# MSAC Application 1738.1

## Investigations supporting use of PBS subsidised lecanemab in people with mild cognitive impairment and mild dementia due to Alzheimer's disease

### Applicant: Eisai Australia Pty Ltd

# PICO Confirmation

# Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

**Table 1 PICO for amyloid-beta pathology testing and *APOE* genotyping to determine eligibility for lecanemab in patients with mild cognitive impairment and mild dementia due to suspected Alzheimer's disease**

| Component | Description |
|---|---|
| Population | **Test**: Patients with mild cognitive impairment (MCI) and mild dementia due to suspected Alzheimer's disease (AD)<br>**Drug**: Patients with mild cognitive impairment and mild dementia due to AD who have tested positive for amyloid beta (Aβ) pathology and negative for apolipoprotein E *(APOE)* ε4 homozygosity |
| Prior tests | Brain magnetic resonance imaging (MRI) scan and basic dementia screen that includes blood tests for routine haematology, electrolytes, calcium, glucose, kidney, liver, and thyroid function, and vitamin B12 and folate levels for all patients with MCI[a,b]. |
| Intervention | **Test**:<br>• Aβ pathology testing using the following methodologies<br>  ○ Amyloid positron emission tomography (PET) of the brain<br>  ○ Immunoassay assessment of t-tau/Aβ[1-42] in cerebrospinal fluid (CSF)<br>  ○ Immunoassay assessment of p-tau217 in plasma<br>• *APOE* ε4 genotype testing by assessment of DNA isolated from plasma<br>• Brain MRI<br>  ○ At initiation of treatment (in the absence of a recent available MRI)<br>  ○ Monitoring during lecanemab treatment for Amyloid-Related Imaging Abnormalities (ARIA)<br>**Drug**: lecanemab |
| Comparators | **Test:**<br>• Amyloid PET scan: no amyloid PET scan and standard medical management.<br>• Immunoassay assessment of t-tau/Aβ[1-42] in CSF*:* amyloid PET or no testing.<br>• Immunoassay assessment of p-tau217 in plasma*:* amyloid PET or no testing.<br>• *APOE* ε4 genotype testing: no testing and standard medical management.<br>• Brain MRI for initiation of treatment: Currently MBS funded item for brain MRI scan.<br>• Brain MRI for monitoring: no monitoring (and no lecanemab treatment).<br>**Drug**:<br>• Main comparator: standard of care.<br>• Near market comparator: donanemab. |

| Component | Description |
|---|---|
| Reference standard | • Amyloid PET scan: post-mortem autopsy.<br>• t-tau/Aβ[1-42] in CSF: amyloid PET scan.<br>• p-tau217 in plasma: amyloid PET scan.<br>• *APOE ε4* genotype testing: Sanger sequencing. |
| Clinical utility standard | The amyloid PET or CSF test and testing conditions employed in the pivotal studies, including the PET tracer used and centralised visual interpretation |
| Outcomes | **Test-related outcomes:**<br><br><u>Amyloid PET of the brain</u><br><br>• Diagnostic performance<br>  ○ Sensitivity, specificity against reference standard, positive likelihood ratio, negative likelihood ratio<br>  ○ Concordance between amyloid PET as conducted in Australia and the evidentiary standard<br>  ○ Yield of testing (proportion of patients identified as having brain amyloid deposition)<br>  ○ Test reliability/validity<br><br>• Test safety<br>  ○ Levels of radiation exposure, rate and nature of adverse events associated with the PET tracer and scanning.<br>  ○ Psychological and physical harms of amyloid PET test results<br><br>• Change in management /clinical utility<br>  ○ Proportion of patients commencing lecanemab following testing<br>  ○ Proportion of patients with a change in diagnosis following testing<br>  ○ Proportion of patients continuing/discontinuing/changing treatment following amyloid PET<br><br>• Healthcare system outcomes<br>  ○ Capacity of healthcare facilities for the increased requests of PET scans from specialists<br>  ○ Waiting times and access to PET services<br>  ○ Equity of access (rural, regional and Indigenous populations)<br><br>• Economic outcomes<br>  ○ Cost per test<br>  ○ Cost-effectiveness<br><br><u>t-tau/Aβ[1-42] in CSF</u><br><br>• Diagnostic performance<br>  ○ Sensitivity and specificity (where evidence available)<br>  ○ Positive, negative, and overall percentage agreement with amyloid PET<br>  ○ Turnaround time |

| | |
|---|---|
| | • Safety<br>  ○ Lumbar puncture-related complications<br>  ○ Other adverse events and harms of CSF testing and test results<br>• Change in management /clinical utility<br>  ○ Proportion of patients commencing lecanemab following testing<br>  ○ Proportion of patients with a change in diagnosis following testing<br>  ○ Proportion of patients continuing/discontinuing/changing treatment following t-tau/Aβ[1-42] in CSF<br>• Healthcare system outcomes<br>  ○ Capacity for lumbar puncture services (infrastructure)<br>  ○ Laboratory capacity<br>  ○ Capacity of health professionals for the increased number of patients requiring lumbar puncture<br>  ○ Capacity of laboratories for the increased amount of CSF samples for testing<br>• Economic outcomes<br>  ○ Cost per test<br>  ○ Cost-effectiveness<br><u>p-tau217 in plasma</u><br>• Diagnostic performance<br>  ○ Sensitivity and specificity (compared with amyloid PET)<br>  ○ positive, negative, and overall percentage agreement with amyloid PET<br>  ○ Turnaround time<br>• Safety<br>  ○ Test-related adverse events<br>• Change in management /clinical utility<br>  ○ Identification of patients likely to have amyloid pathology<br>  ○ Impact on subsequent use of amyloid PET/CSF testing<br>  ○ Proportion of patients proceeding to confirmatory testing<br>  ○ Impact on treatment eligibility decisions<br>• Healthcare system outcomes<br>  ○ Laboratory capacity<br>  ○ Impact on access to biomarker testing<br>• Economic outcomes<br>  ○ Cost per test<br>  ○ Cost-effectiveness<br><u>*APOE* ε4 genotype testing</u><br>• Safety<br>  ○ Test-related adverse events |

| | |
|---|---|
| | • Change in management /clinical utility<br>  ○ Impact on treatment eligibility decisions (proportion of patients commencing lecanemab following testing)<br>  ○ Impact on ARIA risk stratification<br>• Healthcare system outcomes<br>  ○ Laboratory capacity<br>• Economic outcomes<br>  ○ Cost per test<br>  ○ Cost-effectiveness<br><u>Brain MRI (for baseline testing and monitoring purposes)</u><br>• Safety<br>  ○ MRI-related adverse events<br>  ○ Adherence/compliance with monitoring strategy<br>• Change in management /clinical utility<br>  ○ Impact on treatment management following MRI findings (treatment interruption, suspension or discontinuation resulting from MRI findings)<br>  ○ Impact on treatment management after no MRI (e.g. non-compliance, unable to undergo MRI)<br>• Healthcare system outcomes<br>  ○ MRI workforce and scanner capacity<br>  ○ Waiting times<br>  ○ Geographic access<br>• Economic outcomes<br>  ○ Cost per scan<br>  ○ Cost-effectiveness of MRI monitoring strategy<br>**Treatment-related outcomes:**<br>• Primary effectiveness outcome: Change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score<br>• Secondary effectiveness outcomes<br>  ○ Alzheimer Disease Assessment Scale-Cognitive subscale 14 item Version (ADAS-Cog14)<br>  ○ Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL)<br>  ○ Alzheimer's Disease Composite Score (ADCOMS)<br>  ○ EuroQol 5-Dimension 5-Level (EQ-5D-5L)<br>  ○ Quality of Life in Alzheimer's Disease (QOL-AD)<br>  ○ Zarit Burden Interview (ZBI)<br>  ○ Brain amyloid levels measured by amyloid PET centiloids<br>• Safety outcomes<br>  ○ Any adverse event<br>  ○ Any adverse event resulting in discontinuation of treatment |

| Component | Description |
|---|---|
| | ○ Any serious adverse event<br>○ Any adverse event resulting in death<br>○ Other types of adverse event where the frequency or severity differs across groups (e.g. ARIA events and infusion-related reactions)<br>• Other treatment-related considerations<br>○ Capacity of healthcare facilities for the increased number of patients who requires intravenous (IV) infusions of lecanemab every 2 weeks<br>○ Capacity of health professionals for the increased number of patients who are on lecanemab and need monitoring of ARIA<br>○ Cost and cost-effectiveness<br>○ Impact on health equity<br>• Health care system<br>○ Cost of testing<br>○ Capacity for the increased request for testing from specialists<br>○ Cost-effectiveness of testing and treatment<br>○ Cost of monitoring the safety of treatment<br>○ Capacity for the increased demand for the safety monitoring for patients on treatment<br>○ Financial implications |
| Assessment questions | What is the safety, effectiveness and cost-effectiveness of amyloid pathology testing (including amyloid PET, CSF biomarker and plasma biomarker testing) and *APOE* genotyping followed by lecanemab treatment versus no testing and standard medical management for AD in patients with MCI or mild dementia due to suspected AD? |

AD = Alzheimer's disease; ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale, 14-item version; ADCOMS = Alzheimer's Disease Composite Score; ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; APOE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities with oedema/effusions; ARIA-H = amyloid-related imaging abnormalities with haemorrhage/hemosiderin deposition; Aβ = amyloid beta; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; EQ-5D-5L = EuroQol 5-Dimension 5-Level; IV = intravenous; MBS = Medicare Benefits Schedule; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; p-tau217 = phosphorylated tau at threonine 217; PET = positron emission tomography; QOL-AD = Quality of Life in Alzheimer's Disease; t-tau = total tau; ZBI = Zarit Burden Interview.

[a] Basic dementia screen plus blood testing for syphilis serology or human immunodeficiency virus (HIV) for patients with histories suggesting being at risk

[b] Basic dementia screen plus chest X-ray and/or electrocardiogram based on clinical presentation

# Purpose of application

The original codependent application requested:

- Medicare Benefits Schedule (MBS) listing of (1) amyloid-beta (Aβ) pathology testing and (2) apolipoprotein E (*APOE*) ε4 genotype testing; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of lecanemab

for patients with a clinical diagnosis of mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD).

# PICO criteria

### *Population*

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by the extracellular accumulation of amyloid-beta (Aβ) plaques and the intracellular aggregation of neurofibrillary tangles, which are composed of hyperphosphorylated tau protein (Zheng & Wang 2025). AD also results in gliosis (i.e., formation of scar tissues) and loss of synapses and neurons in the brain (Long & Holtzman 2019). AD is characteristically a disease of older age. The genetic contribution to this typical, late-onset AD remains incompletely understood, although the apolipoprotein E epsilon 4 (*APOE* ε4) allele has been the most recognised genetic risk factor, and approximately 60% of people with late-onset AD were found to be carriers of *APOE* ε4 (Myers et al. 1996). People who are homozygous for the *APOE* ε4 allele have been found to be more likely to develop dementia, compared to people who are heterozygous/carriers of the allele (Genin et al. 2011; Myers et al. 1996). Early-onset AD (i.e., onset before 65 years of age) is uncommon and occurs in approximately 5% of patients with AD, with most cases being sporadic (Wolk & Dickerson 2024). AD that is inherited (i.e., familial AD) is rare (accounting for <1% of all AD cases) and routinely has an early onset. In these cases, the autosomal-dominant inheritance pattern is typical, with mutations in genes including the *APP, PSEN1,* and *PSEN2.* Mutations in these genes alter the production or metabolism of Aβ protein (Goate et al. 1991; Renbaum & Levy-Lahad 1998; Sherrington et al. 1995).

AD accounts for 50% - 60% of dementia in Australia (Hsu et al. 2025), a condition manifested as loss of memory, emotion control, language, thinking, and the ability to perform daily activities (World Health Organisation 2025). In the AD disease course, mild cognitive impairment (MCI) may represent the early stage of the disease, manifested as a noticeable decline in memory, language, or ability in complex thinking (Alzheimer's Association 2026). People with MCI caused by AD are 3 to 5 times more likely to develop dementia, compared to MCI with other aetiologies (Alzheimer's Association 2026).

Based on the Australian Dementia Network registry data[1], of the 2,369 patients within the Clinical Quality registry in 2022, 68% had a dementia diagnosis and 32% had MCI (Ward et al. 2023). In 2024, there were an estimated 425,000 Australians living with dementia (equivalent to 16 people with dementia per 1,000 Australians (Australian Institute of Health and Welfare 2025)). The estimated number has grown to 446,500 in 2026 (Dementia Australia 2023), and expected to increase to more than 1 million by 2065 if there is no effective intervention (Australian Institute of Health and Welfare 2025). As AD accounts for around 50 - 60% of all dementia cases, this means there would be an estimated 212,000 - 255,000 people in Australia living with AD (in 2024). Estimating the number of people with MCI due to AD in Australia is

[1] Eligible participants for the Australian Dementia Network registry are individuals aged 18 years and over who receive a new diagnosis of either dementia or MCI at a participating site.

more uncertain as there are no national prevalence data for biomarker-confirmed MCI for AD. The systematic review by Gillis et al (2019) stated that MCI incidence increases substantially with age and is approximately 22.5, 40.9 and 60.1 per 1,000 person-years in people aged 75–79, 80–84 and ≥85, respectively.

Currently, there is no cure for dementia. As the condition progresses, the functional ability of an individual living with dementia declines, leading to reliance on care providers for all aspects of daily living. An estimated 1.7 million people in Australia are involved in the care of someone living with dementia (Australian Institute of Health and Welfare 2024), and 54% of people living in permanent residential aged care have dementia (Livingston et al. 2024). Dementia is also a leading cause of death and the main reason for hospital admission in Australia (Australian Bureau of Statistics 2024; Australian Institute of Health and Welfare 2025). Infections (particularly pneumonia) and eating problems[2] are common complications in advanced stage of dementia and are associated with high mortality (Mitchell 2025). Based on Australian government data for 2022–2023, an estimated spending of $4.7 billion was directly attributed to the diagnosis, treatment and care of people with dementia in the health and aged care sectors (Australian Institute of Health and Welfare 2025).

In the clinical setting in Australia, most people with cognitive impairment (78.3%) first report symptoms to their general practitioners (GPs) (Michaelian et al. 2025). In Australia, the Royal Australian College of General Practitioners Guidelines[3] guide clinicians to the diagnosis of MCI or dementia. The key clinical symptoms and thresholds that lead to the diagnosis of MCI or dementia are summarised in Table 2 below.

**Table 2 Clinical symptoms and thresholds for the diagnosis of MCI and dementia**

| Diagnosis | Symptoms | Threshold |
|---|---|---|
| Mild cognitive impairment (MCI) | Amnestic MCI (most common form of MCI):<br>• Forgetting important information (such as appointments, names, or recent events)<br>• Losing things<br>Non-amnestic MCI:<br>• Problems with language<br>• Trouble paying attention<br>• Finding it harder to make decisions<br>• Changes in visual perception that make it harder to judge distance and identify objects (especially with low-contrast colours) | Patients present with objective cognitive decline (memory, language or executive function) compared to their previous baseline but remain independent and daily functioning. |
| Dementia | • Memory loss<br>• Difficulty communicating<br>• Personality changes<br>• Problems with thinking or behaviour<br>• Problems with recognising people or what things are used for | Cognitive decline is significant enough to interfere with independence and daily functioning |

MCI = mild cognitive impairment.
Source: Dementia Australia https://www.dementia.org.au/

[2] Eating problems are often multifactorial and contributors of eating problems include oral dysphagia (e.g. food pocketing or spitting), pharyngeal dysphagia (which may lead to delayed swallowing, aspiration, and aspiration pneumonia), impaired ability to self-feed, or depression, which may manifest as reduced appetite or refusal to eat.
[3] https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/silver-book/part-a/dementia accessed on 20 Jul 2026

People with a possible diagnosis of dementia should be referred to memory assessment specialists or services for a comprehensive assessment. People identified as having MCI should be offered follow-up after 6 - 18 months by the memory assessment specialist/service, a GP, other medical practitioner, or nurse practitioner to monitor cognitive changes and other signs of possible dementia (Dyer et al. 2016). For people diagnosed with dementia, assessment of medical comorbidities and key psychiatric features associated with dementia (including depression and psychosis) should be made at the time of diagnosis and at regular intervals subsequently, to ensure optimal management of coexisting conditions (Dyer et al. 2016).

