicant had provided a reasonable response to these concerns and advice, and also recognised that replacing SPECT with FDG PET for diagnosis of AD would align with international guidelines.

MSAC noted that the main new source of evidence was the Nadebaum et al (2020) study, which was larger and more applicable than the evidence previously provided to MSAC in 2015. MSAC accepted that the results of paired SPECT and FDG PET patient data presented in this key study (Table 6), showed that FDG PET was significantly more accurate in differentiating AD from non-AD than SPECT, primarily by being significantly more sensitive . MSAC noted the "high" intra-operator reliability (using the categories defined by Landis &

Koch 1977) reported for both FDG PET and SPECT. However, MSAC also noted that inter-operator reliability for FDG PET was only "moderate". Although there was no difference between these kappa scores for FDG PET and SPECT (0.48 vs 0.43, see Table 6), this result highlighted the difficulties and level of subjectivity involved in interpreting imaging data, which it considered significantly impacts how the result of each image is determined.

MSAC noted the Evaluation Sub-Committee's (ESC) concerns related to the design and conduct of the key study. MSAC noted the applicant's pre-MSAC response addressing the following issues raised by ESC, clarifying that:

- participants were referred by specialists for further evaluation (by SPECT or FDG PET) where their diagnosis was otherwise uncertain. MSAC considered the participants included in the trial are therefore likely to be largely representative of the population proposed by the application, although noting the study might have reduced applicability because it was based on a convenience population (via participation in the β-amyloid PET study conducted before late 2015);
- SPECT was performed on all participants and, if results were considered definitive, an FDG PET scan was not performed. Eligible patients were those who went on to have research β-amyloid PET scans to inform another study. Overall, MSAC considered that the paper's reporting of results including and excluding the minority (17/143 = 12%) patients who underwent SPECT but not FDG PET, gave sufficient confidence in accepting the main conclusions of the study, although the magnitude of the reported differences remains uncertain;
- the delay between the two imaging modalities in patients who received both scans was highly unlikely to impact the results, given the relatively slow progression of the disease in most cases. MSAC agreed with this; and
- blinding the readers was not possible given the relative clarity of FDG PET images compared to SPECT. MSAC acknowledged this reality.

Despite the concerns related to the design and conduct of the key study, MSAC concluded that, on balance and from the available evidence, FDG PET has superior sensitivity over SPECT in detecting AD.

MSAC considered the Commentary-proposed item descriptor (Table 3) was appropriate, noting it was also supported by the applicant in the pre-MSAC response. MSAC noted feedback provided by the Australian and New Zealand Society of Nuclear Medicine that "and structural brain imaging are equivocal" should be removed from the item descriptor, given patients with dementia often have normal structural brain imaging. MSAC agreed to the removal of the requirement that structural brain imaging also be equivocal. MSAC advised that, despite any concerns about their subjectivity, the other elements of the item descriptor should remain to better convey the intent of the item, noting that this also aligns with international guidelines. MSAC advised that a limit of three scans per lifetime was reasonable, and that the descriptor should also specify that this should be "no more frequently than once per year" to ensure that FDG PET would not be used for treatment monitoring purposes.

MSAC noted the application proposed a fee of $605.05 (to match the fee for MBS item 61402 for SPECT). MSAC noted the external consultation feedback which suggested that the proposed fee for FDG PET should be commensurate with neurological PET-CT scans at a fee of either $918 for MBS item 61559 (epilepsy) or $901 for MBS item 61538 (recurrent brain tumours), otherwise the lower fee of $605.05 may potentially result in increased out-of-pocket costs. MSAC considered that the fee should remain at $605.05 as proposed by the

applicant, but that out-of-pocket costs should be monitored over the first 12 months after initial MBS listing.

MSAC noted that the cost-minimisation approach assumed cost-neutrality to the MBS if FDG PET purely substitutes for SPECT in the existing MBS SPECT population. MSAC noted estimates of the utilisation of MBS-funded FDG PET for AD were made using a market share approach, which were nominated as the base case. As the services required before and after FDG PET and SPECT were expected to be the same, no additional or concomitant MBS services were costed. However, MSAC considered that the increased sensitivity of PET would result in a greater number of diagnoses of AD, with subsequent greater utilisation of PBS-subsidised medicines for treatment. MSAC considered these downstream effects remained uncertain and would be difficult to quantify in a further economic analysis.

The key areas of uncertainty for the financial implications of listing FDG PET discussed by MSAC included the estimate of the size of the eligible population to be tested, and whether FDG PET would be used beyond the current growth in the use of SPECT. MSAC noted that, given there were no robust Australian data to inform the likely testing population, the Commentary presented a range of alternative approaches to the base case, resulting in the final estimates of the eligible population in 2021 ranging from 3,028 services (using an approach similar to that used in the 1195 ADAR) up to 13,398 services assuming that 13.3% of all incident dementia diagnoses are "equivocal" (Figure 1). MSAC also noted the sensitivity analyses presented by the Commentary (Table 11) which showed a potential net financial impact on the MBS in 2021 which could range from $326,048 if 20% of patients receive both FDG PET and SPECT to $815,120 if the uptake of FDG PET is 50% higher than that assumed in the base case.

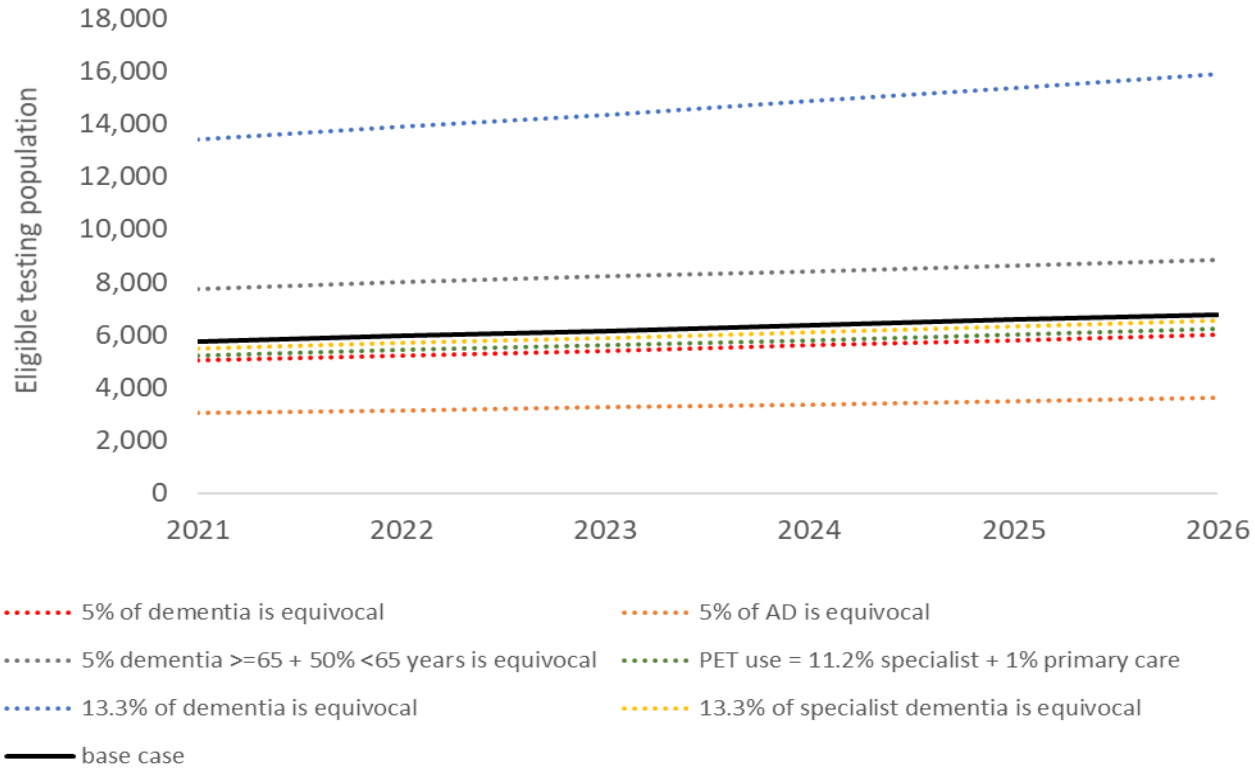

Figure 1 Eligible testing population based on alternative approaches

Source: Tables in Appendix 1 of the Commentary provide calculations and sources.