The diagnosis of MCI or dementia is clinical and relies on a comprehensive assessment which starts with history taking from the affected person and from a person who knows the affected person well, physical examination, cognitive mental state examination using a validated instrument such as the General Practitioner assessment of Cognition (GPCOG)[4] or Standardised Mini-Mental State Examination (SMMSE)[5], review of medication, and consideration of other causes (including delirium or depression) (Dyer et al. 2016). Based on the findings of the initial assessment[6,7], the GP would perform a basic dementia screen, which includes routine haematology, biochemistry test (including electrolytes, calcium, glucose, renal, liver, and thyroid function, serum vitamin B12 and folate levels (Dyer et al. 2016)[8]. The GP may also order a computed tomography (CT) scan of the brain for some people to rule out stroke or brain tumour. If the diagnosis is unclear based on these investigations, or if the patient is young, the GP would refer the patient to a specialist (can be a neurologist, psychiatrist, or geriatrician) who can order a brain magnetic resonance imaging (MRI) or positron emission tomography (PET) scan for further investigation and a confirmed diagnosis.

The applicant stated that brain MRI for the diagnostic workup of MCI or dementia is currently funded under MBS item 63004. However, item 63004 is for MRI of the brain for suspected inflammation of the brain or meninges and is not specific to the assessment of MCI or dementia. In current practice, GPs may request CT brain imaging to exclude alternative structural causes of cognitive impairment before referral, and some patients may undergo privately funded MRI. However, MBS items for brain MRI that may be relevant to excluding alternative intracranial pathology are generally restricted to requests by specialists or consultant physicians. Therefore, while imaging to exclude other causes of cognitive impairment may be available under existing MBS arrangements, existing MRI items may not clearly cover a baseline MRI specifically for determining eligibility for lecanemab. This supports the Department's view, noted in the MSAC 1784 Public Summary Document (PSD), that specific MBS items for baseline MRI (prior to lecanemab treatment) and Amyloid-Related Imaging Abnormalities (ARIA) monitoring may be required.

There are different subtypes of dementia, including AD (most common), vascular dementia, Lewy Body dementia, and frontotemporal dementia (National Institute for Health 2025). Therefore, clinical diagnosis can only reveal "possible" or "probable" cases of AD, even those made by experts, since the accuracy of clinical AD diagnosis has been demonstrated to be variable (a sensitivity ranged from 70.9% to 87.3% and specificity from 44.3% to 70.8%), and up to 23% of patients clinically diagnosed with AD had no or sparse Aβ plaques at autopsy (Beach et al. 2012; Gauthreaux et al. 2020; Sabbagh et al. 2017). Although brain MRI

[4] https://gpcog.com.au/, accessed on 06Jul2026
[5] https://www.ihacpa.gov.au/sites/default/files/2024-09/smmse-guidelines-ihacpa.pdf, accessed on 06Jul2026
[6] In people with histories suggesting being at risk, testing for syphilis serology or human immunodeficiency virus (HIV) should be included.
[7] Based on the clinical presentation, chest X-ray or electrocardiogram should be included in the assessment.
[8] Cerebrospinal fluid examination should not be performed as a routine investigation for dementia unless Creutzfeldt-Jakob disease is suspected or in rapidly progressive dementia.

can identify the structural hallmarks of AD, such as hippocampal atrophy and/or atrophy of the cerebral cortex, major challenges associated with use of MRI in patients included in the proposed population are (1) their impaired cognition, and (2) presence of metal implanted medical device(s).

*PASC considered that the population should be defined as individuals with suspected AD, who are undergoing assessment for potential treatment with lecanemab.*

The current clinical practice guidelines, *Clinical Practice Guidelines and Principles of Care for People with Dementia* (released in 2016), did not include fluorodeoxyglucose positron emission tomography (FDG-PET) scan of the brain[9], as well as testing of cerebrospinal fluid (CSF) biomarkers (including Aβ peptide, total tau protein, and phosphorylated tau) via lumbar puncture, as the investigative tools for the diagnosis of AD.

However, FDG-PET has become available (MSAC application 1195.1, considered by MSAC in November 2020) and listed on the Medicare Benefits Schedule (MBS)[10] to assist in the diagnosis of AD when clinical evaluation by a specialist is inconclusive. In the draft update to the current clinical practice guidelines (hereafter referred to as draft update guidelines) which is currently out for public consultation and are intended to be released by the end of this year, it is recommended that FDG-PET imaging should be considered by the specialist in the diagnostic process for an individual with suspect diagnosis of dementia, when uncertainty persists after comprehensive clinical assessment that includes a detailed history, neurobehavioural assessment, cognitive testing and structural brain imaging (Recommendation 5). However, consultation feedback obtained during the consideration of MSAC application 1784 stated that FDG-PET is unable to detect amyloid burden and therefore would not be a suitable comparator for amyloid PET testing.

Testing of CSF biomarkers (Aβ[1-42], p-tau181 and total tau)[11] is also currently available in Australia but is not listed on the MBS. A recent national survey of medical specialists from 30 clinics across Australia that assess people with MCI demonstrated that approximately 40% of clinics reported using imaging biomarkers, such as FDG- or amyloid PET, in their diagnostic workup and only one clinic performed this routinely (in >70% of patients) (Michaelian et al. 2025). Regarding CSF sampling for the testing of biomarkers, 60% of the surveyed clinics reported never or not available for testing, and a further 30% reported rarely referring their patients for CSF sampling.

Blood-based biomarker testing, such as testing for p-tau181 or p-tau217 (currently both biomarker tests are approved by the Therapeutic Goods Administration [TGA] and listed on the Australian Register of Therapeutic Goods [ARTG]), has recently become available in Australia. The draft update guidelines recommend using a blood-based biomarker test with sensitivity ≥90% and specificity ≥75% as a triaging test, and a test with sensitivity ≥90% and specificity ≥90% as a confirmatory test, to determine the presence or absence of AD pathology in the brain during specialist diagnostic workup of individuals with MCI or dementia (Recommendation 3 and 4).

*PASC raised concerns regarding potential use outside of the intended population i.e. those for whom treatment with amyloid targeting therapies is being considered, if the p-tau217 test is publicly funded. In*

[9] AD affects particular areas of the brain more than others – loss of brain cell activity in these areas leads to less glucose metabolism in those areas. FDG PET has a characteristic AD pattern that shows bilateral temporoparietal and posterior cingulate hypometabolism.

[10] MBS item 61560. URL: https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=61560&qt=ItemID

[11] National Dementia Diagnostic Laboratory (The Florey). URL: https://florey.edu.au/our-research/scientific-facilities-and-research-services/national-dementia-diagnostics-laboratory/ Accessed on 16 July 2026

*addition, equity considerations relating to access to diagnostic investigations and monitoring, particularly for regional, remote, and Aboriginal and Torres Strait Islander populations were raised.*

*PASC considered that to limit the use of tests to the intended population, eligibility criteria and patient characteristics should be clearly specified within the item descriptors.*

Based on the current Australian clinical practice guidelines (released in 2016), *APOE* genotype testing has no role in the diagnostic workup for people with suspected late-onset dementia (Dyer et al. 2016). In this application, genotyping is proposed to be used later in the diagnostic algorithm for the purposes of identifying those who may be at higher risk of side effects of therapy rather than diagnosis of dementia.

*PASC noted that a finding of APOE ε4 homozygosity created a treatment dilemma because individuals with APOE ε4 homozygosity were excluded from eligibility for lecanemab because of the higher adverse event risk and yet these individuals had a significantly elevated risk of late-onset AD.*

*PASC noted that Aboriginal and Torres Strait Islander populations had the highest frequency of carrying at least one APOE ε4 allele among all Australian populations, the highest frequency of APOE ε4/ε4 homozygosity, and more than twice the dementia prevalence of non-Indigenous Australians. PASC also noted that the protective APOE ε2 allele appears to be absent in this population, compared with a reported prevalence of approximately 5% to 8% in other population groups. These factors may influence both treatment eligibility and risk of treatment-related adverse events, and reinforced the importance of culturally appropriate counselling and equitable access to testing and treatment services.*

Currently in Australia, acetylcholinesterase inhibitors (AChEI) and N-methyl-D-aspartate (NMDA) receptor antagonist are listed on the PBS for treatment of mild to severe AD[12]. These treatments are used for symptom management, rather than disease modification. Two amyloid-targeting therapies, donanemab and lecanemab, were recently approved by the TGA for the treatment of early-stage AD[13]. Neither drug is listed on the PBS at the time of PASC's consideration of this application. The PBAC did not recommend the listing of donanemab in the July 2025 PBAC Meeting, and lecanemab is yet to be considered by the PBAC.

### *Intervention*

In the application, proposed health technologies include the following:

- For biomarker testing
    - Amyloid PET scan of the brain (investigative)
    - Immunoassay assessment of t-tau/Aβ[1-42] in CSF (investigative)
    - Immunoassay assessment of phosphorylated tau 217 (p-tau217) in plasma (investigative)
    - *APOE* ε4 genotype testing in plasma (investigative)
- Other tests to determine treatment eligibility
    - Brain MRI as part of the diagnostic workup (investigative)

[12] PBS listed acetylcholinesterase inhibitors include donepezil, rivastigmine, and galantamine; PBS listed NMDA antagonist includes memantine.

[13] Donanemab was approved by the TGA in May 2025; lecanemab was approved by the TGA in September 2025.

- For treatment
    - Lecanemab (therapeutic)
- For treatment safety monitoring
    - Brain MRI scans (investigative)

It should be noted that the TGA information clearly states that brain MRI should be done prior to the 3rd, 5th, 7th and 14th infusions of lecanemab and therefore (for the purpose of an economic model) the proposed arm should be lecanemab plus MRI monitoring (both are given together, or neither are given).

The application proposes that (1) all patients with MCI or mild dementia due to suspected AD would be eligible to undergo biomarker testing associated with determining eligibility to access lecanemab through the PBS; (2) patients who have commenced on lecanemab treatment receive brain MRI scans for monitoring of the development of ARIA.

For patients who did not receive a brain MRI as part of their AD diagnostic workup, a new MBS item was proposed to support baseline MRI before lecanemab treatment to ensure there is no pathology that would preclude treatment. The MRI exclusion criteria used in the pivotal Phase III CLARITY AD trial and subsequently reflected in published "Appropriate Use Recommendations" (Cummings 2023) included more than four cerebral microhaemorrhages, any macrohaemorrhage greater than 10 mm, superficial siderosis, vasogenic oedema, multiple lacunar infarcts, prior major territorial stroke, severe cerebral small-vessel disease, cerebral amyloid angiopathy-related inflammation (CAA-ri), amyloid β-related angiitis (ABRA), or other clinically significant intracranial pathology (van Dyck et al. 2023).

The biomarker tests (amyloid PET and immunoassay assessments) are proposed to confirm the presence of beta-amyloid deposition in the brain, thereby supporting AD pathology as the underlying cause of the condition. The *APOE* ε4 genotype testing is proposed to determine which patients are at substantial risk of developing ARIA, with the aim of identifying those who would be considered ineligible for lecanemab treatment before it is initiated (due to their increased risk profile).

Amyloid PET

Amyloid PET is a diagnostic test that utilises radioactive tracer (a positron emitter) such as 18F-florbetaben (FBB) or 18F-Florbetapir (FBP)[14] to detect the presence of amyloid plagues in the brain which are a hallmark of AD (QueenslandXRay). Ordered by a specialist (primarily a neurologist, geriatrician, or psychiatrist), amyloid PET scan occurs in a radiology clinic. An intravenous (IV) cannula is first placed into a patient's arm for the injection of the PET tracer. Once the infusion of the tracer is completed, a 60–90 minute period will be allowed for the patient to rest and for tracer uptake to take place. Thereafter, the patient would lie on the bed passing through the middle of the PET scanner, while the scanner acquires images of the patient's brain (QueenslandXRay). The distribution of radiotracers in the brain is then analysed and interpreted by a PET-credentialled specialist (i.e., the traditional visual assessment based on a qualitative judgement rather than a numerical threshold). A PET-credentialled specialist is a specialist or consultant physician, including nuclear medicine physicians and radiologists, who has been recognised and credentialled to supervise and report on PET scanning services under the Australian Department of Health and Aged Care guidelines.

[14] In Australia, both 18F-florbetaben and 18F-Florbetapir are commercially manufactured and distributed by Cyclotek. Amyloid PET radiopharmaceuticals may also be produced by hospital nuclear medicine departments in Australia with onsite cyclotrons.

The key finding of amyloid PET imaging in AD is increased radiotracer binding to its targets (Aβ plaques in the cerebral cortex) resulting in loss of grey-white matter distinction, which is categorised as the positive finding (Mallik, Drzezga & Minoshima 2017).

While a negative amyloid PET scan may exclude AD with high degree of certainty, a positive amyloid PET by itself (in the absence of a comprehensive clinical assessment) does not confirm the diagnosis of AD since Aβ plaques are not specific for AD. Among people with normal cognition, the prevalence of amyloid deposition was found to increase with age — from approximately 10% (95% confidence interval [CI], 8–13%) at the age of 50 years, rising to 44% (95% CI, 37–51%) by age 90 years (Jansen et al. 2015). Considering this, the draft update guidelines recommend that amyloid PET is not routinely used for diagnosing dementia subtype in patients with suspected AD during a specialist assessment. The Guideline Development Group of the updated guidelines (hereafter referred to as the Guideline Development Group) considered that the diagnostic value of amyloid PET may be greater in specific scenarios when diagnostic uncertainty remains after standard evaluation and the result is expected to influence eligibility to clinical treatment or prognosis (e.g. clarifying the diagnosis in a patient with younger-onset dementia with an atypical clinical presentation) (*DRAFT FOR PUBLIC CONSULTATION: Dementia Clinical Practice Guidelines and Principles of Care* May 2026).

Regarding the safety of amyloid PET, the Guideline Development Group noted that the available evidence did not indicate clinically important harms (*DRAFT FOR PUBLIC CONSULTATION: Dementia Clinical Practice Guidelines and Principles of Care* May 2026). Nevertheless, the National Institute for Health and Care Excellence (NICE) noted that PET imaging may be distressing for certain patients (e.g. claustrophobia) (National Institute for Health and Care Excellence 2018). A study of participant views in the UK revealed that around 4% of patients rated their experience with FDG-PET/CT as "unpleasant" (Bamford et al. 2016). This was mostly due to physical (dis)comfort and the scanning experience itself, specifically: discomfort from lying on the scanner bed and difficulties with remaining still during the scan. These issues may pose challenges to patients with cognition impairment. For patients with significantly reduced kidney function or those with tracer allergies, the amyloid PET scan may not be a safe investigative modality.