Overall, MSAC advised that the Department's modelling of the financial implications of listing FDG PET were reasonable, which estimated that the total cost to the MBS of FDG PET over four years would be $1.757 million for a fee of $605.05. However, MSAC also advised that monitoring the utilisation of FDG PET and SPECT would be required, as well as out-of-pocket costs, and the FDG PET item should be reviewed 12 months after initial MBS listing. This monitoring should also include geospatial analysis to determine whether patients in rural or remote areas were more likely to have SPECT instead of FDG PET, which may indicate access issues. MSAC also noted that the management of AD will continue to evolve with the upcoming MSAC Application No. 1643 for β-amyloid PET scans to diagnose AD, and advised that this might affect the interpretation of this recommended monitoring of FDG PET utilisation and costs.

Department modelling - potential costs

	2022	2023	2024	2025
Eligible population	5,960	6,165	6,371	6,576
Percent uptake	70%	80%	90%	100%
Utilisation	4,172	4,932	5,734	6,576
Reduction of SPECT	50%	60%	70%	80%
	2021-22	**2022-23**	**2023-24**	**2024-25**
Cost with fee $605	$185,000	$428,000	$532,000	$612,000

4. Background

This reapplication (Applicant Developed Assessment Report [ADAR]) is the second iteration of this application. The initial application for FDG PET for the diagnosis of AD (Application 1195) was considered by MSAC at its April 2015 meeting. At that time, MSAC did not support public funding because of uncertain cost effectiveness compared to single-photon emission computed tomography (SPECT), due to weak clinical comparative data and unclear translation of imaging performance to improved health outcomes.

MSAC advised that a reapplication should include:

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

The public summary document detailing MSAC's consideration of application 1195 is available on the MSAC website.

5. Prerequisites to implementation of any funding advice

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

6. Proposal for public funding

The previously proposed MBS item descriptor, with suggestions in red text from ESC, is shown in Table 1.

Table 1 Previous ESC-proposed MBS item descriptor (ESC amendments in red text)

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

- **Suspected early stage and "equivocal"**

The ADAR proposed to remove the criterion that suspected AD be "early stage". The ADAR argued that the use of "early stage" would exclude cases where diagnosis is equivocal due to language and cultural issues, or other factors that cause unreliable performance on cognitive tests. The Commentary noted that while this appears to be reasonable, it may increase considerably the population eligible to receive FDG PET for the diagnosis of AD. The sole remaining criterion for limiting the population is "where clinical evaluation […] and structural brain imaging are equivocal".

The remaining criterion is simply "equivocal". The Commentary noted that a study reporting on the impact of floretaben (β-amyloid tracer) PET on an initial diagnosis of "probable AD" (note, this is the highest likelihood that can be ascribed by clinical diagnosis) found that the scan results changed the confidence associated with the initial clinical diagnosis in almost all (>80%) cases (Schipke et al. 2012). If clinical diagnosis was commonly unequivocal, it would follow that the likelihood of a scan result altering the confidence of diagnosis would be low. Clinical diagnoses are not described to be certain in some of the literature (Sabbagh et al. 2017). Furthermore, the Commentary noted a diagnosis of AD without a scan may be "definitionally" rendered equivocal should the use of biomarkers be accepted as integral for the diagnosis of AD (Jack Jr et al. 2018; Morris et al. 2014).

- **Removal of MRI**

The ADAR proposed changing the requirement that "clinical evaluation [….] and MRI are equivocal" to "clinical evaluation [….] and structural brain imaging are equivocal". The Commentary considered this change is unlikely to significantly impact the interpretation of the proposed MBS item descriptor.

- **Frequency and SPECT**

The ADAR recommended that the service only be available once per patient per year.

The Commentary noted it is unclear how useful repeat scans would be, with no studies provided to show that patients whose diagnosis remains equivocal following FDG PET would later receive a definitive diagnosis using the same modality. It was noted in the key study that the sensitivity of the scan was lower in patients with MCI, and if there is a trend toward earlier diagnosis of AD, then repeat scans may be required. However, the Commentary considered MSAC may wish to place a limit on the number of scans permitted in a lifetime rather than permit serial scans every year.

The ADAR noted that the MBS item descriptor is "not applicable if a cerebral perfusion SPECT study has been performed within the same calendar year". The Commentary queried why the proviso includes "same calendar year" and is not related to the duration separating the two scans: for example, within 12 months of a cerebral perfusion SPECT.

The Commentary considered the way in which this proviso was written was confusing, as it may be interpreted that the limitation of one scan per patient per year is not applicable if

SPECT has been performed. While this limit was proposed for the FDG PET MBS item descriptor (not to be used if SPECT has been used in the same calendar year), the same is not true for the MBS item descriptor for SPECT. Therefore, the Commentary considered it was unclear whether clinicians would be prevented from performing SPECT following the use of FDG PET.

- **Amyloid Imaging Task Force**

The criteria included in the proposed MBS descriptor are broad. However, there are some specific cases where the use of FDG PET may be useful for the differentiation of AD from non-AD pathologies. A publication of the Amyloid Imaging Task Force was identified during the preparation of the Commentary, which provided recommendations for the use of β-amyloid PET. The availability and cost of β-amyloid PET in Australia may prohibit its use. However, the recommendations of the Amyloid Imaging Task Force may be relevant to assist in the selection of patients for FDG PET in Australia, where it may be used in place of β-amyloid PET. The recommendations include three cases for the use of β-amyloid PET, and seven situations where it is not indicated (Johnson et al. 2013).

Appropriate candidates for β-amyloid PET include:

- patients with persistent or progressive unexplained memory problems or confusion and who demonstrate impairments using standard tests of cognition and memory
- individuals meeting tests for possible AD, but who are unusual in their clinical presentation
- individuals with progressive dementia and atypically early age of onset (before the age of 65 years).

The Commentary noted that MSAC may wish to consider whether restrictions for the use of FDG PET should be consistent with the current guidelines for the use of β-amyloid PET for the diagnosis of AD.

- **NICE recommendations (ng97)**

NICE updated its guidance for the assessment, management and support for people living with dementia and their carers in June 2018 (National Institute for Health and Care Excellence June 2018). Relevant recommendations relating to imaging are presented below:

> *Recommendation 14*
> Only consider further diagnostic tests (recommendations 15-28) if:
> - it would help to diagnose a dementia subtype and
> - knowing more about the dementia subtype would change management.
>
> *Recommendation 15*
> If the diagnosis is uncertain (see recommendation 14) and Alzheimer's disease is suspected, consider either:
> - FDG-PET (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable. OR
> - examining cerebrospinal fluid for:
>   - either total tau or total tau and phosphorylated-tau 181 and
>   - either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40.
>
> If a diagnosis cannot be made after one of these tests, consider using the other one.
> *Recommendation 17*
> Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.

The Commentary noted the NICE recommendations state that the appropriate population for the use of FDG PET is in those where AD is suspected, and the diagnosis of AD would change management.

Table 2 Applicant-proposed MBS item descriptor in the current re-application (1195.1)

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS [item number] FDG PET study of the brain that includes quantitative comparison to a normal database, performed for the diagnosis of Alzheimer's disease where clinical evaluation by a specialist, or in consultation with a specialist, and structural brain imaging are equivocal. **Fee: $605.05 (as per MBS item 61402)** Limitation of one scan per patient per year and not applicable if a cerebral perfusion SPECT study has been performed within the same calendar year.

Table 3 Commentary-proposed MBS item descriptor in the current re-application (1195.1)

Category 5 – DIAGNOSTIC IMAGING SERVICES
MBS [item number] ^{18}F-FDG PET study of the brain that includes quantitative comparison to a normal database, performed for the diagnosis of Alzheimer disease where: • clinical evaluation by a specialist, or in consultation with a specialist, and structural brain imaging are equivocal; AND • ^{18}F-FDG PET would assist in the differentiation of Alzheimer disease from other aetiologies; AND • differentiating Alzheimer disease from an alternative aetiology would alter the management of the patient. **Fee: $605.05 (as per MBS item 61402)**. Limit of one scan per patient per year and not applicable if a cerebral perfusion SPECT study has been performed within the previous 12 months.

Access to PET

The ADAR stated that PET cameras are now available across many large regional / rural centres, including Darwin, Cairns, Townsville, Bundaberg, Mackay, Sunshine Coast, Lismore, Coffs Harbour, Port Macquarie, Newcastle, Gosford, Albury-Wodonga, Bendigo, Ballarat, Geelong, and Bunbury.

The Commentary noted that as is the case for SPECT, access to PET may still be limited in some regional / rural areas. However, the service is limited to once per year, and re-scans for ongoing equivocal cases are less likely. The Commentary considered that as patients from rural / regional centres are likely to have to travel to access specialist dementia centres, concerns with access to PET machines due to remoteness are somewhat reduced.

7. Summary of public consultation feedback/consumer issues

A total of nine consultation comments were received for this application. Seven (7) comments were received from peak advocacy/industry/professional organisations and two (2) comments were received from medical professionals.

Peak organisations supported the MBS listing of FDG PET for the diagnosis of AD, whilst highlighting the importance of this being one component a multi-disciplinary approach in the diagnosis and management of AD patients. Organisations considered that FDG PET would allow earlier diagnosis of AD, which may result in earlier intervention and lead to improved outcomes for patients and their families. One organisation identified equity of access to FDG PET for patients in rural areas as a potential issue and another organisation highlighted that

the availability of FDG PET should not preclude the use of SPECT for diagnosis of AD, as to not disadvantage patients who would not be able to access FDG PET.

Two medical professionals provided their comments in support of the availability of FDG PET for the diagnosis of AD, considering FDG PET as being superior to SPECT. The comments noted that the diagnosis of AD will be improved with the use of FDG PET and help families and patients plan for ongoing care. Another benefit noted by the medical professionals was that this would reduce the use of unnecessary or insensitive tests such as SPECT, MRI and CT scans.

No individual consumer comments were received for this application.

8. Proposed intervention's place in clinical management

Description of proposed intervention

It was proposed that FDG PET brain imaging be used to diagnose AD in patients with evidence of decline in memory or other areas of cognition when current diagnostic methods are inconclusive. AD affects particular areas of the brain more than others. Loss of brain cell activity in these areas causes reduction in glucose use in these areas. This produces a characteristic pattern of reduced glucose use that can be seen with an FDG PET brain scan. FDG is a slightly radioactive form of glucose that can be safely injected into a patient. By showing areas of brain malfunction, the scan may assist doctors in making a diagnosis. FDG PET brain scans are currently used to help surgeons identify the area of the brain causing focal seizures.

Description of medical condition(s)

AD is the most common cause of dementia, with the prevalence increasing as Australia's population ages. It is relentlessly progressive and leads to severe disability and then death on an average of seven years from diagnosis. Symptoms of AD are present for several years before diagnosis and the pathological process that leads to the dementia of AD begins a decade or more before diagnosis.

For the clinical management algorithm, refer to the 1195 PSD.

9. Comparator

The comparator was unchanged from the previous application.

10. Comparative safety

The comparative safety was unchanged from the previous application.

11. Comparative effectiveness

The key study provided with the ADAR was a "A head-to-head comparison of cerebral blood flow SPECT and 18F-FDG PET in the diagnosis of Alzheimer's Disease" (Nadebaum et al. 2020).

The study was a retrospective analysis of 126 patients who had completed both SPECT and FDG PET as part of their diagnostic assessment, and who had subsequently received β-amyloid PET for research purposes. Patients had been clinically referred by a memory disorder specialist to the Nuclear Department of Austin Health for the assessment of cognitive impairment.

The study included a convenience population, stated to be "All patients […] that had both a SPECT and 18F-FDG PET scans within a twelve month period and subsequently completed β-amyloid PET through participation in research studies prior to late 2015" (population described in Table 3). A limitation identified in the previous MSAC consideration was the lack of studies comparing FDG PET and SPECT in an appropriate population. Only two studies were identified, one published in 2005 and a second published in 2014. Neither of the included studies were performed in Australia, and the applicability to the Australian setting was uncertain. The Austin Health Study provides an up-to-date comparison of SPECT and FDG PET in an Australian setting. It is likely that the referral patterns and population characteristics of the included patients in the current study are applicable to the target population. The Commentary considered the quality of the study is likely to be moderate. Although the current study is more applicable than the comparative studies previously considered by MSAC, the Commentary considered there are some key concerns relating to the applicability of the population and procedures as they might relate to current or proposed clinical practice. These are summarised in Table 4.

Table 4 Key risk of bias and applicability concerns

Study characteristic	Proposed target population	Comments
Patients referred by memory disorder specialists.	Diagnosis of AD is equivocal following assessment by a specialist (or in consultation with a specialist).	The purpose for the referral was not provided in the article. It is unclear whether the patients referred for a scan represent those with equivocal diagnoses, or whether the diagnosis is more certain, and the purpose of the scan is for benchmarking / monitoring progression (Berti, Pupi & Mosconi 2011)[a].
Patients received SPECT and FDG PET within 12 months. The article does not state why patients received both scans, only that they did.	FDG PET is intended to be used for all patients referred for diagnosis of AD.	The study is retrospective – therefore, the scans were not planned for the purpose of the study. It remains unclear why patients received both SPECT and FDG PET. The concern is that, if SPECT provided a definitive diagnosis of AD or non-AD, what would be the purpose of the subsequent FDG PET scan? It is unclear from the article whether the identified patients represent all patients with an equivocal diagnosis or a particular sub-population in whom SPECT performed poorly (which would artificially raise the comparative accuracy of FDG PET). A question relating to this concern was presented to the applicant. The response is provided below.
Patients received a β-amyloid PET prior to late 2015.	NA	The article does not describe the circumstances under which β-amyloid PET was used in the Austin Molecular Imaging department. It is unclear whether it was only applied in patients without a definitive diagnosis of AD, or whether the use of β-amyloid PET was unrelated to the diagnosis of AD. A concern is that patients with clear non-AD pathology on SPECT or FDG PET would be less likely to be offered β-amyloid PET. This may have enriched the study population with patients diagnosed with AD.
Median time from SPECT to FDG PET is 92 days and median time from FDG PET to β-amyloid PET is 185 days.	NA	The study reports that there is a delay between SPECT and PET, and that this might be up to 12 months. As AD is progressive, the scan that is performed at a later stage may be more definitive. Furthermore, as FDG PET was closer in timing to the reference test, the two tests are more likely to be measuring the same severity of pathology.
Definition of the reference standard is unclear, and may or may not include information derived from prior tests.	NA	It is stated in the article that the reference standard is final diagnosis dichotomised as either AD or non-AD. The diagnosis is obtained from patient's research and clinical files in July 2019. This information would contain all information relating to SPECT, FDG PET and β-amyloid PET. However, at the time of reporting the β-amyloid PET results, it is stated that the expert reader was blinded to other data. The article notes that there was perfect correlation between AD and non-AD diagnoses derived from the clinical files (which included all information including scans) and from the β-amyloid PET scan results alone.