Amyloid PET for AD was previously reviewed by MSAC. The MSAC PSD for application 1784[15] (donanemab) (hereafter refer to as 1784 MSAC PSD) (pp52-53) states: "The ESCs noted the commentary's review concluded that amyloid PET using 18F-flutemetamol (FMM), 18F-florbetaben (FBB), or 18F-florbetapir (FBP) showed relatively high sensitivity and specificity (pooled estimate, 93% and 91%, respectively) and provides a reliable test for determining Aβ pathology. However, the ESCs considered that the correlation between Aβ pathology and AD to be unclear, noting that Aβ may also be found in the brains of individuals without symptoms of MCI or AD. Indeed, a proportion (20% - 30%) of cognitively normal individuals or individuals with other non-AD dementia, test positive on amyloid PET and this proportion increases to 50% in older individuals who are *APOE4* positive. Additionally, the ESCs noted that the positive predictive value of amyloid PET to detect AD is highest in younger patients (late 40s to early 50s) with a high pretest probability of AD, based on clinical evaluation. Both positive and negative predictive values of amyloid PET are less reliable in older patients, particularly in those who are *APOE4* positive." MSAC also noted the limited availability and geographical inequity of access to PET machines in Australia (1784 MSAC PSD, p6)[15]. Access may also be limited by structural factors such as availability of trained staff and specialised infrastructure (*DRAFT FOR PUBLIC CONSULTATION: Dementia Clinical Practice Guidelines and Principles of Care* May 2026).

[15] Available from: https://www.msac.gov.au/applications/1784

Regarding the uptake of FDG-PET in Australia, which is currently funded by the MBS for the diagnosis of AD (Item 61560), it was pointed out in the draft update guidelines that acceptability of FDG-PET in Australian clinical practice is limited by capacity constraints, long wait times, and inadequate infrastructure, which restrict actual test uptake rather than willingness (*DRAFT FOR PUBLIC CONSULTATION: Dementia Clinical Practice Guidelines and Principles of Care* May 2026).

Immunoassay assessment of t-tau/Aβ[1-42] in CSF

In the application, CSF biomarker testing for t-tau/Aβ[1-42] is proposed to be a test to confirm amyloid pathology in the brain which is part of the eligibility criteria for a patient with MCI or mild dementia to be treated with the proposed treatment (lecanemab). CSF biomarker testing was not included in the current practice guidelines as an investigative tool for the diagnosis of AD as the routine use of this diagnostic technology was still under evaluation and was considered to be premature at the time when the guidelines were released in 2016 (p20 of the guidelines) (Dyer et al. 2016). The testing was later approved by the TGA and became available at the National Dementia Diagnostic Laboratory (NDDL)[16] in Melbourne since late 2024. Other pathology laboratories in the country that analyse specialised biomarkers of AD include the Concord Hospital Diagnostic Pathology Unit (NSW), St. Vincent's Hospital Melbourne (VIC), SA Pathology/Royal Adelaide Hospital (SA), Sullivan Nicolaides Pathology Brisbane (QLD)[17], Austin Pathology (VIC)[18], and PathWest (WA)[19].

Immunoassay assessment of t-tau/Aβ[1-42] in CSF is requested by a specialist, usually a neurologist, geriatrician or physician in a local cognitive clinic. CSF is collected by lumbar puncture in a consulting room, hospital outpatient setting, pathology laboratory, or other specialist service, with local anaesthesia or mild sedation available if required. In some centres, diagnostic imaging providers may also coordinate or facilitate CSF collection and testing. The procedure is performed by a medical practitioner or trained nurse practitioner with documented competency. During lumbar puncture, a needle is inserted into the spine, and a 2.5 mL CSF sample is collected directly into a specified blue-capped tube, then stored refrigerated at 2°C - 8°C. In the laboratory, an immunoassay kit, such as Roche Elecsys® Generation II, is used to measure t-tau (a protein associated with the formation of neurofibrillary tangles in the brain) and Aβ[1-42] (the main component of amyloid plaques) in CSF. The application does not specify the manufacturer of the assay kit proposed for this testing.

A high t-tau/Aβ[1-42] (cut-off point established by Roche using the Elecsys® assay is 0.28[20]) is consistent with a diagnosis of AD, with a sensitivity of 85% - 90% and specificity of 85% - 90% against autopsy verification (Holtzman 2011).

[16] https://florey.edu.au/our-research/scientific-facilities-and-research-services/national-dementia-diagnostics-laboratory/ accessed on 02Jul2026

[17] https://diagnostics.roche.com/au/en/c/elecsys-alzheimers-disease-testing-sites.html accessed on 02Jul2026

[18] https://www.austinpathology.org.au/test-directory/2197 accessed on 02Jul2026

[19] https://www.pathwest.health.wa.gov.au/Our-Services/Clinical-Services/Diagnostic-Genomics/Neurogenetics accessed on 02Jul2026

[20] https://assets.roche.com/f/173850/x/9ad8e46bb4/total-tau-08846685190-en-can.pdf accessed on 02Jul2026. A note from the manufacturer: "Please note that due to the sticky properties of the β-Amyloid (1-42) protein, the cut-off for the ratio tTau/Abeta42 (calculated based on results of the Elecsys Total-Tau CSF and the Elecsys β-Amyloid (1-42) CSF II assays) provided in this document is only valid if the required pre-analytical handling procedure (described in the section "Specimen collection and preparation" of the Elecsys β-Amyloid (1-42) CSF II assay Method Sheet) is strictly followed."

In the 1784 MSAC PSD (p6), it was stated that, "MSAC noted from the commentary that the discordance between the PET and CSF test results for Aβ[42][21] testing could be as high as 28%. MSAC also noted that the CSF test is less sensitive and less specific than amyloid PET." In the 1784 MSAC PSD[15] (p53), "The ESCs noted the commentary's systematic review on the diagnostic test accuracy of CSF AD biomarker (Aβ[42]) testing in AD reported a pooled sensitivity and specificity of 89.4% and 70.5%, respectively, when compared to neuropathology at autopsy". Regarding the comparative effectiveness of CSF AD biomarker testing, in the 1784 MSAC PSD (p28), it was stated that, "The proportion of discordant results between CSF AD biomarker tests and amyloid PET scans was higher for single CSF AD biomarkers than for most ratio combinations. All three biomarker ratio combinations[22] included Aβ[42] and all had an improved positive percent agreement (PPA) over Aβ[42] alone (92–98% versus 87% when compared to visual assessment of amyloid PET). The negative percent agreement (NPA) for p-tau181/Aβ[42] and t-tau/Aβ[42] were higher compared with Aβ[42] alone (91% and 87% versus 79%), when compared to visual assessment of amyloid PET scan".

MSAC considered the safety of the lumbar puncture procedure in AD patients. In the 1784 MSAC PSD[15] (p54), it was stated that, "The ESCs noted the adverse events associated with CSF AD biomarker testing, including those related to lumbar puncture, CT guidance, and anaesthesia if required." MSAC noted that lumbar puncture is an invasive and potentially unpleasant procedure and acknowledged adverse events such as post-dural puncture headache (PDPH), which may occasionally require treatment with an epidural blood patch. While these risks are recognised and generally manageable in clinical practice, MSAC considered that the safety of lumbar puncture had not been adequately characterised in the evidence presented and identified this as an area of uncertainty in its assessment of CSF biomarker testing[15].

In the 1784 MSAC PSD (p6), MSAC noted that the limited availability and geographical inequity of access to amyloid PET imaging in Australia increased the potential importance of CSF biomarker testing in the Australian setting. Therefore, CSF testing may be considered a clinically relevant alternative to amyloid PET for confirming amyloid pathology, particularly in regions where access to PET imaging is limited.

Immunoassay assessment of p-tau217 in plasma

The application proposes immunoassay assessment of p-tau217 in plasma to be an alternative test for determining amyloid positivity and eligibility of patients with MCI or mild dementia due to suspected AD to lecanemab treatment. The use of plasma biomarkers to determine amyloid positivity and treatment eligibility was not evaluated in the CLARITY-AD trial, where amyloid status was confirmed using amyloid PET or CSF biomarkers (van Dyck et al. 2023). However, an emerging body of evidence suggests that plasma p-tau217 is highly concordant with established measures of amyloid pathology. For example, Asken et al. (2024) assessed the concordance of plasma p-tau217 with amyloid PET in a cohort of 239 ethnically diverse older adults and reported excellent discrimination of amyloid PET-positive versus amyloid PET-negative individuals (Area Under the Curve (AUC) 0.91 using visual PET reads and 0.90 using Centiloid quantification). Agreement was particularly high between low plasma p-tau217 levels and negative amyloid PET findings (95.8%), while agreement between high p-tau217 levels and positive amyloid PET findings was 86.3% (Asken et al. 2024).

Similarly, Ashton et al. (2024) evaluated a commercially available plasma p-tau217 immunoassay across three independent cohorts comprising 786 participants and found high accuracy for identifying elevated

[21] Aβ[42] and Aβ[1-42] are interchangeable.
[22] The proposed t-tau/Aβ[1-42] ratio for this application is one of the ratio combinations being referred to here.

amyloid pathology, with AUCs ranging from 0.92–0.96 compared with amyloid PET or CSF-defined amyloid status. The authors concluded that plasma p-tau217 demonstrated diagnostic performance comparable to CSF biomarkers for detecting abnormal amyloid PET findings and may substantially reduce the need for confirmatory testing in some clinical settings (Ashton et al. 2024).

These studies support the potential role of plasma p-tau217 as a less invasive and more accessible alternative for identifying patients likely to have amyloid pathology.

In Australia, the TGA approved the Roche Elecsys® immunoassay of plasma p-tau181 for AD in September 2025, and have recently approved the testing of plasma p-tau217 for AD. Recent comparative evidence suggests that plasma p-tau217 has higher diagnostic accuracy than plasma p-tau181 for identifying cerebral amyloid pathology. In a recent network meta-analysis of 18 studies including 4,736 participants, p-tau217-based assays consistently ranked highest for amyloid pathology detection and outperformed standard p-tau181 immunoassays (Chen et al. 2026). The 1784 MSAC PSD[15] also noted that plasma p-tau217 demonstrated median ROC-AUC values of approximately 0.918–0.93 for predicting amyloid pathology (Table 3).

**Table 3 Comparison between p-tau 181 and p-tau217 in plasma**

| Characteristic | Plasma p-tau181 | Plasma p-tau217 (proposed plasma test for application 1738.1) |
|---|---|---|
| Ability to identify amyloid-positive patients | Good diagnostic accuracy; one MCI study reported sensitivity of 94% and specificity of 72% (Cano et al. 2024). | Good diagnostic accuracy; the 1784 MSAC PSD cited median ROC-AUC values of approximately 0.918–0.93 for plasma p-tau217 or p-tau217/non-phosphorylated tau217 ratio. |
| Comparative performance | Lower ranking than p-tau217 in recent network meta-analysis of plasma p-tau biomarkers (Chen et al. 2026). | Highest-performing plasma phosphorylated tau biomarker for amyloid pathology detection in recent network meta-analysis (Chen et al. 2026). |
| TGA approval | Yes, ARTG 200275 | Yes, ARTG 200275 |

ARTG = Australian Register of Therapeutic Goods; AUC = area under the curve; MCI = mild cognitive impairment; MSAC = Medical Services Advisory Committee; p-tau181 = phosphorylated tau at threonine 181; p-tau217 = phosphorylated tau at threonine 217; PSD = Public Summary Document; ROC = receiver operating characteristic; ROC-AUC = receiver operating characteristic area under the curve; TGA = Therapeutic Goods Administration.

Table 3The plasma biomarker testing is requested by a specialist or consultant physician. Blood is sampled through a routine venous blood draw in a consultation room or a local pathology clinic. In Australia, the testing of plasma AD biomarkers is performed in the specialised laboratories that analyse CSF AD biomarkers (see above). Automated immunoassay platforms approved by authorities for testing plasma p-tau217 for AD in medical laboratories include the Elecsys® system (Roche). In the submission, the applicant does not specify the manufacturer of the immunoassay platform to be used for the assessment.

Testing of plasma p-tau217 was briefly discussed in the 1784 MSAC PSD[15] (p49). In the PSD, it was stated that, "p-tau217 had comparable performance in both plasma and CSF and has potential for use in the diagnosis and screening for AD. When measuring plasma p-tau217 levels or the ratio of phosphorylated to non-phosphorylated tau217 (p-tau217/np-tau217), the median ROC-AUC varies from 0.918 to 0.93. This is very comparable to the median receiver operating characteristic (ROC) – area under the curve (AUC) values for CSF ratios of Aβ42/Aβ40, p-tau181/Aβ42 and t-tau/Aβ42, which vary from 0.894 to 0.953. Thus, the commentary considered that p-tau217 is a robust candidate for predicting Aβ pathology via a blood test, potentially reducing the need for either amyloid PET or lumbar puncture for CSF AD biomarker testing

in the near future." It was also noted in the 1784 MSAC PSD[15] (p49) that the Australian Dementia network is conducting a trial of the p-tau217 blood biomarker test in primary care settings in Adelaide, Newcastle and north-eastern Melbourne, and submitted a proposal for Federal Government funding of an Australian testing centre at the NDDL.

*PASC discussed the role and sequence of the proposed investigations within the diagnostic pathway and noted uncertainty regarding the optimal testing algorithm. PASC noted one possible pathway involved plasma p-tau217 testing in the algorithm as an initial triage test to identify patients requiring further assessment (e.g. via amyloid PET or CSF testing) although this was not performed in the main trial and evidence to support this approach would be needed. PASC noted the applicant's comments that p-tau217 testing may also have a future role as a standalone diagnostic test. PASC noted that alternative testing pathways will have different clinical and economic consequences and considered that further evidence may be required to justify the proposed sequence of investigations.*

*The applicant stated at the PASC meeting that ptau217 testing is now ARTG listed under the ARTG 200275 entry. PASC noted that the proposed CSF test is also ARTG listed under the same ARTG 200275 entry. This ARTG entry designates the CSF and ptau217 tests as a Class 2 IVD test. However, if there were claims that these tests were companion diagnostics (tests that are essential for safe and effective use of a medication i.e. as specified in the medicine's Product Information), then they would be classified as Class 3 IVDs and would require separate inclusion in the ARTG.*

<u>*APOE* ε4 genotype testing in plasma</u>

In the application, *APOE* ε4 genotype testing is proposed to be part of the biomarker testing to determine patient's eligibility to lecanemab treatment. In the CLARITY AD trial, *APOE* ε4 genotype (allele carrier or non-carrier) was used as a randomisation stratifier to measure the adverse event risks for ARIA in lecanemab-treated patients (van Dyck et al. 2023).

*APOE* ε4 genotype testing is requested by a specialist or consultant physician. Patient's deoxyribonucleic acid (DNA) sample is collected through a routine venous blood draw in a consultation room or a local pathology clinic. Blood sample is collected using a 6mL EDTA tube. Currently, testing is available through four Royal College of Pathologists of Australasia (RCPA) member laboratories in Australia: Genomic Diagnostics (VIC), Pathology Queensland (QLD), Queensland Medical Laboratory Pathology (QLD), and the Royal Prince Alfred Hospital (NSW)[23]. Regarding the methodology for the testing, in the Royal Prince Alfred Hospital, the Taqman reverse transcription polymerase chain reaction (RT-PCR) genotyping assay by Thermo Fisher is used. Thermo Fisher Scientific Australia Pty Ltd was registered on the ARTG for Human genetics-related IVDs (ARTG entry 461285). Among the currently available methods used for genotyping in the laboratories, for example, Sanger sequencing (considered the benchmark of genetics testing) and Next Generation Sequencing (NGS), RT-PCR analysis is the recommended method for identifying *APOE* ε4 homozygosity due to its relatively short turnaround time (around 7 business days)[24], elimination of post-PCR processing steps, suitability for high-throughput applications, and reduced contamination risk (Rajič Bumber et al. 2025). In the CLARITY AD trial, PCR was the method used to determine patients' *APOE* genotype. In the submission, the applicant does not specify the particular method to be used for the testing.