[a]Berti et al 2011 reported that "Due to its sensitivity to detect changes over time, [18F]FDG PET can be useful not only for AD diagnosis, but also to monitor disease progression and therapeutic interventions."

During preparation of the Commentary, the assessment group sought further information about whether the population in the published study represents the target population, or whether it represented a population with equivocal results following SPECT. Specifically, further information on why all patients received both SPECT and FDG PET; whether patients at the institution that received only SPECT or only FDG PET without receiving the other; and whether the population in the study is only those for whom SPECT provided equivocal results.

Further information provided by the applicant in response to this request clarified that SPECT was always done as it had an MBS item to support its use (while FDG PET does not) and if SPECT gave a "clear answer" then FDG PET was not done. However, this was noted by the

applicant as rare, citing that only 17 of the 143 patients included in the study received only SPECT. The Commentary considered this practice was not consistent with the results of the study, given the reported accuracy of SPECT indicates that it likely correctly identified many more patients than 17. In addition, reviewers from the same study reported "high confidence" in differentiating AD from other diagnoses 67.2% of the time for SPECT. Therefore, the Commentary noted it would appear that FDG PET was used even when SPECT gave a "clear answer".

The applicant stated that the population may include patients for whom SPECT results were equivocal, potentially resulting in an exaggerated difference between SPECT and FDG PET. However, the dual use of SPECT and FDG PET may not have entirely been due to the underperformance of SPECT, which may more closely align with the proposed population.

Table 5 Study population characteristics

Patient characteristics	Number of patients (% of cohort)
Age (years)	
<60	20 (15.9%)
60-69	47 (37.3%)
70-79	45 (35.7%)
>80	14 (11.1%)
Gender:	
- Male	65 (51.5%)
- Female	61 (48.5%)
Diabetes	
- Insulin dependent	3 (2.3%)
- Non-insulin dependent	10 (7.9%)
Referral diagnosis	
- Mild cognitive impairment	70 (55.6%)
- Dementia	51 (40.5%)
- Primary progressive aphasia	5 (3.9%)
β-amyloid deposition on PET	
- Negative	35 (27.8%)
- Positive	91 (72.2%)

Source: Table 1, Nadebaum et al 2020.

Key results

The primary endpoint nominated in the study was accuracy. The authors presented both the area under the receiver operator characteristic (AUROC) curve and an estimate of percentage accuracy. Accuracy of FDG PET and SPECT was measured against β-amyloid PET as the reference standard. As five nuclear medicine clinicians reviewed the FDG PET and SPECT scans, a positive scan (positive diagnosis of AD) was determined based on a majority. Results are shown in Table 6.

The accuracy of FDG PET was significantly greater than SPECT for differentiating AD from non-AD. The AUROC curve was greater for FDG PET compared with SPECT when using a majority read, and also for each individual reviewer. The improvement in accuracy was consistent across those with mild cognitive impairment and dementia, and was driven by an improvement in the sensitivity of FDG PET. There was no significant difference in the specificity of SPECT and FDG PET.

Intra-operator reliability was "high" for both FDG PET and SPECT (using the categories defined by Landis & Koch 1977). Of some concern is that inter-operator reliability for FDG PET was only "moderate", however there was no difference between these kappa scores for FDG PET and SPECT (0.48 vs 0.43).

The article also reported on the confidence of reviewers in making their diagnoses. On average, reviewers were more confident about their diagnoses when using FDG PET than SPECT. The Commentary noted that nuclear medicine clinicians were not blinded to the type of scan (or would identify SPECT from FDG PET). As rating confidence in a diagnosis is a subjective outcome, results may be biased.

MSAC previously raised the concern that it was unclear whether the same patients were diagnosed with SPECT and FDG PET. This has not been addressed in this study and remains an area of uncertainty. The Commentary considered a 2x2 table showing the concordance of SPECT and FDG PET would illustrate the number of patients diagnosed with AD with SPECT who are missed by FDG PET.

Table 6 Results presented in the Nadebaum et al (2020) key study

Outcome	18F-FDG PET	SPECT[f]	PET vs SPECT
Accuracy[a]			
- AUROC	0.71	0.61	P=0.02
- Combined (%)	75.4	54.0[e]	P=0.0001[g]
- MCI (%)	68.6	50.0	P=0.02
- Dementia (%)	81.4	65.1	P=0.1
Sensitivity (%)	75.8	42.9	P=0.0001
Specificity (%)	74.3	82.9	P=0.45
Reviewer confidence			
- Average confidence level (%)[b]	75.5	64.6	P<0.001
- Reported "high confidence" in differentiating AD from non-AD (%)[c]	83.1	67.2	P=0.001
Reproducibility			
- Intra-operator reliability, kappa (% agreement)[d]	0.79 (91.3)	0.70 (85.0)	P=0.12
- Inter-operator reliability, kappa (% agreement)	0.48 (75.4)	0.43 (73.2)	P=0.49

[a]Accuracy was measured using the majority read of the five reviewers.
[b]Reviewers graded their confidence on a scale from 0% (no confidence) to 100% (full confidence). It is not reported whether the scale was continuous or contained discrete bands of confidence.
[c]It is not reported what constitutes "high confidence".
[d]Intra-operator reliability was analysed using a single operator who reviewed the dataset twice, separated by 30 days.
[e]Not provided in the article. Accuracy (%) for SPECT was calculated from the sensitivity, specificity and prevalence. (Accuracy = sensitivity x prevalence + specificity x (1-prevalence). The accuracy for SPECT including the additional 17 patients who received SPECT but not FDG PET (n=143) was unchanged and reported in Table 2 of the article as 54.0%.
[f]It is unclear whether the analyses provided for SPECT are based on the 126 patients who received both SPECT and FDG PET, or whether they include the additional 17 patients who received only SPECT. The results presented in Table 2 are the same as those presented in the body of the article. However, Table 1 only presents the characteristics of the 126 patients who received both scans.
[g]P-value from Table 2, which included the full population (n=143 for SPECT).

The Commentary considered that although there are multiple concerns relating to the study design and conduct, the study reasonably establishes that the sensitivity of FDG PET is greater than that for SPECT, for the population and the circumstances of use within the study. If the population represents a selected patient group for whom a diagnosis using SPECT was equivocal, then the large improvement in sensitivity (favouring FDG PET) may not be replicated in the target population. In addition, the delay between SPECT and FDG PET, and the closer timing between FDG PET and β-amyloid PET, may have increased the likelihood of diagnosis with FDG PET and concordance with β-amyloid PET.

While the accuracy of FDG PET may be greater than SPECT, the Commentary noted that it remains unclear whether the additional diagnoses are the same spectrum of disease or whether the additional sensitivity is derived from identifying patients at earlier stages of AD. If there is a change in the spectrum of the disease diagnosed, it is unclear whether the earlier detection of the disease would result in: meaningful benefit to the patient; added cost to the patient; added cost to the Australian Government; or cost-effective use of downstream therapies.