MSAC reviewed the effectiveness and safety of *APOE* genotyping during a previous application: MSAC application 1784[15]- Detection of amyloid-beta for inclusion and *APOE4* homozygosity for exclusion to

[23] Information is based on the 1784 MSAC PSD (p10). Currently, and updated list of laboratories providing the testing is not available on the Royal College of Pathologists of Australasia (RCPA) website.
[24] https://www.genomicdiagnostics.com.au/testing-guide/apoe-genotyping accessed on 06Jul2026

inform treatment with donanemab. In the 1784 MSAC PSD (pp5-6), it was stated that, "MSAC noted that *APOE4* genetic testing would be straightforward and that many laboratories in Australia could perform the test. MSAC considered the proposed MBS fee ($154.00) for *APOE4* genotyping to be appropriate, accounting for a relatively small proportion of the overall costs of diagnostics, monitoring and treatment. MSAC had no concerns regarding the performance of the test. MSAC considered the results of *APOE4* genetic testing may have implications for family members because having one or two copies is an inherited risk factor of developing Alzheimer disease."

Regarding the prerequisites to implementation of the proposed testing, MSAC noted that, "timely processing of all patient samples would require increased capacity to meet demand, which would likely require additional laboratories being accredited to offer *APOE* genotyping. A Quality Assurance Program (QAP) would also need to be established." (1784 MSAC PSD[15], p10).

With regard to the frequency of *APOE* ε4 homozygosity within the Australian population, data from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing demonstrated the frequency of *APOE4* homozygosity to be 6.0% in patients with MCI and 5.6% in patients with severe AD[25].

*PASC discussed whether amyloid PET and APOE ε4 testing should be undertaken concurrently or whether APOE ε4 testing should be reserved for patients with confirmed amyloid pathology.*

*PASC noted the applicant's comments that, in clinical practice, amyloid pathology testing (amyloid PET, CSF biomarkers or plasma biomarkers) and APOE ε4 genotyping (neither of which are currently MBS listed) are often requested concurrently to minimise delays in determining treatment eligibility, particularly where access to some investigations may be associated with extended waiting times. The applicant further advised that the proposed MBS item descriptors were intended to provide flexibility regarding the order of testing rather than mandate a specific sequence. PASC acknowledged these comments but noted that APOE ε4 testing has implications beyond treatment eligibility, including the discovery of inherited genetic risk and potential impacts for biological relatives. PASC therefore considered that the timing of APOE ε4 testing relative to confirmation of amyloid pathology remains an important consideration and that alternative sequencing approaches may have different clinical, ethical, operational and economic implications. PASC considered that the assessment should investigate the consequences of different testing pathways rather than assume a single mandated order of testing.*

Lecanemab

In the application, lecanemab is proposed to be used in patients with MCI or mild dementia who are diagnosed with AD and are tested positive for amyloid pathology (using brain amyloid PET scan, immunoassay of t-tau/Aβ[1-42] in CSF or p-tau217 in plasma) and tested negative for *APOE* ε4 homozygosity (using DNA isolated from plasma for genotyping). Lecanemab is a recombinant humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) produced in Chinese Hamster Ovary cells. The drug preferentially binds to large soluble Aβ protein aggregates, known as protofibrils, while still maintaining high affinity for fibrillar Aβ, the main component of amyloid plaques. The accumulation of amyloid plaques in the brain is a defining pathophysiological feature of AD (Cummings 2023)[26]. As a result, lecanemab reduces Aβ plaques in the brain (Swanson et al. 2021; van Dyck et al. 2023). Lecanemab is approved by the TGA for treating adult patients with a diagnosis of MCI and mild dementia due to AD disease (i.e., early Alzheimer's disease) who are *APOE* ε4 non-carriers or heterozygotes[26]. In terms of

[25] Information based on the 1784 MSAC PSD (p16), available from https://www.msac.gov.au/applications/1784.
[26] Lecanemab Production Information. URL: https://www.tga.gov.au/sites/default/files/2025-09/auspar-lecembi-pi-250924.pdf

safety, lecanemab is subjected to additional monitoring in Australia[26]. Therefore, healthcare professionals are requested to report any suspected adverse events to the TGA[27]. The TGA-approved lecanemab Product Information (PI)[26] includes warnings that lecanemab may cause ARIA[28], which can be serious or life-threatening (in rare cases), and must not be used in patients who are homozygous for *APOE* ε4 (approximately 15% of patients with AD)[26]. The PI also advises health professionals to carefully consider the safety of lecanemab in patients receiving thrombolytic therapy[26].

Lecanemab (100mg/mL concentrated injection) must be diluted then administered as an IV infusion over approximately one hour, once every 2 weeks. The treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of AD. Lecanemab should be administered in specialised centres under the supervision of a multidisciplinary team trained in detection, monitoring and management of ARIA and experienced in detecting and managing infusion related reactions[29]. In the TGA-approved PI of lecanemab[26], it is stated that the benefit-risk of continued treatment should be re-assessed at regular intervals on an individual basis, and treatment should be discontinued if the patient progresses to moderate AD, since the effectiveness of lecanemab in patients with moderate or severe AD is not established.

In the application, it is indicated that lecanemab for subcutaneous injection via an autoinjector will be included in the ARTG at the time of PBAC consideration. The subcutaneous injection of lecanemab can be administered at home or in a residential care facilities by a nurse, a trained carer, or the patient. The FDA has approved the once weekly subcutaneous lecanemab as the initial and maintenance treatment for early AD and considered that subcutaneous lecanemab is associated with the same side effects including ARIA and injection-related reactions which are localised at the site of injection, and can include redness, swelling, rash pain, and/or bruising[30].

*PASC noted the applicant's comments that a subcutaneous formulation of lecanemab is under development and may have implications for future treatment pathways, service delivery and access considerations. A future codependent submission is anticipated.*

In the submission, lecanemab is proposed to be used alongside the current PBS listed treatment for AD (AChEI or NMDA antagonist) in a proportion of patients. In the CLARITY AD trial, approximately half of the enrolled patients with MCI or mild dementia due to AD received concomitant treatment with AChEI or NMDA antagonist (van Dyck et al. 2023).

In the draft update of the current clinical practice guidelines, the Guideline Development Group judged that, (1) there was insufficient evidence that lecanemab benefits cognition, and there was a large increase

[27] Report at www.tga.gov.au/reporting-problems

[28] Amyloid related imaging abnormalities (ARIA), characterised as ARIA with oedema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H), usually occurs early in treatment and is usually asymptomatic, although serious intracerebral haemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications. ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke. ARIA symptoms may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulties.

[29] Infusion related reactions may include fever and flulike symptoms (chills, generalised aches, feeling shaky, and joint pain) nausea, vomiting, hypotension, hypertension, and oxygen desaturation. According to the TGA approved lecanemab PI (p5), in case an infusion reaction occurs, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids should be considered.

[30] Food & Drug Administration. FDA approves first at-home starting dose for alzheimer's disease treatment. URL: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-home-starting-dose-alzheimers-disease-treatment accessed on 16 Jul 2026

in the incidence of ARIA and infusion reactions. Therefore, lecanemab resulted in trivial desirable effects and moderate undesirable effects, with low certainty evidence, (2) important variability exists in how people living with dementia valued the desirable and undesirable effects of lecanemab, and the balance of effects probably favoured the comparison (i.e., to not use lecanemab), (3) successful implementation and monitoring of lecanemab requires large resource requirements and use of lecanemab probably reduces equity, and (4) acceptability of lecanemab was variable, and use of lecanemab is probably not feasible to implement (*DRAFT FOR PUBLIC CONSULTATION: Dementia Clinical Practice Guidelines and Principles of Care* May 2026). These judgments on the use of anti-amyloid therapy however are in draft form, and the guidance in the upcoming finalised version of the clinical practice guidelines may differ.

Brain MRI

The application requests that brain MRI scans be funded by the MBS for patients with MCI or mild dementia due to AD who are receiving lecanemab treatment, for the purpose of follow-up and monitoring, given that patients treated with lecanemab are most at risk for developing ARIA within the first 6 months of starting treatment (Honig et al. 2023). In the CLARITY AD trial, any ARIA occurred in around 21% of patients treated with lecanemab, with most ARIA events being asymptomatic and detected on MRI. The application proposes that the follow-up brain MRI scans are to be performed before the 3rd, 5th, 7th, and 14th infusions of lecanemab (with infusions every 2 weeks) at a facility that is accredited under the Diagnostic Imaging Accreditation Scheme and approved as a Medicare-eligible MRI unit. The TGA-approved PI of lecanemab stated that, for monitoring ARIA, a recent (within 6 months) brain MRI should be available prior to initiating the treatment, and follow-up brain MRI scans should be performed within approximately one week before the 3rd, 5th, 7th and 14th scheduled infusion of lecanemab and reviewed prior to proceeding with the infusion[31]. Based on the TGA-approved PI of lecanemab, images acquired by brain MRI will determine whether a dosing suspension is needed for a patient under lecanemab treatment who has developed ARIA. ARIA MRI classification criteria and dosing recommendations for patients based on ARIA radiographic severity on MRI are summarised in Table 4 and Table 5 below.

**Table 4 ARIA MRI classification criteria**

| ARIA type | Radiographic severity | | |
|---|---|---|---|
| | **Mild** | **Moderate** | **Severe** |
| ARIA-E | FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location < 5 cm | FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm | FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted. |
| ARIA-H Microhaemorrhage | ≤4 new incidents microhaemorrhages | 5 to 9 new incident microhaemorrhages | 10 or more new incident microhaemorrhages |
| ARIA-H Superficial siderosis | 1 focal area of superficial siderosis | 2 focal areas of superficial siderosis | >2 areas of superficial siderosis |

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities with oedema/effusions; ARIA-H = amyloid-related imaging abnormalities with haemorrhage/hemosiderin deposition; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging.
Source: Table 2, TGA-approved Product Information of lecanemab (p4) [26].

[31] Lecanemab Production Information. URL: https://www.tga.gov.au/sites/default/files/2025-09/auspar-legembi-pi-250924.pdf

**Table 5 Dosing recommendations for patients with ARIA-E and ARIA-H**

| ARIA type | ARIA-E and ARIA-H severity on MRI | | |
|---|---|---|---|
| | **Mild** | **Moderate** | **Severe** |
| Asymptomatic | Consider suspending dosing | Suspend dosing | Suspend dosing |
| Symptomatic | Suspend dosing | | |

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities with oedema/effusions; ARIA-H = amyloid-related imaging abnormalities with haemorrhage/hemosiderin deposition; MRI = magnetic resonance imaging.
Source: Table 1, TGA-approved Product Information of lecanemab
[i] ARIA symptoms may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulties.

The application states that the brain MRI performed prior to the initiation of lecanemab is currently funded by the MBS (item number 63004)[32]. However, this item is for a brain MRI scan for inflammation of the brain or meninges, and whether the item is relevant to patients will depend entirely on their clinical condition and the requesting practitioner's decision to request that scan. As per the 1784 MSAC PSD[15], the Department proposed MBS items specific for a baseline MRI scan prior to donanemab treatment and for monitoring MRI scans during treatment, respectively, to remove ambiguity about what items can be used and avoid the situation where some patients cannot access an MBS-funded MRI scan for these purposes. In the 1784 MSAC PSD[15] (p3), it was stated that MSAC considered it would be difficult for patients to access MRI scans in regional areas. MSAC also noted that MRI monitoring before the second, third, fourth and seventh doses of donanemab (typically over 6 months) was estimated to cost more than $1 billion over 6 years, excluding medicine costs.

*PASC considered that brain MRI monitoring was recognised as an integral component of the intervention pathway given the need to monitor for treatment-related ARIA.*

*PASC noted the applicant's comments that MRI monitoring is an established component of anti-amyloid therapy and that the TGA-approved Product Information for lecanemab requires MRI monitoring for ARIA during treatment. PASC also noted the applicant's advice that a controlled access program forms part of the TGA risk-minimisation measures for lecanemab, including requirements for participating centres to confirm compliance with baseline and ongoing MRI monitoring requirements. While acknowledging these measures, PASC considered that uncertainty remains regarding implementation in routine Australian practice, particularly in relation to MRI capacity, geographic access, patient burden and the potential consequences of missed or delayed monitoring scans. PASC considered that the assessment should examine the feasibility of frequent MRI monitoring, the impact of adherence to monitoring requirements, and the potential implications of access constraints for safe and equitable delivery of treatment.*

As previously mentioned, patients in the identified population in the submission may have challenges undergoing MRI because of impaired cognition and/or contraindications such as some implanted metal medical device(s). In the 1784 MSAC PSD[15] (p8), it was stated that, "MSAC considered the capacity of Australian health system to provide equity of safe access to treatment uncertain, given the frequent clinical monitoring and brain MRI scans required especially during the early stages of treatment, and with considerable opportunity costs for other patient populations who required access to these services."

### *Comparators*

The nominated comparators for the proposed health technologies are presented in the Table 6 below.

[32] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=63004&qt=item accessed on 16 July 2026.

**Table 6 Nominated comparators for the proposed health technologies**

| Proposed health technology | Nominated comparator |
|---|---|
| Amyloid PET | No amyloid PET and standard medical management |
| t-tau/Aβ[1-42] in CSF | Amyloid PET or no testing |
| p-tau217 in plasma | Amyloid PET or no testing |
| *APOE* ε4 genotype testing | No testing and standard medical management |
| Brain MRI for treatment initiation | Currently MBS funded item for brain MRI scan |
| Brain MRI for monitoring | No monitoring (and no lecanemab treatment) |
| Lecanemab | Main comparator: standard medical management<br>Near-market comparator: donanemab |

APOE = apolipoprotein E; Aβ = amyloid beta; CSF = cerebrospinal fluid; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging; p-tau217 = phosphorylated tau at threonine 217; PET = positron emission tomography; t-tau = total tau.

According the 1784 MSAC PSD[15] (p18), PASC considered amyloid PET scanning as a comparator for CSF AD biomarker testing to determine its diagnostic accuracy.

The nominated comparators are broadly appropriate for a codependent assessment because they reflect the key decisions faced in practice: whether to undertake amyloid biomarker testing before lecanemab eligibility is considered, and, if testing is undertaken, which modality should be used to establish amyloid positivity. For amyloid PET itself, the most relevant comparator is no amyloid PET with standard medical management, because amyloid PET is not currently routine in the diagnostic workup for most patients with MCI or mild dementia in Australia.

Amyloid PET is also a reasonable comparator for CSF t-tau/Aβ[1-42] and plasma p-tau217 testing, because it is the most established *in vivo* method for detecting cerebral β-amyloid deposition and was one of the methods used to confirm amyloid positivity in the pivotal lecanemab trial. It therefore provides a clinically meaningful benchmark for assessing whether CSF or plasma biomarkers can identify a similar group of patients as amyloid PET, particularly where the purpose of testing is to determine eligibility for an anti-amyloid therapy. In this context, comparisons with amyloid PET should include diagnostic agreement or concordance, the proportion of discordant results, and the consequences of discordance for treatment eligibility decisions.