The ADAR provided arguments to support that earlier diagnosis may result in additional benefit to the patient and to society, however these benefits have not been quantified, and any change in healthcare resources to achieve these benefits have not been costed.

12. Economic evaluation

The ADAR proposed a cost-minimisation approach based on the fee for FDG PET being the same as for SPECT. The ADAR stated that this approach was decided following discussion with nuclear medicine specialists and after accounting for the cost of the FDG and CBF tracers for PET and SPECT, respectively, and the comparative scanning times.

Cost-minimisation
The cost-minimisation approach assumed cost-neutrality to the MBS if FDG PET purely substitutes for SPECT in the existing MBS SPECT population. As the services required prior to and following a FDG PET and a SPECT scan were expected to be the same, no additional or concomitant MBS services were costed.

The Commentary indicated that, although a cost-minimisation approach would seek to implement a new technology for no additional expense to the health care system, the key evidence suggested an increase in the sensitivity of FDG PET compared with SPECT, which would result in a greater number of diagnoses of AD. In addition, the Commentary considered it was unclear whether the utilisation of FDG PET would be the same as the current utilisation of SPECT.

The Commentary considered the approach taken in the ADAR was likely to be acceptable based on the following assumptions.

- More accurate diagnosis of AD would permit more appropriate interventions (including AChEIs), and would reduce inappropriate interventions in patients found not to have AD.
- Earlier diagnosis of AD would permit earlier pharmacological intervention and might be associated with greater opportunity to prepare for more progressive states of the disease.
- AChEIs are currently PBS listed for the treatment of AD, and, based on a recent NICE review (National Institute for Health and Care Excellence 2011), are likely to be highly cost-effective or cost-saving.

Therefore, the Commentary considered that, assuming that increased use of FDG PET compared with SPECT may result in more appropriate and earlier interventions that are likely to be cost-effective, adopting the SPECT fee for FDG PET may be conservative.

Change in the spectrum of disease
The ADAR stated that FDG PET may result in earlier or more accurate diagnosis of AD. If FDG PET is more accurate (particularly more sensitive), as reported in the key study, the characteristics of some of the subjects diagnosed with AD by FDG PET may differ from those diagnosed with SPECT.

The ADAR described, but did not quantify, the following potential benefits associated with an earlier diagnosis of AD:

- reduction in repeat testing
- earlier preparation to prolong home-based care
- reduce crisis admissions to hospitals and nursing homes
- appropriate use of medication
- more opportunity to participate in clinical trials.

The Commentary noted the extent of any change in the spectrum of the disease diagnosed with FDG PET compared to SPECT is uncertain. In addition, in most cases, diagnosis would simply be brought forward due to a more sensitive test, rather than an increase in the number of subjects who are ultimately diagnosed. The ADAR also conceded that the value of earlier or more accurate diagnosis is difficult to quantify.

Change in the number of patients
The use of FDG PET may be more desirable than SPECT, given its improved sensitivity, and the recent inclusion of biomarkers (including FDG PET) into the United States' National Institute on Aging and Alzheimer's Association (NIA-AA) definition of "Alzheimer's disease". The NIA-AA definition states:

> The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined in vivo by biomarkers and by post-mortem examination, not by clinical symptoms (Jack Jr et al. 2018).

The NIA-AA guidelines are intended as a "research framework", as the recommendations are intended to be used in patients involved in observational or interventional research. An "in vivo" biomarker includes FDG PET. The NIA-AA recommended the AT(N) classification system, which describes the likely diagnosis of AD based on (A) amyloid-related biomarkers, (T) tau-related biomarkers, and (N) neurodegeneration-related biomarkers. The neurodegeneration category of biomarkers includes anatomic MRI, FDG PET and CSF total tau. The NIA-AA recognises the limitations of the (N) biomarker group (hence it is presented in parentheses), and states that a diagnosis of AD based on neurodegeneration biomarkers alone is not possible.

While the use of β-amyloid PET appears to be a recognised biomarker for the diagnosis of AD, it is less likely to be used than FDG PET. β-amyloid PET tracers are proprietary and costly, compared with FDG PET tracers that are relatively inexpensive, and delivered to nuclear medicine departments around Australia on a daily basis.

Any increase in the use of FDG PET compared with currently reimbursed SPECT is difficult to estimate, but has been explored below in Section 13.

13. Financial/budgetary impacts

Estimates of the utilisation of MBS-funded FDG PET for AD were made using a market share approach (the nominated base case) and three epidemiological approaches. The market share approach began with the current number of SPECT services undertaken and determined the likely proportion that will be replaced by FDG PET. The epidemiological approaches estimated the eligible population from the incident diagnoses of dementia in Australia. A summary of the results for all approaches is included in Table 7 below.

Base case (Approach 1)
The market share approach was to assume that the majority of current SPECT services are used for the assessment of dementia. An Australian article in 2013 explained that "the most common use of cerebral perfusion studies is in the differential diagnosis of suspected dementia in patients presenting with cognitive impairment"(Lee, Harvey & Khafagi 2013). The article explains that SPECT can be used for localising the epileptogenic focus in patients with refractory epilepsy, but that this indication is uncommon, and for the investigation of cerebrovascular disease, but that the narrow therapeutic time window for the management of stroke prohibits its use in the acute setting.

Table 7 Base case estimate of the eligible population for testing using observed MBS services for SPECT

STEP	Estimate	Source
1	Total number of SPECT services performed each year	MBS utilisation reports for MBS item 61402. Extrapolated based on the estimated growth of dementia.
2	80% of all SPECT services are used for the differential diagnosis of dementia	Assumption based on the Australian article noting that the majority of SPECT is used for this purpose (Lee, Harvey & Khafagi 2013).

Abbreviations: MBS, Medicare Benefits Schedule; SPECT, single-photon emission computed tomography.

The annual use of SPECT services has increased in a reasonably linear pattern in recent years. As the incidence of dementia has also increased in a linear pattern, forecasting the increase in the use of SPECT was done with a single linear equation. The resulting estimate was an increase of approximately 250 services per year. This is roughly a 3.8% increase in SPECT imaging from 2019 to 2020.

Table 8 Estimated eligible population for testing (base case)

Step	Description	2021	2022	2023	2024	2025	2026
#1	Projected use of SPECT in the absence of FDG PET	7,193	7,450	7,707	7,964	8,221	8,478
#2	Assume that the majority of SPECT services (80%) are for dementia	5,754	5,960	6,165	6,371	6,576	6,782

Abbreviations: FDG PET, fluorodeoxyglucose positron emission tomography; MBS, Medicare Benefits Schedule; SPECT, single-photon emission computed tomography
Projected numbers based on linear growth using MBS item report data (61402) from 2000 to 2019.

Other approaches

As there were no robust Australian data to inform the likely testing population, several epidemiological approaches were used to provide a range of estimates. The final estimates of the eligible population in 2021 range from 3,028 services (using an approach similar to that used in the 1195 Assessment Report) up to 13,398 services assuming that 13.3% of all incident dementia diagnoses are "equivocal". The Commentary noted that it was difficult to determine which approach results in the most likely estimate; however, the results for Approach 1 are similar to the average across the four approaches taken.