However, amyloid PET is not a perfect comparator. A positive amyloid PET result demonstrates amyloid deposition but does not, by itself, establish that AD is the cause of the patient's cognitive impairment, because amyloid deposition may also occur in cognitively normal older adults and in people with non-AD dementias. Its predictive value therefore depends on the pre-test probability of AD after specialist clinical assessment. Amyloid PET is also less suitable as a pragmatic comparator if the question is what would replace CSF or plasma testing in routine Australian practice, because access to amyloid PET is constrained by scanner availability, radiotracer supply, specialist workforce, cost and geographic inequity.

For *APOE* ε4 genotype testing, CSF and plasma biomarker testing, "no testing" is also an appropriate comparator because, in the absence of these tests, patients would generally continue with standard medical management based on clinical diagnosis, structural imaging and available symptomatic therapies. This comparison is particularly important for estimating the incremental clinical and economic impact of adding these tests to the current diagnostic pathway.

For a baseline brain MRI before lecanemab initiation, the nominated comparator of a currently MBS-funded brain MRI item is partly appropriate, because structural brain MRI is already used in the diagnostic workup of cognitive impairment to exclude alternative or reversible causes, and the application notes that

an MRI before treatment may be available under existing MBS arrangements. However, it may not be a fully adequate comparator if the proposed baseline MRI has a more specific purpose: identifying MRI features that would preclude treatment with lecanemab (e.g. prior haemorrhage, multiple microhaemorrhages, superficial siderosis, severe small-vessel disease, vasogenic oedema, prior major stroke or other clinically significant intracranial pathology).

For MRI monitoring during treatment, "currently MBS-funded brain MRI" may be less appropriate as the main comparator. Monitoring MRI is not being used to diagnose AD or exclude alternative pathology; it is being used as a required safety-monitoring component of lecanemab treatment to detect ARIA and guide treatment interruption, suspension or discontinuation. Because the TGA-approved PI for lecanemab specifies scheduled MRI scans before particular infusions, MRI monitoring is effectively part of the treatment pathway rather than an optional diagnostic test. Therefore, a more appropriate comparator may be lecanemab without scheduled MRI monitoring (not allowed as per TGA-approved PI) or no lecanemab (and no monitoring) and standard medical management, depending on the assessment question. However, "lecanemab without MRI monitoring" may be clinically unrealistic or unacceptable if MRI monitoring is required for safe use and is embedded in the Product Information.

In an economic model, it may be most appropriate to treat MRI monitoring as a co-intervention required for lecanemab, rather than as a standalone investigative test with an independent comparator. That is, the relevant comparison is likely to be testing plus lecanemab plus MRI monitoring versus no testing and standard medical management, with MRI costs, capacity implications, adherence issues and consequences of missed scans included in the lecanemab arm. This avoids presenting MRI as if it were an optional alternative to usual care when, in practice, patients would either receive lecanemab with the required MRI monitoring schedule or not receive lecanemab.

Donanemab is a TGA-approved (ARTG ID 420194) amyloid targeting drug for treating early-stage AD but was not recommended for listing on the PBS by the Pharmaceutical Benefits Advisory Committee (PBAC) in the July 2025 PBAC Meeting[33]. The applicant nominates donanemab as a near-market comparator as a contingency for a scenario whereby the manufacturer of donanemab has lodged a resubmission to the PBAC requesting PBS listing of donanemab prior to the applicant lodging the codependent submission requesting that lecanemab be listed on the PBS.

*PASC agreed with the proposed comparators listed, and that 'no testing' was the appropriate comparator for most of the proposed investigations.*

*PASC noted the applicant's comments that brain MRI monitoring is required for the safe use of lecanemab and that MRI performed through existing MBS items is therefore a more appropriate comparator for MRI monitoring than "no monitoring". PASC considered that MRI monitoring should be viewed as part of the overall treatment pathway and that the assessment should examine the clinical and economic implications of MRI monitoring requirements in routine practice.*

*PASC noted the applicant's comments that donanemab was nominated as a contingency near-market comparator. PASC considered that standard medical management remains the principal comparator, but that the appropriateness of donanemab as a near-market comparator will depend on its PBS status and relevance to Australian clinical practice at the time of the assessment.*

[33] https://www.pbs.gov.au/medicinestatus/document/1383 accessed on 06Jul2026

### *Reference standard (for investigative technologies only)*

- The reference standard for a positive amyloid PET finding for AD would be post-mortem autopsy of the brain.
- The reference standard for a positive test of t-tau/Aβ[1-42] in CSF would be amyloid PET scan.
- The reference standard for a positive testing of p-tau217 in plasma would be amyloid PET scan.
- The reference standard for *APOE* ε4 genotype testing would be Sanger sequencing.

For the evaluation of biomarker tests used to identify AD pathology, the choice of reference standard depends on the test being assessed. Histopathological confirmation of amyloid deposition in the brain at post-mortem autopsy is considered the definitive reference standard for a positive amyloid PET result, as it directly confirms the presence of AD-related neuropathology. However, because autopsy data are rarely available in clinical studies, amyloid PET is commonly used as the reference standard for evaluating CSF and plasma biomarkers. Accordingly, the diagnostic accuracy of CSF t-tau/Aβ1–42 and plasma p-tau217 would be assessed against amyloid PET findings, which are currently considered the most established *in vivo* measure of cerebral β-amyloid pathology.

Although amyloid PET is a clinically relevant reference standard for assessing CSF and plasma biomarkers because it is an established *in vivo* measure of cerebral β-amyloid deposition, it is an imperfect reference standard. The performance of amyloid PET may vary according to tracer, acquisition protocol, reader expertise, visual versus quantitative interpretation and threshold used to define positivity. These limitations are important when amyloid PET is used as the reference standard for CSF or plasma biomarkers because diagnostic accuracy estimates will reflect concordance with amyloid PET rather than direct confirmation of AD neuropathology or clinical treatment benefit.

*PASC noted the applicant's comments that amyloid PET is the accepted reference standard for validation of CSF and plasma biomarkers and that post-mortem neuropathology is rarely available in diagnostic studies. PASC considered that amyloid PET was the appropriate practical reference standard for assessment of biomarker tests, while recognising its limitations as an indirect measure of AD pathology. PASC also noted the applicant's comments regarding brain MRI and agreed that MRI represents the relevant reference standard for anatomical assessment and ARIA monitoring, such that a separate reference standard for MRI was not required.*

*PASC agreed with the other reference standards presented in the PICO.*

### *Clinical utility standard (for codependent investigative technologies only)*

The analytical validity of each of the testing options available in Australia will need to be assessed against the clinical utility standard to confirm their clinical utility. In the pivotal Phase III CLARITY-AD trial, amyloid positivity was determined using amyloid PET and/or CSF biomarkers, with amyloid PET representing one of the principal methods used to confirm eligibility for treatment (van Dyck et al. 2023) (Table 7). The amyloid PET test and testing conditions employed in the pivotal studies, including the tracer used and centralised visual interpretation, are regarded as the evidentiary standard for this assessment. The analytical validity of the testing options proposed for use in Australia should therefore be assessed by comparison with this evidentiary standard. Measures of diagnostic performance, including sensitivity, specificity and concordance, should be used to determine the extent to which each testing option can reproduce the

evidentiary standard. For amyloid PET, this assessment should be conducted for each individual radiopharmaceutical available in Australia.

*PASC noted the applicant's comments that the CLARITY AD trial protocol used the CSF t-tau/Aβ1-42 ratio, rather than a single CSF Aβ1-42 biomarker (as stated in the published CLARITY AD trial), to confirm amyloid positivity. PASC acknowledged that the proposed CSF biomarker approach may therefore be more closely aligned with the evidentiary standard used in the pivotal trial than initially described in the published CLARITY AD trial. PASC considered that the assessment should clearly describe the CSF testing methodology used in the pivotal evidence base and evaluate whether the proposed assays and testing conditions used in Australian practice are sufficiently comparable to those used in CLARITY AD.*

**Table 7 Tests included in determining eligibility for lecanemab and monitoring patients while on treatment**

| Test/technology | Role in CLARITY AD trial | Relevance to this assessment |
|---|---|---|
| Amyloid PET | One of the methods used to determine amyloid positivity in patients eligible for lecanemab. | Represents an evidentiary standard for confirming amyloid pathology and treatment eligibility. |
| t-tau/Aβ[1-42] in CSF[a] | The trial protocol used CSF t-tau/Aβ[1-42] testing to determine amyloid positivity. | Represents an evidentiary standard for confirming amyloid pathology and treatment eligibility. The proposed ratio measure is the same as the CSF approach used in the key study, as described by the trial protocol. The assessment should describe the CSF methodology used in the evidence base and evaluate whether the proposed assays and testing conditions used in Australian practice are sufficiently comparable to those used in the trial. |
| p-tau217 in plasma | Not used to determine amyloid positivity or treatment eligibility in CLARITY AD. | Additional evidence should be presented because p-tau217 is not currently TGA-approved in Australia. There is evidence available on the accuracy/concordance of plasma p-tau217. |
| *APOE* ε4 genotype testing | Used as a randomisation stratification factor to evaluate ARIA risk among lecanemab-treated patients. | Relevant to treatment eligibility and ARIA risk stratification, particularly exclusion of *APOE* ε4 homozygotes. |
| Brain MRI | Used to determine eligibility for treatment.<br>Also performed at the 3rd, 5th, 7th and 14th infusion of lecanemab for safety monitoring. | Identifies features that would preclude lecanemab treatment because they indicate a high risk of ARIA or intracerebral haemorrhage.<br>Relevant to monitoring for ARIA and assessing feasibility, capacity and adherence in routine practice. |
| Lecanemab | Associated with moderately less decline in cognition and function and reduced amyloid markers over 18 months compared with placebo. | Forms the linked therapeutic component of the codependent assessment. |

AD = Alzheimer's disease; APOE = apolipoprotein E; ARIA = amyloid-related imaging abnormalities; Aβ = amyloid beta; CSF = cerebrospinal fluid; HTA = health technology assessment; MRI = magnetic resonance imaging; p-tau217 = phosphorylated tau at threonine 217; PASC = PICO Advisory Sub-Committee; PET = positron emission tomography; PICO = population, intervention, comparator and outcome; t-tau = total tau; TGA = Therapeutic Goods Administration.

[a]The published CLARITY AD trial states that the CSF test measured a single biomarker Aβ[1-42] (van Dyck et al., 2023). However, the trial protocol states that the CSF test consisted of t-tau/Aβ[1-42] testing, and this was confirmed by the applicant.

### *Outcomes*

*PASC considered that outcomes should focus on the clinical utility of the overall diagnostic pathway and its ability to support appropriate access to lecanemab.*

*PASC noted the applicant's comments that the primary purpose of amyloid pathology testing in this application is to determine eligibility for lecanemab rather than to establish a diagnosis of AD, and that follow-up amyloid pathology testing to guide treatment continuation or discontinuation has not been proposed by the applicant. PASC acknowledged that the proposed tests are intended to support treatment selection; however, considered that testing may also influence diagnostic confidence and subsequent clinical management in routine practice. Therefore, PASC considered that outcomes relating to possible change in management and treatment remain relevant to the assessment of clinical utility.*

*PASC also noted the applicant's comments that APOE ε4 genotyping had previously been considered by MSAC, that MSAC had not raised any substantial concerns regarding test performance, and that MRI is already an established component of clinical practice for structural brain assessment and ARIA monitoring. PASC agreed that there is limited uncertainty regarding the analytical performance of APOE ε4 genotyping and MRI as technologies. However, PASC considered that outcomes related to their role within the overall treatment pathway, including impact on treatment eligibility, ARIA risk stratification, treatment management, service utilisation, implementation, access and costs, remain relevant for the assessment.*

*PASC noted the applicant's clinical expert stated that emerging real-world evidence (registry data) is available and may provide additional information regarding the effectiveness, safety and implementation of anti-amyloid therapies in routine practice which could inform the related PBAC assessment of the treatment.*

**Test-related outcomes**

<u>Amyloid PET of the brain:</u>

Outcomes:

- Diagnostic performance
    - Sensitivity, specificity against reference standard, positive likelihood ratio, negative likelihood ratio
    - Concordance between amyloid PET as conducted in Australia and the evidentiary standard
    - Yield of testing (proportion of patients identified as having brain amyloid deposition)
    - Test reliability/validity
- Test safety
    - Levels of radiation exposure, rate and nature of adverse events associated with the PET tracer and scanning.
    - Psychological and physical harms of amyloid PET test results
- Change in management /clinical utility
    - Proportion of patients commencing lecanemab following testing
    - Proportion of patients with a change in diagnosis following testing
    - Proportion of patients continuing/discontinuing/changing treatment following amyloid PET

- Healthcare system outcomes
    - Capacity of healthcare facilities for the increased requests of PET scans from specialists
    - Waiting times and access to PET services
    - Equity of access (rural, regional and Indigenous populations)
- Economic outcomes
    - Cost per test
    - Cost-effectiveness

<u>t-tau/Aβ[1-42] in CSF</u>

Outcomes:

- Diagnostic performance:
    - Sensitivity and specificity (where evidence available)
    - Positive, negative, and overall percentage agreement with amyloid PET
    - Turnaround time
- Safety
    - Lumbar puncture-related complications
    - Other adverse events and harms of CSF testing and test results
- Change in management /clinical utility
    - Proportion of patients commencing lecanemab following testing
    - Proportion of patients with a change in diagnosis following testing
    - Proportion of patients continuing/discontinuing/changing treatment following t-tau/Aβ[1-42] in CSF
- Healthcare system outcomes
    - Capacity for lumbar puncture services
    - Laboratory capacity
    - Capacity of health professionals for the increased number of patients requiring lumbar puncture
    - Capacity of laboratories for the increased amount of CSF samples for testing
- Economic outcomes
    - Cost per test
    - Cost-effectiveness

<u>p-tau217 in plasma</u>

Outcomes:

- Diagnostic performance
    - Sensitivity and specificity (compared with amyloid PET)
    - Positive, negative, and overall percentage agreement with amyloid PET

- Turnaround time

- Safety
  - Test-related adverse events
- Change in management /clinical utility
  - Identification of patients likely to have amyloid pathology
  - Impact on subsequent use of amyloid PET/CSF testing
  - Proportion of patients proceeding to confirmatory testing
  - Impact on treatment eligibility decisions
- Healthcare system outcomes
  - Laboratory capacity
  - Impact on access to biomarker testing
- Economic outcomes
  - Cost per test
  - Cost-effectiveness

<u>*APOE* ε4 genotype testing</u>

Outcomes:

- Safety
  - Test-related adverse events
- Change in management /clinical utility
  - Impact on treatment eligibility decisions (proportion of patients commencing lecanemab following testing)
  - Impact on ARIA risk stratification
- Healthcare system outcomes
  - Laboratory capacity
- Economic outcomes
  - Cost per test
  - Cost-effectiveness

<u>Brain MRI</u>

- Safety
  - MRI-related adverse events
  - Adherence/compliance with monitoring strategy
- Change in management /clinical utility
  - Impact on treatment management following MRI findings (treatment interruption, suspension or discontinuation resulting from MRI findings)

- Impact on treatment management after no MRI (e.g. non-compliance, unable to undergo MRI)

- Healthcare system outcomes
  - MRI workforce and scanner capacity
  - Waiting times
  - Geographic access
- Economic outcomes
  - Cost per scan
  - Cost-effectiveness of MRI monitoring strategy

**Treatment-related outcomes**

- Primary effectiveness outcome: Change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score[34]
- Secondary effectiveness outcomes
  - Alzheimer Disease Assessment Scale-Cognitive subscale 14 item Version (ADAS-Cog14)[35]
  - Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL)[36]
  - Alzheimer's Disease Composite Score (ADCOMS)[37]
  - EuroQol 5-Dimension 5-Level (EQ-5D-5L)[38]
  - Quality of Life in Alzheimer's Disease (QOL-AD)[39]
  - Zarit Burden Interview (ZBI) [40]
  - Brain amyloid levels measured by amyloid PET centiloids[41]
- Safety outcomes
  - Any adverse event
  - Any adverse event resulting in discontinuation of the randomised treatment
  - Any serious adverse event

[34] CDR-SB is a quantitative measure of cognitive and functional impairment. It sums scores across 6 domains: memory, orientation, judgement/problem solving, community affairs, home/hobbies and personal care. The total range of score is from 0 (normal) to 18 (severe dementia).
[35] Designed to assess cognitive function in people with Alzheimer's disease. Domains assessed are memory, language, praxis, orientation and executive type functions.
[36] Designed to assess real-world functional performance in people with mild cognitive impairment. Domains assessed relate to cognitive complex daily tasks such as shopping, navigating out of the home and using household appliances.
[37] A composite measure consists of cognitive and functional components from the ADAS-Cog (4 items), Mini-Mental State Examination (2 items) and CDR-SB (6 items) instruments.
[38] A universal health-related quality of life instrument including 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
[39] Designed to be used specifically by people with Alzheimer's disease and their caregivers. The instrument contains 13 domains to be rated.
[40] Designed to assess caregiver burden.
[41] A standardised metric allowing PET results from difference tracers, scanners and analysis methods to be expressed on a common scale. The amyloid PET centiloids scale uses two anchor points: 0 and 100. Higher centiloid levels represent higher amyloid burden.

- Any adverse event resulting in death
- Other types of adverse event where the frequency or severity differs across groups (e.g. ARIA events and infusion-related reactions)

- Other treatment related considerations
  - Capacity of healthcare facilities for the increased number of patients who require IV infusions of lecanemab every 2 weeks
  - Capacity of health professionals for the increased number of patients who are on lecanemab and need monitoring of ARIA
  - Cost and cost-effectiveness
  - Impact on health equity

## Assessment framework (for investigative technologies)

The aim of the codependent submission will be to demonstrate that testing for amyloid pathology (using amyloid PET, biomarker testing in CSF or plasma), as well as testing for *APOE* ε4 genotype, followed by lecanemab treatment and brain MRI scans during the treatment period, results in superior effectiveness and inferior safety compared to no testing plus standard medical management in individuals with MCI or mild dementia due to AD who test positive for amyloid pathology and negative for *APOE* ε4 homozygosity. The pivotal trial, CLARITY AD, is a Phase III, 18-month, randomised trial comparing lecanemab versus placebo in patients with MCI or mild dementia due to AD and amyloid positivity (confirmed by amyloid PET or AD biomarker in CSF). The CLARITY AD trial provides evidence of (1) lecanemab resulting in a delay in decline of cognition and function as well as reducing markers of amyloid in treated patients; (2) *APOE* ε4 genotype testing assisting in categorising patient's risk for developing ARIAs (ε4 allele non-carrier — low risk, heterozygote — moderate risk, homozygote — high risk); (3) the role of MRI scans during treatment period in monitoring the occurrence of ARIA and in assisting clinical decision-making (dose suspension or termination). The CLARITY AD trial does not provide evidence to support the link between plasma AD biomarker testing and its result in change in clinical decision-making and a subsequent improved health outcome. Further evidence will be required to supplement the key trial, in order to demonstrate that testing of AD biomarker in plasma results in change in clinical decision-making, whether it selects the population that would most benefit from lecanemab, and its association with an improved health outcome.

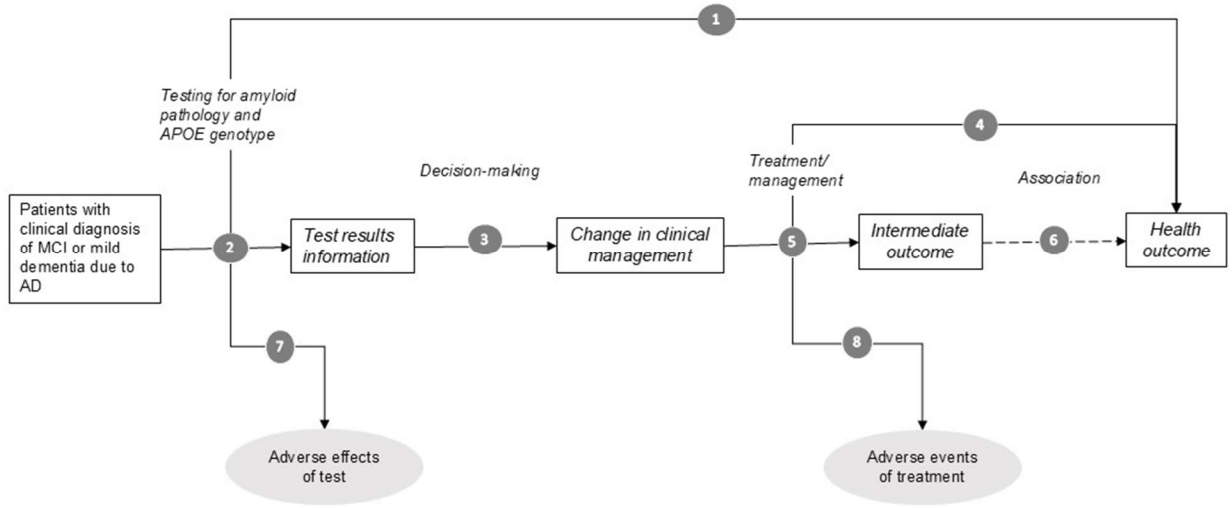



**Figure 1 Generic assessment framework showing the links from the test population to health outcomes**

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Research questions mapped to the assessment framework (Figure 1):

1. What is the effectiveness and safety of testing of amyloid pathology (using the amyloid PET and immunoassay of t-tau/Aβ[1-42] in CSF and p-tau217 in plasma) and testing of *APOE* ε4 genotype, as well as lecanemab treatment versus no testing and standard medical management of AD?
2. What is the accuracy of the testing of amyloid pathology (using the amyloid PET and immunoassay of t-tau/Aβ[1-42] in CSF and p-tau217 in plasma, respectively) in patients with MCI or mild dementia due to suspected AD, compared with the comparator?
3. Does the availability of new information from the proposed tests lead to a change in management for the patient (i.e. does the patient receive lecanemab), compared to the information gained from the comparator?
4. What is the effectiveness of lecanemab in long-term cognition and function benefit in patients with MCI and mild dementia due to AD versus standard medical management of AD?
5. What is the effectiveness of lecanemab in short-term (18-month) cognition and function benefit in patients with MCI and mild dementia due to AD versus standard medical management of AD?
6. How valid is the link between short-term and long-term cognition and function benefit in patients with MCI or mild dementia due to AD?
7. What are the adverse events associated with the proposed tests (e.g. amyloid PET, lumbar puncture, blood tests, MRI)?
8. What is the safety of lecanemab versus standard medical management of AD in patients with MCI or mild dementia due to AD?

*PASC considered that evidence should demonstrate the clinical utility of the overall diagnostic pathway, rather than focusing solely on the performance of the individual tests.*

*Overall, the proposed assessment framework was supported by PASC.*

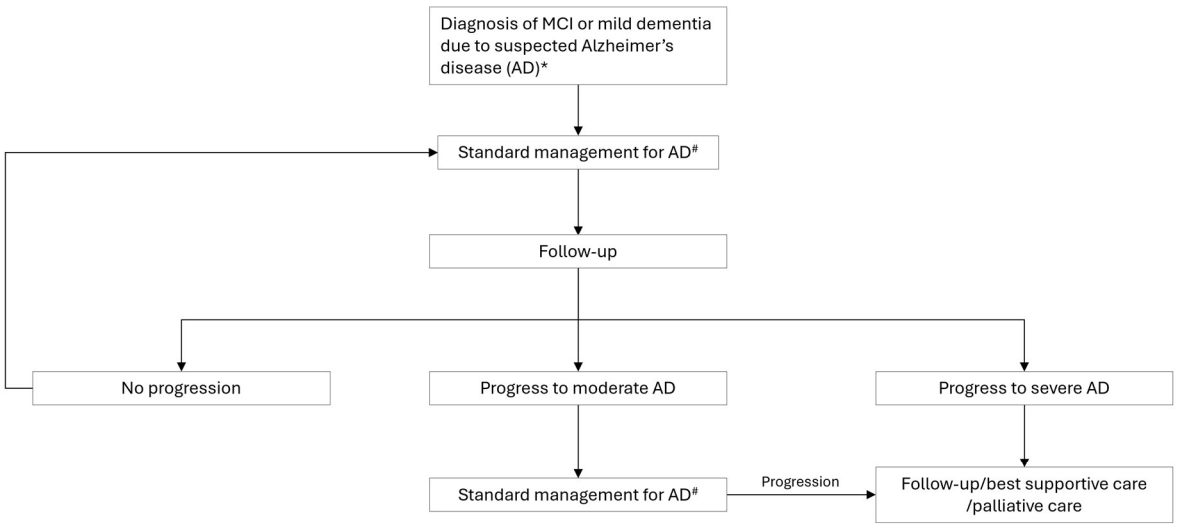
# Clinical management algorithms

**Current clinical management algorithm for the identified population**

Based on the *Clinical Practice Guidelines and Principles of Care for People with Dementia* (released in 2016) (Dyer et al. 2016), the diagnostic workup for patient presenting with cognition impairment begins with a comprehensive clinical assessment that includes history taking (from the affected person and from a person who knows the affected person well), physical examination, cognitive mental state examination using a validated instrument, review of medication, and consideration of other causes. Also included in the diagnostic workup are the basic dementia screen that includes routine haematology, biochemistry test (including electrolytes, calcium, glucose, renal, liver, and thyroid function, serum vitamin B12 and folate levels). Imaging study including MRI (preferred) or CT (when MRI is contraindicated) of the brain are currently funded by the MBS for patients where there is need to exclude other reversible causes of cognition impairment. FDG-PET became available and listed on the MBS (Item 61505) in 2021 to assist in the diagnosis of AD when clinical evaluation by a specialist is inconclusive. In late 2024, testing of biomarker in CSF became available in Australia (but not listed on the MBS) to assist diagnosis of AD.

For patients diagnosed with MCI or mild dementia caused by AD, the current standard medical management include observation, nutrition support, rehabilitation interventions that aim to optimise independence, behavioural and psychological symptom control, and in some patients, consider medication such as AChEI or NMDA receptor antagonist for symptom management. As there is no cure for AD and the condition always progresses, a palliative approach may be required in patients with dementia due to AD who have progressed to an advanced stage.

The current clinical management algorithm for the identified population is shown in Figure 2.




Abbreviation: MCI = mild cognition impairment; AChEI = acetylcholinesterase inhibitors; FDG = fluorodeoxygloucose; NMDA = N-methyl-D-aspartate; PET = positron emission tomography
*Diagnosis of AD may be assisted by FDG-PET (listed on the MBS) and/or biomarker testing in CSF (not listed on the MBS)
#Standard management for AD includes observation, nutrition support, rehabilitation, behavioural/ psychological symptom control, consider AChEI/NMDA

**Figure 2 Current clinical management algorithm**

### *Proposed clinical management algorithm for the identified population*

The proposed clinical management algorithm for the identified population is shown in Figure 3. In the proposed clinical management algorithm, the same steps are followed to establish the clinical diagnosis as in the current clinical management algorithm. Patients are assessed comprehensively with history taking, physical examination, cognitive examination, review of medication, and basic tests for the identification of dementia. Those patients who receive a clinical diagnosis of MCI or mild dementia due to AD then undergo brain MRI for exclusion of other possible aetiologies leading to cognition impairment and for baseline screening for contraindication to lecanemab treatment[42]. Patients whose brain MRI scan identifies a contraindication to lecanemab treatment[42] would receive standard medical management for AD. Patients with no contraindications identified on brain MRI would be tested for amyloid pathology using plasma p-tau217. Individuals with an equivocal plasma biomarker test result would undergo amyloid PET or the testing of t-tau/Aβ[1-42] in CSF for a confirmation of amyloid pathology.

It is currently unclear whether a positive plasma biomarker test result using p-tau217 alone would be considered adequate to determine eligibility for lecanemab, or whether confirmatory testing using amyloid PET or CSF biomarkers would be required. This distinction is important because plasma biomarker testing was not used to determine amyloid positivity or treatment eligibility in the CLARITY-AD trial, where eligibility was based on amyloid PET or CSF biomarkers.. Where less accurate plasma biomarkers are used, their role may be limited to triage or rule-out testing, with positive or equivocal results requiring confirmation by amyloid PET or CSF testing.

[42] According to the TGA approved lecanemab PI, pre-treatment MRI findings that are contraindicated to lecanemab treatment include prior intracerebral haemorrhage >1cm, microhaemorrhages >2, superficial siderosis or vasogenic oedema (ARIA-E), which are suggestive of cerebral amyloid angiopathy, severe white matter disease, or any finding that could prevent a satisfactory MRI evaluation for safety monitoring during lecanemab treatment.

Early evidence suggests that plasma p-tau217 may have diagnostic performance approaching that of CSF biomarkers for detecting amyloid pathology (Therriault et al. 2023) (Khalafi et al. 2025), and clinical input at the Pre-PASC teleconference indicated a preference for p-tau217 over other plasma biomarkers. However, the proposed role of plasma p-tau217 in the algorithm requires clarification, including whether clearly positive results are sufficient to establish amyloid positivity, whether only equivocal results proceed to PET or CSF testing, or whether all positive plasma results require confirmation.

*PASC considered there was uncertainty regarding how emerging blood-based biomarkers, particularly p-tau217, would be incorporated into clinical practice and whether they may reduce the need for more expensive or invasive investigations such as amyloid PET.*

Individuals with a positive amyloid test result will then undergo *APOE* ε4 genotyping before consideration of treatment with lecanemab. *APOE* ε4 genotyping should occur only after other eligibility criteria for lecanemab have been established, including clinical eligibility, absence of MRI contraindications and confirmation of amyloid pathology. Clinical input indicated that *APOE* ε4 testing should not be performed before these criteria are met. For the purpose of this assessment, *APOE* ε4 testing is not intended to diagnose AD or determine future AD risk; rather, it is intended to identify patients at increased risk of ARIA and to exclude patients who are *APOE* ε4 homozygotes (for whom lecanemab is contraindicated). This order of testing is also important because *APOE* ε4 homozygosity has implications for relatives and may disclose information about inherited risk of AD. It was stated during the pre-PASC teleconference that ethical issues associated with identifying future AD risk in patients and relatives should be avoided in circumstances where the patient is otherwise ineligible for treatment with lecanemab. The consent process prior to *APOE* ε4 testing should consider the genetic implications of identifying homozygosity.