Table 9 Results of alternative approaches for estimating the eligible population for testing

	2021	2022	2023	2024	2025	2026
APPROACH 1 – base case market share approach (from Table 8)						
Assume that the majority of SPECT services (80%) are for dementia	5,754	5,960	6,165	6,371	6,576	6,782
APPROACH 2 – epidemiological approach						
Assume 5% of all dementia diagnoses are equivocal	5,046	5,232	5,412	5,600	5,795	5,994
Assume 5% of all AD diagnoses represent the number of equivocal dementia diagnoses	3,028	3,139	3,247	3,360	3,477	3,596
Assume 5% of all dementia diagnoses in subjects ≥65 are equivocal, and 50% of diagnoses <65 are equivocal	7,757	7,991	8,211	8,427	8,634	8,830
APPROACH 3 – epidemiological approach						
Pooled use of nuclear imaging across specialist and primary care settings	5,230	5,422	5,609	5,804	6,005	6,212
APPROACH 4 – epidemiological approach						
Proportion of dementia diagnoses that are regarded as "possible AD" (interpreted as equivocal)	13,398	13,890	14,370	14,870	15,385	15,914
Assume that the Beach et al 2012 study is only representative of a specialist setting	5,493	5,695	5,892	6,097	6,308	6,525

Abbreviations: AD, Alzheimer disease; SPECT, single-photon emission computed tomography.
Source: see Tables in Appendix 2 of the Commentary for calculations and sources.

The proposed MBS fee for FDG PET is the same as the current fee for SPECT (MBS 61402). It has been assumed that all FDG PET services would be performed in an outpatient setting. Using the current MBS services for 61402 (SPECT), the average MBS benefit per service is $566.40 (based on the 2019 calendar year), or 93.6% of the MBS schedule fee. To achieve this benefit, approximately 85% of services would be bulk billed (attracting a 95% fee) and 15% would receive a fee of $520.35 (equivalent to $605.05 minus the Greatest Permissible Gap of $84.70). The estimated MBS benefits for FDG PET over six years are summarised in Table 10.

Table 10 Estimated total MBS expenditure for FDG PET over 6 years

Step	Description	2021	2022	2023	2024	2025	2026
#1	Base case eligible testing population	5,754	5,960	6,165	6,371	6,576	6,782
#2	FDG PET uptake in eligible population	50%	60%	70%	80%	90%	100%
#3	Number of FDG PET services per year	2,877	3,576	4,316	5,097	5,919	6,782
#4	MBS benefit for the proportion of FDG PET that is bulk billed (attracting 95% fee)	$1,405,676	$1,747,078	$2,108,569	$2,490,149	$2,891,818	$3,313,575
#5	MBS benefit for the proportion of FDG PET that is not bulk billed	$224,563	$279,104	$336,853	$397,812	$461,981	$529,358
#6	Total MBS benefit for FDG PET	$1,630,239	$2,026,182	$2,445,422	$2,887,961	$3,353,798	$3,842,934

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

The total MBS expenditure associated with the MBS listing of FDG PET was estimated to increase from $1.6 million to $3.8 million over six years.

Estimate of net financial implications to the MBS
If FDG PET is listed on the MBS, it was assumed in the base case that each use of FDG PET would replace SPECT on a one-to-one basis, and that no increase in demand will occur. As such, the base case financial implications to the MBS were assumed to be zero.

Identification, estimation and reduction of uncertainty
The key areas of uncertainty included the estimate of the size of the eligible population to be tested, and whether FDG PET would be used beyond the current use of SPECT.

External factors, such as an increased focus on dementia in clinical practice, new guidelines or novel treatments for early dementia, may have large implications on the extent of use of FDG PET. However, such external factors may have the same impact on SPECT.

Two sensitivity analyses were undertaken.

- The first analysis assumed that SPECT is replaced in 80% of cases. The testing population remains the same, however 20% of patients will receive both SPECT and FDG PET (this would have to occur in separate calendar years).
- The second analysis assumed that FDG PET is used in greater number of diagnoses than SPECT is forecast to have been used in. This may occur if specialists consider FDG PET to be a more useful diagnostic tool.

Table 11 Sensitivity analyses

Step	Description	2021	2022	2023	2024	2025	2026
Sensitivity analysis 1 (20% of patients receive both FDG PET and SPECT)							
#1	Total MBS benefits for FDG PET	$1,630,239	$2,026,182	$2,445,422	$2,887,961	$3,353,798	$3,842,934
#2	Total MBS savings for replaced SPECT (@ 80% replacement)	$1,304,191	$1,620,945	$1,956,338	$2,310,369	$2,683,039	$3,074,347
#3	Net financial impact of successful listing of FDG PET on the MBS	$326,048	$405,236	$489,084	$577,592	$670,760	$768,587
Sensitivity analysis 2 (uptake of FDG PET is 50% higher than base case)							
#4	Tested population for FDG PET	4,316	5,364	6,474	7,645	8,878	10,173
#5	Total SPECT services replaced	2,877	3,576	4,316	5,097	5,919	6,782
#6	Net MBS cost of higher uptake of FDG PET	$815,120	$1,013,091	$1,222,711	$1,443,981	$1,676,899	$1,921,467
#7	Indicative growth in combined FDG PET and SPECT services	125%	130%	135%	140%	145%	150%

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

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Interpretation of the Nadebaum et al. 2020 analytical validity comparison of SPECT and FDG PET	The Nadebaum et al. 2020 study is larger and more applicable than the previously considered studies; however, there are some residual concerns relating to the applicability of the population. Due to the uncertainties associated with the key study, the true difference in diagnostic accuracy of FDG PET and SPECT is uncertain, but FDG PET does appear to have superior sensitivity over SPECT.
Improved MBS item descriptor	The proposed item descriptor is largely consistent with MSAC's previous advice. The proposed population differs from "suspected early stage Alzheimer disease", which may increase the size of the population. The reference to aetiology/ies in the item descriptor should be clarified as being "of dementia" (as suggested by the Department). MSAC should also consider restricting the MBS item to three FDG PET scans for the diagnosis of AD per lifetime (as suggested by the applicant).
Understanding full consequences of listing FDG PET	Consistent with the previous MSAC suggestion, the re-application adopted a cost-minimisation approach by proposing FDG PET be listed at the same fee as SPECT. If MSAC accepts that FDG PET is more sensitive than SPECT, the overall effect of listing FDG PET could mean increased costs and better outcomes from increased use of PBS-subsidised medicines.
Cost-minimisation from the patient's perspective	Cost-neutrality of imaging for patients is claimed but not certain. Changes in downstream use of health care resources could result in other out-of-pocket costs.
Financial implications	The use of mixed sources and multiple approaches reflects the uncertainty in the financial estimates, and it is likely that the listing will increase costs to the MBS. This is because awareness of the superior accuracy of and greater confidence in the results of FDG PET over SPECT may encourage greater uptake of FDG PET than SPECT. However, this growth will be difficult to discern beyond the likely bigger growth in the population eligible for testing due to the changing definition of AD and an ageing population in Australia, which are not specific to FDG PET.

ESC discussion

ESC noted that this is a reapplication for the Medicare Benefits Schedule (MBS) listing for the use of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) to establish a diagnosis of Alzheimer disease (AD) where other diagnostic methods are inconclusive. The

initial application for FDG PET for the diagnosis of AD (Application No. 1195) was considered by MSAC at its April 2015 meeting. MSAC did not support public funding because of uncertain cost-effectiveness compared with single-photon emission computed tomography (SPECT) due to weak clinical comparative data and unclear translation of imaging performance to improved health outcomes.

ESC noted that the reapplication focussed on MSAC's concerns and advice from April 2015. As a result, some of the information expected in an application was not provided.

ESC noted the support from Dementia Australia, which stated more timely diagnosis and equity in accessing PET as the main benefits for consumers. Another benefit noted for consumers was the reduction in patient and family distress, as a result of the certainty a diagnosis can offer and the opportunity for earlier intervention.