Those who are tested as *APOE* ε4 non-carrier or heterozygote would be eligible for lecanemab treatment, subject to other clinical criteria, and would require MRI monitoring for the development of ARIA and other adverse events related to lecanemab. Patients who test negative for amyloid pathology or who are *APOE* ε4 homozygotes will receive standard medical management for AD.

*PASC discussed the proposed diagnostic and treatment pathway and noted uncertainty regarding the optimal sequencing of investigations. PASC queried whether plasma p-tau217 testing should be used as an initial triage test to identify patients requiring further assessment. PASC also discussed the optimal timing of APOE ε4 genotyping, noting that testing may be more appropriate after amyloid pathology has been established, given the implications of communicating genetic risk information and the need for genetic counselling. PASC discussed whether amyloid PET and APOE ε4 testing should occur sequentially or concurrently and considered that different approaches may have different clinical and economic consequences. Specifically, under a sequential approach, if amyloid PET is negative, then APOE e4 genotyping will not be required.*

*PASC noted the applicant's comments that the proposed clinical management algorithm (Figure 3) did not fully reflect the testing pathway proposed by the applicant in their original application. The applicant's main concern was that the proposed clinical management algorithm (Figure 3) suggested that APOE ε4 genotyping should only occur in patients found to be amyloid positive. However, the applicant advised that the proposed MBS item descriptors were intended to provide flexibility regarding the sequencing of investigations and that, in clinical practice, amyloid pathology testing and APOE ε4 genotyping are often requested concurrently to minimise delays in obtaining the information required to inform treatment decisions. PASC noted concerns about ethical and legal implications of genotyping remain important.*

*PASC considered that the assessment should investigate the proposed algorithm and explore the impact of alternative testing pathways (with a different sequence of tests) on patient selection, access, counselling safety, resource utilisation and cost-effectiveness.*

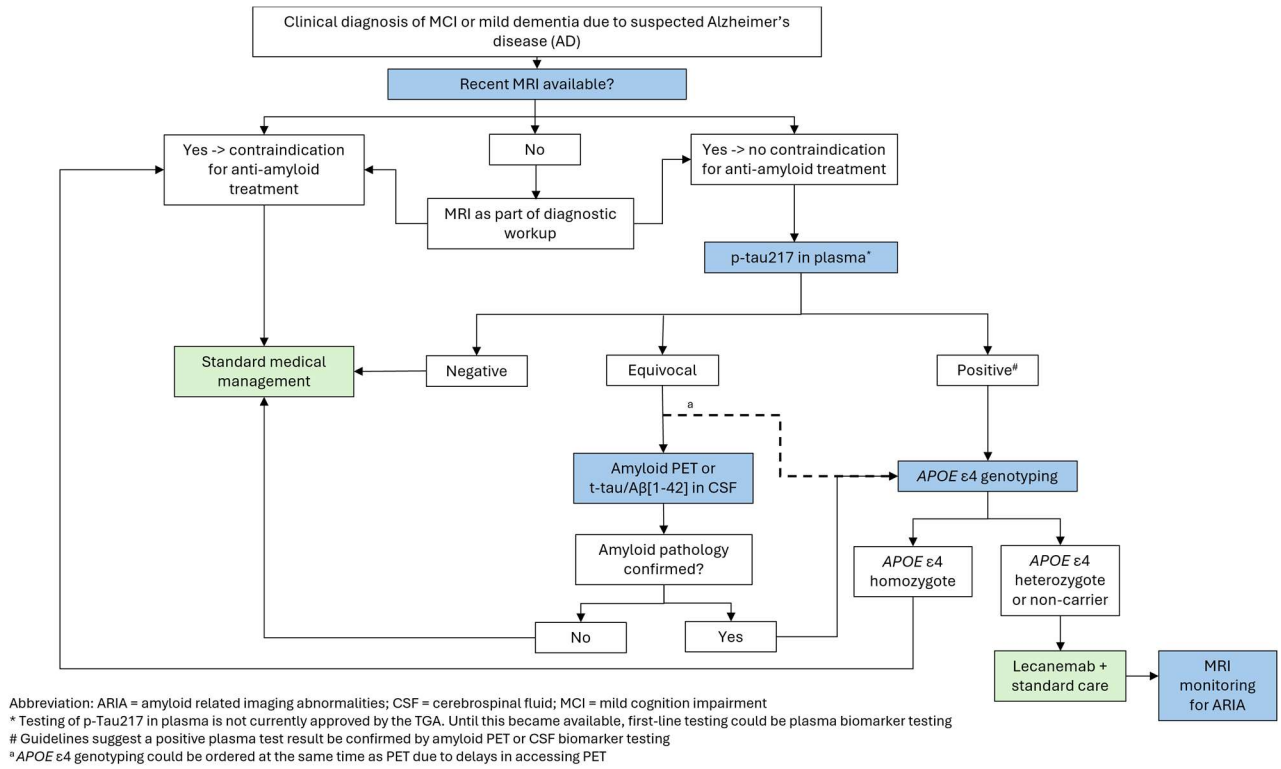



**Figure 3 Proposed clinical management algorithm**

# Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (testing for amyloid pathology using amyloid PET, biomarker in CSF or in plasma, as well as testing for *APOE* ε4 genotype, followed by amyloid-targeting lecanemab treatment and follow-up MRI scans during treatment period) result in superior effectiveness in cognition and function benefit and inferior safety compared to no testing plus standard medical management in individuals with MCI or mild dementia due to AD who have tested positive for amyloid pathology and negative for *APOE* ε4 homozygosity. The appropriate type of economic evaluation to be included in the assessment report would be a cost-utility analysis (CUA) (Table 8).

*PASC supported the economic evaluation to be a CUA. PASC considered that the economic evaluation should compare alternative diagnostic and clinical management pathways, including different sequencing approaches for ptau217, amyloid PET, CSF and APOE ε4 testing, and should assess the implications of testing uptake, brain MRI monitoring requirements, safety management and equitable access on overall cost-effectiveness.*

**Table 8 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation**

| Comparative safety | Comparative effectiveness | | | |
|---|---|---|---|---|
| | Inferior | Uncertain[a] | Noninferior[b] | Superior |
| Inferior | Health forgone: need other supportive factors | Health forgone possible: need other supportive factors | Health forgone: need other supportive factors | ? Likely CUA |
| Uncertain[a] | Health forgone possible: need other supportive factors | ? | ? | ? Likely CEA/CUA |
| Noninferior[b] | Health forgone: need other supportive factors | ? | CMA | CEA/CUA |
| Superior | ? Likely CUA | ? Likely CEA/CUA | CEA/CUA | CEA/CUA |

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis.
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

# Proposal for public funding

Currently, a brain MRI before initiating lecanemab treatment may be performed using existing MBS items. However, the Department noted that using some items for baseline MRI scans associated with lecanemab treatment eligibility may deplete access to an item that is subject to annual service limits. Therefore, a new MBS item specifically for MRI before treatment initiation was proposed (EEEE) for the exclusion of ambiguity about available MBS items. Amyloid PET, testing of t-tau/Aβ[1-42] in CSF and p-tau217 in plasma, *APOE* ε4 genotyping, and follow-up MRI scans during the lecanemab treatment period are not yet listed. The six different proposed MBS item descriptors for these tests are shown in Table 9 to Table 14 below. Edits proposed by the HTA group are shown in red.

It should be noted that the proposed population in many of the proposed MBS item descriptors is "patients with a clinical diagnosis of MCI due to suspected AD or mild AD dementia" (with "suspected" added by the HTA group.

The proposed item descriptor BBBB is broad "Analysis of amyloid and tau proteins in cerebrospinal fluid" and does not specify which biomarkers are eligible for testing.

*PASC noted the importance of minimising the potential for unintended utilisation of publicly funded testing. PASC noted that the wording of the item descriptors is important in limiting test use to patients undergoing assessment for lecanemab eligibility, given concerns about broader uptake of blood-based biomarker testing outside the intended population. PASC considered that the proposed item descriptors should clearly specify the target population, intended purpose and sequencing of the proposed investigations within the assessment and treatment pathways.*

*PASC noted that there may be genetic counselling requirements associated with APOE ε4 testing and considered that these will need to be appropriately addressed in an explanatory note.*

On proposed MBS item FFFF, an annual service limit of 4 scans per patient has been included. However, ARIA monitoring is typically linked to specific infusion milestones rather than an arbitrary annual

frequency. If the PBS/TGA schedule changes, the MBS descriptor may become misaligned. Further, clinical practice with regard to anti-amyloid monoclonal antibodies is evolving in Australia as these treatments become available. A major Australian radiology provider has adopted standardised protocols for ARIA monitoring based on recommendations developed by the American Society of Neuroradiology[43], and has implemented these protocols across its MRI network to support patients receiving anti-amyloid monoclonal antibody therapies. This protocol includes monthly MRI scans when ARIA is detected, regardless of whether symptoms are present, until the ARIA resolves or stabilises.

*PASC noted the applicant's comments that the proposed limit of four brain MRI scans per year may not accommodate additional monitoring required following detection of ARIA and that greater flexibility in MRI utilisation may be warranted. PASC considered that MRI monitoring requirements, including the need for additional scans beyond the routine schedule, should be considered in the assessment of implementation, service utilisation and costs, along with supporting evidence.*

**Table 9 Proposed MBS item descriptor for amyloid PET**

| Category 5 – Diagnostic imaging service | *Group I4 – Nuclear Medicine Imaging* |
|---|---|
| Proposed item descriptor ~~XXXXX~~AAAA<br>Beta-amyloid positron emission tomography (PET) study of the brain, requested by a specialist or consultant physician, for the evaluation of patients with a clinical diagnosis of Mild Cognitive Impairment (MCI) due to suspected Alzheimer's disease or Mild Alzheimer's dementia, to determine eligibility for treatment with an anti-amyloid monoclonal antibody agent to treat Alzheimer disease under the Pharmaceutical Benefits Scheme, if (1) the patient considered for this service also meets specific PBS eligibility criteria; and (2) the patient has not previously been treated and is not currently undergoing treatment with the pharmaceutical. | |
| Fee: $1,800 | |

MBS = Medicare Benefits Schedule; MCI = mild cognitive impairment; PBS = Pharmaceutical Benefits Scheme; PET = positron emission tomography.

**Table 10 Proposed MBS item descriptor for t-tau/Aβ[1-42] in CSF**

| Category 6 – Pathology service | *P2 – Chemical (TBC)* |
|---|---|
| Proposed item descriptor ~~XXXXX~~BBBB<br>Analysis of amyloid and tau proteins in cerebrospinal fluid, requested by a specialist or consultant physician, from a patient with a clinical diagnosis of Mild Cognitive Impairment (MCI) due to suspected Alzheimer's disease or Mild Alzheimer's dementia, to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme | |
| Fee: $400 | |

Aβ = amyloid beta; CSF = cerebrospinal fluid; MBS = Medicare Benefits Schedule; MCI = mild cognitive impairment; t-tau = total tau; TBC = to be confirmed.

**Table 11 Proposed MBS item descriptor for p-tau217 in plasma**

| Category 6 – Pathology service | *P2 – Chemical (TBC)* |
|---|---|
| Proposed item descriptor ~~XXXXX~~CCCC<br>Quantitation of phosphorylated at threonine 217 (ptau217) in plasma, requested by a specialist or consultant physician, from a patient with a clinical diagnosis of Mild Cognitive Impairment (MCI) due to suspected Alzheimer' disease or Mild Alzheimer's dementia, to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme. | |
| Fee: TBC | |

[43] I-MED Radiology Network. MRI Protocols for ARIA monitoring. URL: https://i-med.com.au/mri-protocols-for-aria-monitoring#gsc.tab=0 accessed on 17 Jul 2026

MBS = Medicare Benefits Schedule; MCI = mild cognitive impairment; p-tau217 = phosphorylated tau at threonine 217; TBC = to be confirmed.

**Table 12 Proposed MBS item descriptor for *APOE* genetic testing**

| Category 6 – Pathology service | *P7 – Genetics* |
|---|---|
| Proposed item descriptor ~~XXXXX~~DDDD<br>Genetic testing to determine apolipoprotein E ε4 (APOE ε4) genotype as requested by a specialist or consultant physician for patients with a clinical diagnosis of Mild Cognitive Impairment (MCI) due to suspected Alzheimer's disease or Mild Alzheimer's dementia to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme. | |
| Fee: $154.00 | |

APOE = apolipoprotein E; MBS = Medicare Benefits Schedule; MCI = mild cognitive impairment.

**Table 13 Proposed MBS item descriptor for brain MRI scan prior to initiating treatment**

| Category 5 – Diagnostic imaging service | *I5 – Magnetic Resonance Imaging*<br>*Subgroup 1 – Scan of head – for specified conditions* |
|---|---|
| Proposed item descriptor ~~XXXXX~~EEEE<br>Magnetic resonance imaging (MRI) scan of the head (including MRA, if performed) for the baseline assessment of patients who will be treated with an anti-amyloid monoclonal antibody agent intended to treat patients with a clinical diagnosis of Mild Cognitive Impairment (MCI) due to suspected Alzheimer's disease or Mild Alzheimer's dementia under the Pharmaceutical Benefits Scheme (PBS), to ensure the patient does not have pathology which would preclude treatment with this agent.<br>One scan per patient | |
| ~~Fee: $452.05~~ **Fee:** $463.80 **Benefit:** 75% = $347.85 85% = $394.25 | |

MBS = Medicare Benefits Schedule; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PBS = Pharmaceutical Benefits Scheme.

**Table 14 Proposed MBS item descriptor for monitoring brain MRI scan during treatment**

| Category 5 – Diagnostic imaging service | *I5 – Magnetic Resonance Imaging*<br>*Subgroup 1 – Scan of head – for specified conditions* |
|---|---|
| Proposed item descriptor ~~XXXXX~~FFFF<br>Magnetic resonance imaging (MRI) scan of the head (including MRA, if performed) for the evaluation of patients currently receiving treatment with an anti-amyloid monoclonal antibody agent intended to treat patients with a clinical diagnosis of Mild Cognitive Impairment (MCI) due to suspected Alzheimer's disease or Mild Alzheimer's dementia under the Pharmaceutical Benefits Scheme (PBS), to ensure the patient does not have pathology which would preclude further treatment with this agent.<br>The assessment will be performed to determine the continuing safety of treatment.<br>Applicable not more than four times in a 12-month period. | |
| ~~Fee: $452.05~~ **Fee:** $463.80 **Benefit:** 75% = $347.85 85% = $394.25 | |

MBS = Medicare Benefits Schedule; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PBS = Pharmaceutical Benefits Scheme

# Summary of public consultation input

*PASC noted and welcomed consultation input from 13 organisations and no individual input was received. The 13 organisations that submitted input were:*

- Australia Diagnostic Imaging Association (ADIA)
- Cyclotek
- Dementia Australia
- Eli Lilly Australia Pty Ltd

- NSW Faculty of Psychiatry of Old Age Subcommittee, The Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- Public Pathology Australia (PPA)
- Roche Diagnostics Australia
- The Australasian Association of Nuclear Medicine Specialists (AANMS)
- The Australian & New Zealand Association of Neurologists (ANZAN) and the Australian Cognitive Neurology Association (ACNA)
- The Australian and New Zealand Society for Geriatric Medicine (ANZSGM)
- The Australian and New Zealand Society of Nuclear Medicine (ANZSNM)
- The Royal Australian and New Zealand College of Psychiatrists (RANZCP)
- The Royal Australian and New Zealand College of Radiologists (RANZCR).