ESC noted the amendments to the MBS item descriptor as proposed by the applicant (Table 2). ESC noted the applicant's request to remove suspected "early stage" from the MBS item descriptor, with the rationale being that the use of "early stage" would exclude cases where clinical evaluation is equivocal due to language and cultural issues, or other factors that cause unreliable performance on cognitive tests. ESC considered this was reasonable. ESC noted the Commentary's concern that this may increase the population considerably, given the main criterion left to limit eligibility in the item descriptor would be the subjective term "equivocal" in the context of the prior clinical evaluation and structural brain imaging, however ESC considered that this was not a major issue.

ESC noted the Commentary's suggestion that recommendations of the Amyloid Imaging Task Force may be relevant to assist in the selection of patients for FDG PET in Australia, where it may be used in place of β-amyloid PET. ESC considered these recommendations were relevant and appropriate for consideration by MSAC. ESC also noted that NICE had updated its guidance for NHS England in June 2018 on the assessment, management and support of people living with dementia and their carers. ESC considered that, consistent with the proposed MBS item descriptor, Recommendation 14 of this guidance was particularly relevant to the consideration of this reapplication, given it recommends further diagnostic tests should only be considered if:

- it would help to diagnose a dementia subtype and;
- knowing more about the dementia subtype would change management.

ESC supported the suggestions in the Commentary-proposed MBS item descriptor (Table 3) was the most appropriate item descriptor and agreed with the applicant's Pre-ESC Response, which both supported use of this item descriptor and also suggested FDG PET for diagnosis of AD should be limited to three scans per lifetime. ESC also agreed with the Department's suggestion clarifying that reference to aetiology/ies in the item descriptor should be "of dementia".

ESC noted that the reapplication included a retrospective analysis of paired SPECT and FDG PET patient data from the Austin Health Department of Molecular Imaging, as requested by MSAC. This published study (Nadebaum et al. 2020) of 126 patients demonstrated an improvement of accuracy, sensitivity and reader confidence with FDG PET compared with SPECT, supporting the clinical claim of superiority. ESC considered this study was larger and more applicable than the studies included in the previous application. However, ESC had some residual concerns about the applicability of the population and procedures as they might relate to current or proposed clinical practice:

- The purpose for the referral was not provided in the article. ESC noted the analysis used a convenience population (via participation in the β-amyloid PET study before late 2015). Therefore, it was unclear whether the patients referred for an FDG PET scan represented those with equivocal diagnoses (i.e. the proposed population), or whether the diagnosis was more certain and the purpose of the scan in the study was for benchmarking or for monitoring progression. ESC noted the Pre-ESC Response affirmed that scans in the study were not performed for benchmarking or for monitoring progression.
- It was unclear why or which patients received both SPECT examining cerebral blood flow (CBF) and FDG PET. No rationale was presented for why a patient may have one scan or the other, or both scans.
- It was unclear from the article whether the identified patients represented all patients with an equivocal diagnosis as defined for the proposed item descriptor or a particular subpopulation for whom SPECT also performed poorly. Exclusion of patients for whom SPECT performed well would artificially raise the comparative accuracy of FDG PET.
- Regarding the use of β-amyloid PET as the reference standard test to specify inclusion in the study population, ESC was concerned that patients with clear non-AD pathology on SPECT or FDG PET would have been less likely to be offered β-amyloid PET, which may have enriched the study population with patients diagnosed with AD.

ESC noted the applicant's clarification that SPECT was always performed in the study because it had an MBS item to support its use and, if SPECT gave a "clear answer", then FDG PET was not performed. However, ESC considered this was not consistent with the purpose of the study, given 17 of the 143 patients included in the study received SPECT only, and were not included in some analyses of the study. This would result in these study results for SPECT being underestimated, and thus a bias in favour of FDG PET. However, the reported sensitivity for SPECT of 42.9% in the analysis stated as including these 17 patients was significantly less than the reported sensitivity for FDG PET of 75.8% stated as excluding these 17 patients (P=0.0001). Overall, ESC agreed with the Commentary that the size of the true difference in diagnostic accuracy of FDG PET and SPECT was uncertain.

ESC noted that, in the study, the median time from SPECT to FDG PET was 92 days and median time from FDG PET to β-amyloid PET was 185 days. ESC noted the Commentary's concern that the closer timing of FDG PET to β-amyloid PET may have increased concordance. The applicant's Pre-ESC Response argued that the delay is a fraction of the natural history of AD and that it was unlikely that timing affected the study results. The Pre-ESC Response also noted other studies where these scans were performed within 1 month of each other that demonstrated a similar superiority for FDG PET. ESC considered this difference in median time from SPECT to FDG PET and FDG PET to β-amyloid PET was unlikely to have significantly affected the results of the study.

ESC noted the Commentary's concern regarding the perfect correlation between AD and non-AD diagnoses derived from the clinical files and the β-amyloid PET scan results alone. At the time of reporting the β-amyloid PET results, it was stated that the expert reader was blinded to other data. The applicant noted in the pre-ESC response that although the expert reader was blinded to other data at the time of reporting the β-amyloid PET results, the treating clinicians were not blinded and had access to all information contained in the patient's files. ESC considered the perfect correlation between AD and non-AD diagnoses derived from the clinical files and the β-amyloid PET scan results was therefore likely due to clinicians being unblinded to the results of the β-amyloid PET scan. ESC also noted that β-amyloid PET is an

imperfect reference standard, as it can produce false-positive results from a clinical perspective, although ESC was not presented with any data regarding the specificity of β-amyloid PET.

ESC noted that accuracy was the key result reported in the study, presented as both the area under the receiver operator characteristic curve (AUROC) and an estimate of percentage accuracy. ESC noted the results of the study that showed the accuracy of FDG PET was significantly greater than SPECT for differentiating AD from non-AD, which was driven by improved sensitivity of FDG PET compared to SPECT, with no significant difference reported in specificity. ESC also noted the Commentary's concern regarding the moderate intra-operator readability reported for FDG PET, however it noted there was no difference between the kappa score for FDG PET and SPECT (0.48 vs 0.43) (Table 6).

ESC considered the claim of superior accuracy of FDG PET over SPECT was reasonable, however it noted the remaining uncertainty around whether the additional diagnoses from FDG PET compared with SPECT are within the same spectrum of disease or whether the additional sensitivity of FDG PET is derived from identifying patients at earlier stages of AD.

ESC noted MSAC did not require the reapplication to address whether earlier detection of AD would result in meaningful benefit to the patient. ESC noted the ADAR provided arguments to support that earlier diagnosis of AD may result in additional benefits to the patient and society. However ESC considered that any health improvements of earlier diagnosis remain uncertain, noting they have not been quantified, and any potential subsequent changes to health care have not been costed.

ESC noted the initial application (1195), presented a cost-utility analysis where FDG PET was dominant over SPECT over a five-year time horizon. MSAC had considered the model's results were optimistic and had suggested that any reapplication should adopt a cost-minimisation approach, considering costs to both the MBS and patients.

ESC noted the reapplication reduced the fee proposed for FDG PET in the initial application to match that of SPECT in the reapplication ($605.05), presenting a cost-minimisation approach based on a 1:1 replacement of SPECT by FDG PET. This approach led to cost neutrality for diagnostic imaging on a per patient basis. This assumed no change would occur to co-administered services, which ESC considered may be reasonable given MSAC's previous suggestion, but it also assumed no change in downstream healthcare utilisation, which ESC considered was uncertain.

ESC noted potential consequences of the substitution of SPECT with FDG PET, if it were to lead to more accurate diagnosis of AD, including:

- enabling earlier/more appropriate pharmacological interventions
- reducing inappropriate interventions in patients who do not have AD
- reducing repeat testing
- earlier preparation to prolong home-based care
- reducing crisis admissions to hospitals and nursing homes.

ESC considered the extent and value of these potential benefits was uncertain.

Given the superior sensitivity of FDG PET versus SPECT, ESC considered that a cost-minimisation approach may not be appropriate, and that further modelling of the cost-effectiveness consequences of replacing SPECT with FDG PET may be beneficial for decision-making. ESC considered that, if MSAC accepts that FDG PET is more sensitive

than SPECT, the overall effect could mean increased costs and better outcomes from increased use of PBS-subsidised medicines.

ESC considered that charging practice may differ across SPECT and FDG PET as this may be affected by the demand for these imaging technologies and their supply. From the patient's perspective, this may result in greater out-of-pocket costs for FDG PET.

ESC noted the base case estimates of the utilisation of MBS-funded FDG PET for AD used a market share approach, with three alternative epidemiological approaches also presented. ESC noted that, without Australian data on the number of equivocal diagnoses of dementia, the size of the population eligible for testing and the financial implications were both uncertain.

ESC considered that the estimated uptake of FDG PET was another area of uncertainty. As many factors influence clinical decisions on which diagnostic test to use, such as availability and capacity of the test, and clinical preference, there may be reasons to assume there would not be a 100% substitution of SPECT with FDG PET. Instead, ESC also considered the uptake of FDG PET may be greater than the current utilisation of SPECT, given awareness of the superior accuracy of and greater confidence in the results of FDG PET over SPECT. However, this growth will be difficult to discern beyond the likely bigger growth in the population eligible for testing due to the changing definition of AD and an ageing population in Australia, which are not specific to FDG PET.

Given the key areas of uncertainty included the estimate of the size of the eligible population to be tested, and whether FDG PET would be used beyond the current use of SPECT, two sensitivity analyses were presented. ESC noted that the sensitivity analysis no longer resulted in cost-neutrality being achieved. ESC considered it was reasonable to expect that changes to other Australian Government funded health care resources may also occur, such as use of specialist services and prescription of acetylcholinesterase inhibitors (AChEIs).

15. Other significant factors

Reference standard
The key study performed in the Nuclear Medicine Department of Austin Health reported the use of β-amyloid PET as a reference standard. The study reported that this is consistent with international recommendations, and the cited article states:

> In conclusion, amyloid PET is a validated pathophysiological marker for fibrillar amyloid, particularly neuritic plaques and amyloid angiopathy. In view of the good correlation with post-mortem diagnosis of AD, a positive amyloid PET can be considered, by extension, as a good marker of Alzheimer's pathology (Dubois et al. 2014).

There is substantial evidence to support the diagnostic accuracy of β-amyloid PET. However, there are several different β-amyloid PET tracers. The earliest identified β-amyloid tracer for imaging AD is N-methyl-[11C]2-(4′-methyl-aminophenyl)-6-hydroxybezothiazole, or ^{11}C-PiB (Pittsburgh Compound-B)(Klunk et al. 2004), however it has the disadvantage of a 20 minute half-life, limiting routine use to nuclear medicine departments with on-site cyclotrons. The images of ^{11}C-PIB PET have been compared with post-mortem amyloid deposits and found to be correlated (Ikonomovic et al. 2008). Subsequently, several ^{18}F tracers (which have longer 110 minute half-lives) have been developed including ^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben and NAV4694. The key study stated that the amyloid tracers used included ^{11}C-PiB and all of the ^{18}F tracers mentioned above. A comparison of the ^{18}F-based tracers with ^{11}C-PiB (based on small studies) was reported in a publication of the

Amyloid Imaging Task Force[1], and showed that concordance was high or 100% (Johnson et al. 2013). These studies were based on small numbers.

The Commentary noted that a major issue that has complicated the understanding of a reference standard is the rapidly changing definition of AD. Over recent times, the definition of AD has moved from a clinical definition, to a clinicobiological definition (Dubois et al. 2010) to a purely biological definition (Jack Jr et al. 2018). This has had some major impacts on how diagnostic studies are interpreted. If the objective of the diagnostic technology is to identify the underlying pathology, regardless of the presence or absence of the clinical syndrome, then β-amyloid PET is likely a very good reference standard. However, if used in the general population, β-amyloid PET will identify a proportion of subjects with the underlying pathology, but without any clinical syndrome features. This may be less of a concern if it is used only in those with clinical symptoms to determine whether those symptoms can be attributed to an underlying AD pathology. The biological definition of AD, and the detection of the underlying pathological process using biomarkers, is likely more relevant if clinical practice develops interventions that are intended to target the underlying pathology.

In support of the diagnostic accuracy of β-amyloid PET, several studies have reported on the ability of the scans to differentiate between AD and healthy controls (Rowe et al. 2007), the ability to predict the progression of mild cognitive impairment to symptomatic AD (Villemagne et al. 2011; Zhang et al. 2014), and the ability to distinguish from other forms of dementia (Rabinovici, G et al. 2011). However, while the sensitivity is high against both a histopathological and clinical definition of AD, specificity is not high against a clinical definition. Therefore, the accuracy of β-amyloid PET for diagnosing AD as a syndrome in an unselected population is lower.

The Commentary considered that, for the purposes of the key study, where included subjects have clinical symptoms, the use of β-amyloid PET as a reference standard was appropriate.

Change in management
MSAC previously noted concern relating to the quality of evidence regarding change in management. The Commentary considered the relevance of this question was lessened given the claim of non-inferiority, and the proposed equivalence of the MBS fee to SPECT.

The use of FDG PET (in place of SPECT) may result in changes in the number and type of patients diagnosed via the following mechanisms:

- increase in accuracy (sensitivity) of FDG PET compared with SPECT would result in an increase in diagnoses (which may represent earlier diagnosis)
- increase in the use of FDG PET compared with the current use of SPECT may occur should FDG PET be reimbursed. The magnitude of change in use is uncertain. However, the ADAR suggested that clinicians know that FDG PET is superior to SPECT for the detection of AD. Despite FDG PET not being reimbursed, a survey has identified that it is used almost as commonly as SPECT, which does receive reimbursement (Black et al. 2019).

Therefore, if FDG PET results in a greater number of diagnoses, and is used more commonly, there is some indication that there is value in early or more accurate diagnosis.

There is now substantial evidence supporting both a change in diagnostic thinking and a change in management following a definitive diagnosis of AD. Evidence has been generated

[1] A joint task force of the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association.

for both diagnosis via β-amyloid PET and FDG PET (Getsios et al. 2012; Hornberger et al. 2017; Rabinovici, GD et al. 2019; Rice & Bisdas 2017). Change in management evidence typically relates to the use of AChEIs.

The ADAR stated that consumers and clinicians ascribe great value to earlier and more accurate diagnosis of AD to facilitate early interventions that appear to slow cognitive decline. It was proposed that early diagnosis may lead to better preparation of home supports and access to respite services, delaying the move into permanent residential care. The ADAR noted that a high proportion of permanent residential care admissions are due to dementia, and stated that the cost of residential care for AD costs over $12 billion per year. Therefore, even a small delay in the use of residential care may result in substantial savings.

The ADAR noted the benefits in early use of AChEIs with early AD. The ADAR also noted that there are some data to show that earlier diagnosis is important to facilitate lifestyle and dietary intervention, which appears to be recommended by clinicians (Cummings et al. 2019).

Finally, the ADAR noted that earlier diagnosis may increase participation in clinical trials, which it noted generated income for participating health services.

The Commentary considered evidence reporting on the magnitude of benefits associated with a change in diagnosis or a change in management is lacking, and it is unlikely that an effect could easily be quantified. The Commentary noted the ADAR did not address possible negative consequences associated with earlier diagnosis. However, as patients are not asymptomatic at the point of testing, harms associated with chance findings are less relevant.

16. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

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