Consultation input was largely supportive of public funding for investigations to support the use of PBS-subsidised lecanemab in people with mild cognitive impairment and mild dementia due to AD. The consultation input raised concerns predominantly in relation to the clinical management pathway, equitable access, MBS item descriptors and service fees.

**Consumer Experience**

Dementia Australia highlighted the significant impact of dementia on individuals, families and carers, including delays to diagnosis and challenges accessing specialist assessment and support services. Public funding of biomarker testing, genetic testing and MRI monitoring was considered important to support equitable access to treatment and informed decision-making, particularly for people in rural and remote areas and other underserved populations.

**Benefits and Disadvantages**

The main benefits of public funding reported in the consultation input included improved access to biomarker testing and MRI monitoring to support earlier and more accurate diagnosis of AD, appropriate patient selection for treatment, and safer use of lecanemab. Public funding was also considered likely to reduce reliance on self-funded diagnostic testing and support more consistent access to the proposed diagnostic pathway. Roche Diagnostics Australia stated that plasma biomarker testing increased accessibility for diagnosing AD, whilst reducing the need for more invasive testing or complex radiology scans with limited capacity.

The main disadvantages of public funding reported in the consultation input included potential inequities in access to specialist assessment, testing and treatment, particularly for people living in rural and remote areas. Consultation input also highlighted the need for adequate workforce capacity and specialist services to support implementation of the proposed pathway. The NSW Faculty of Psychiatry of Old Age Subcommittee of the RANZCP stated that only a small proportion of people with MCI or dementia are likely to be eligible for treatment yet the impact on the budget will be huge.

**Population, Comparator (current management) and Delivery**

The consultation input largely agreed with the proposed population and considered the proposed population consistent with the intended use of lecanemab. Consultation input from multiple stakeholders

including ANZSGM considered amyloid PET to be the preferred first-line biomarker test for identifying the eligible population with AD most likely to benefit from anti-amyloid therapies. While CSF and plasma biomarkers remained an appropriate alternative when amyloid PET is unavailable or contraindicated, amyloid PET was viewed as providing the most accurate *in vivo* assessment of cerebral amyloid burden and the strongest alignment with the evidence base supporting anti-amyloid therapies. Consultation input also highlighted that amyloid PET can quantify cerebral amyloid plaque deposition, avoid treatment of false-positive cases identified through plasma or CSF biomarkers, detect potential alternative contributors to cognitive impairment, and provide a quantitative baseline for monitoring treatment response. RANZCR recommended that genetic and biochemical testing occur prior to amyloid PET imaging, given the cost of imaging.

The consultation input agreed with the proposed comparator. Eli Lilly, AANMS and ANZSNM considered the comparator reflective of current Australian clinical practice, noting that standard medical management remains the current approach in the absence of publicly funded anti-amyloid therapies and associated diagnostic testing.

Other services identified as being needed before or after the intervention included accessible pre-test and post-test information, supported decision-making, specialist clinical assessment, and genetic counselling or equivalent supports, particularly in relation to *APOE* ε4 and amyloid biomarker results.

**MBS Item Descriptor and Fee**

The consultation input generally agreed with the proposed service descriptors, with Eli Lilly, PPA and RANZCP supporting the proposed diagnostic pathway. ADIA recommended amendments to the MRI item descriptors to clarify the circumstances in which magnetic resonance angiography (MRA) may be required. ANZSNM, ANZSGM and AANMS suggested amendments to the amyloid PET item descriptors to include post-treatment monitoring and quantification requirements.

The consultation input ranged from agreeing to disagreeing with the proposed service fees. Eli Lilly agreed with the proposed fees and Cyclotek agreed with the proposed fee for amyloid PET imaging. ANZSNM, ADIA and AANMS considered a higher fee for amyloid PET would be required to prevent out of pocket costs to patients and stated that the tracer costs approximately $1,200 in addition to the service delivery. ADIA stated that the proposed fee for MRI did not account for the additional time required for reporting MRA should this be included in the same MBS item.

*PASC noted that public consultation feedback was broadly supportive of improving access to investigations that may support the use of anti-amyloid therapies in appropriately selected patients. PASC considered that consultation feedback reinforced the importance of equitable access to testing, specialist assessment, treatment and monitoring services, particularly for patients in regional and remote areas.*

*PASC noted consistent feedback regarding the need for appropriate pre- and post-test counselling and support, particularly where biomarker and genetic testing may influence treatment decisions. PASC noted that stakeholders expressed differing views regarding the preferred sequencing of investigations, with some favouring amyloid PET as the primary investigation and others supporting greater use of blood-based biomarkers or genetic testing earlier in the pathway. PASC considered that these differing perspectives highlighted ongoing uncertainty regarding the optimal diagnostic pathway and supported consideration of alternative testing algorithms within the assessment.*

*PASC noted concerns raised regarding MRI, PET and infusion service capacity, implementation challenges, and the adequacy of proposed MBS fees. PASC considered that these issues were relevant to the feasibility, equity and sustainability of implementing the proposed pathway in Australian clinical practice.*

## Next steps

*PASC noted that the applicants are planning on submitting an applicant developed assessment report.*

## Applicant Comments on Ratified PICO

Eisai welcomes the ratified PICO and the progress achieved through the PASC process in establishing a comprehensive assessment framework for investigations and treatment pathways supporting access to lecanemab for Australians with mild cognitive impairment and mild dementia due to suspected Alzheimer's disease. Eisai appreciates the consideration of emerging diagnostic technologies, including blood-based biomarkers, alongside established approaches to amyloid pathology assessment, and acknowledges the importance of ensuring appropriate patient selection, safety monitoring and appropriate access.

# References


Alzheimer's Association 2026, *Mild Cognitive Impairment (MCI)*, viewed June 2026, <https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment>.

Ashton, NJ, Brum, WS, Di Molfetta, G, Benedet, AL, Arslan, B, Jonaitis, E, Langhough, RE, Cody, K, Wilson, R, Carlsson, CM, Vanmechelen, E, Montoliu-Gaya, L, Lantero-Rodriguez, J, Rahmouni, N, Tissot, C, Stevenson, J, Servaes, S, Therriault, J, Pascoal, T, Lleó, A, Alcolea, D, Fortea, J, Rosa-Neto, P, Johnson, S, Jeromin, A, Blennow, K & Zetterberg, H 2024, 'Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology', *JAMA Neurology*, vol. 81, no. 3, pp. 255-263.

Asken, BM, DeSimone, JC, Wang, WE, McFarland, KN, Arias, F, Levy, SA, Fiala, J, Velez-Uribe, I, Mayrand, RP, Sawada, LO, Freytes, C, Adeyosoye, M, Barker, WW, Crocco, EA, DeKosky, ST, Adjouadi, M, Rosselli, M, Marsiske, M, Armstrong, MJ, Smith, GE, Cid, RC, Loewenstein, DA, Vaillancourt, DE & Duara, R 2024, 'Plasma p-tau217 concordance with amyloid PET among ethnically diverse older adults', *Alzheimers Dement (Amst)*, vol. 16, no. 3, Jul-Sep, p. e12617.

Australian Bureau of Statistics 2024, *Cause of Death, Australia*, viewed June 2026, <https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/2024>.

Australian Institute of Health and Welfare 2024, *2023 Aged Care Provider Workforce Survey Report*, viewed June 2026, <https://www.gen-agedcaredata.gov.au/getmedia/aa6c9983-5ee1-42c2-a7a8-183d76fad46b/2023_ACPWS_Report>.

Australian Institute of Health and Welfare 2025, *Dementia in Australia*, viewed June 2026, <https://www.aihw.gov.au/reports/dementia/dementia-in-aus/contents/summary#Risks>.

Bamford, C, Olsen, K, Davison, C, Barnett, N, Lloyd, J, Williams, D, Firbank, M, Mason, H, Donaldson, C & O'Brien, J 2016, 'Is there a preference for PET or SPECT brain imaging in diagnosing dementia? The views of people with dementia, carers, and healthy controls', *International Psychogeriatrics*, vol. 28, no. 1, pp. 123-131.

Beach, TG, Monsell, SE, Phillips, LE & Kukull, W 2012, 'Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010', *J Neuropathol Exp Neurol*, vol. 71, no. 4, Apr, pp. 266-273.

Cano, A, Capdevila, M, Puerta, R, Arranz, J, Montrreal, L, de Rojas, I, García-González, P, Olivé, C, García-Gutiérrez, F, Sotolongo-Grau, O, Orellana, A, Aguilera, N, Ramis, M, Rosende-Roca, M, Lleó, A, Fortea, J, Tartari, JP, Lafuente, A, Vargas, L, Pérez-Cordón, A, Muñoz, N, Sanabria, Á, Alegret, M, Morató, X, Tárraga, L, Fernández, V, Marquié, M, Valero, S, Alcolea, D, Boada, M & Ruiz, A 2024, 'Clinical value of plasma pTau181 to predict Alzheimer's disease pathology in a large real-world cohort of a memory clinic', *EBioMedicine*, vol. 108, Oct, p. 105345.

Chen, X, Huang, T, Shi, C, Xu, S & Fan, S 2026, 'Diagnostic performance of plasma p-Tau217, p-Tau181, and p-Tau231 across the Alzheimer's disease continuum: a network meta-analysis', *Frontiers in Aging Neuroscience*, vol. Volume 18 - 2026, 2026-June-03.

Cummings, J 2023, 'Anti-Amyloid Monoclonal Antibodies are Transformative Treatments that Redefine Alzheimer's Disease Therapeutics', *Drugs*, vol. 83, no. 7, May, pp. 569-576.

Dementia Australia 2023, *Dementia in Australia 2024-2054 dementia prevalence data estimates and projections - All forms of dementia*, viewed June 2026, <https://www.dementia.org.au/sites/default/files/2024-03/Prevalence-Data-2024-Updates-All-forms-of-dementia.pdf>.

*DRAFT FOR PUBLIC CONSULTATION: Dementia Clinical Practice Guidelines and Principles of Care* May 2026, Monash University, Faculty of Medicine, Nursing and Health Science, viewed June 2026, <https://files.magicapp.org/guideline/998b1183-3b5e-4b69-b3a5-956bac4682e4/published_guideline_11262-0_5.pdf>.

Dyer, SM, Laver, K, Pond, CD, Cumming, RG, Whitehead, C & Crotty, M 2016, 'Clinical practice guidelines and principles of care for people with dementia in Australia', *Aust Fam Physician*, vol. 45, no. 12, Dec, pp. 884-889.

Gauthreaux, K, Bonnett, TA, Besser, LM, Brenowitz, WD, Teylan, M, Mock, C, Chen, YC, Chan, KCG, Keene, CD, Zhou, XH & Kukull, WA 2020, 'Concordance of Clinical Alzheimer Diagnosis and Neuropathological Features at Autopsy', *J Neuropathol Exp Neurol*, vol. 79, no. 5, May 1, pp. 465-473.

Genin, E, Hannequin, D, Wallon, D, Sleegers, K, Hiltunen, M, Combarros, O, Bullido, MJ, Engelborghs, S, De Deyn, P, Berr, C, Pasquier, F, Dubois, B, Tognoni, G, Fiévet, N, Brouwers, N, Bettens, K, Arosio, B, Coto, E, Del Zompo, M, Mateo, I, Epelbaum, J, Frank-Garcia, A, Helisalmi, S, Porcellini, E, Pilotto, A, Forti, P, Ferri, R, Scarpini, E, Siciliano, G, Solfrizzi, V, Sorbi, S, Spalletta, G, Valdivieso, F, Vepsäläinen, S, Alvarez, V, Bosco, P, Mancuso, M, Panza, F, Nacmias, B, Bossù, P, Hanon, O, Piccardi, P, Annoni, G, Seripa, D, Galimberti, D, Licastro, F, Soininen, H, Dartigues, JF, Kamboh, MI, Van Broeckhoven, C, Lambert, JC, Amouyel, P & Campion, D 2011, 'APOE and Alzheimer disease: a major gene with semi-dominant inheritance', *Mol Psychiatry*, vol. 16, no. 9, Sep, pp. 903-907.

Gillis, C, Mirzaei, F, Potashman, M, Ikram, MA & Maserejian, N 2019, 'The incidence of mild cognitive impairment: A systematic review and data synthesis', *Alzheimers Dement (Amst)*, vol. 11, Dec, pp. 248-256.

Goate, A, Chartier-Harlin, MC, Mullan, M, Brown, J, Crawford, F, Fidani, L, Giuffra, L, Haynes, A, Irving, N, James, L & et al. 1991, 'Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease', *Nature*, vol. 349, no. 6311, Feb 21, pp. 704-706.

Holtzman, DM 2011, 'CSF biomarkers for Alzheimer's disease: current utility and potential future use', *Neurobiol Aging*, vol. 32 Suppl 1, no. Suppl 1, Dec, pp. S4-9.

Honig, LS, Barakos, J, Dhadda, S, Kanekiyo, M, Reyderman, L, Irizarry, M, Kramer, LD, Swanson, CJ & Sabbagh, M 2023, 'ARIA in patients treated with lecanemab (BAN2401) in a phase 2 study in early Alzheimer's disease', *Alzheimers Dement (N Y)*, vol. 9, no. 1, Jan-Mar, p. e12377.

Hsu, JL, Park, KH, Panegyres, PK, Huang, YH, Eom, YI, Prusty, V, Tan, LS & Shea, YF 2025, 'Early Alzheimer's disease (mild cognitive impairment or mild dementia): Prevalence, diagnostics, treatment options, and guidelines in Asia, Australasia, and Pacific nations countries', *J Prev Alzheimers Dis*, vol. 12, no. 9, Nov, p. 100362.

Jansen, WJ, Ossenkoppele, R, Knol, DL, Tijms, BM, Scheltens, P, Verhey, FR, Visser, PJ, Aalten, P, Aarsland, D, Alcolea, D, Alexander, M, Almdahl, IS, Arnold, SE, Baldeiras, I, Barthel, H, van Berckel, BN, Bibeau, K, Blennow, K, Brooks, DJ, van Buchem, MA, Camus, V, Cavedo, E, Chen, K, Chetelat, G, Cohen, AD, Drzezga, A, Engelborghs, S, Fagan, AM, Fladby, T, Fleisher, AS, van der Flier, WM, Ford, L, Förster, S, Fortea, J, Foskett, N, Frederiksen, KS, Freund-Levi, Y, Frisoni, GB, Froelich, L, Gabryelewicz, T, Gill, KD, Gkatzima, O, Gómez-Tortosa, E, Gordon, MF, Grimmer, T, Hampel, H, Hausner, L, Hellwig, S, Herukka, SK, Hildebrandt, H, Ishihara, L, Ivanoiu, A, Jagust, WJ, Johannsen, P, Kandimalla, R, Kapaki, E, Klimkowicz-Mrowiec, A, Klunk, WE, Köhler, S, Koglin, N, Kornhuber, J, Kramberger, MG, Van Laere, K, Landau, SM, Lee, DY, de Leon, M, Lisetti, V, Lleó, A, Madsen, K, Maier, W, Marcusson, J, Mattsson, N, de Mendonça, A, Meulenbroek, O, Meyer, PT, Mintun, MA, Mok, V, Molinuevo, JL, Møllergård, HM, Morris, JC, Mroczko, B, Van der Mussele, S, Na, DL, Newberg, A, Nordberg, A, Nordlund, A, Novak, GP, Paraskevas, GP, Parnetti, L, Perera, G, Peters, O, Popp, J, Prabhakar, S, Rabinovici, GD, Ramakers, IH, Rami, L, Resende de Oliveira, C, Rinne, JO, Rodrigue, KM, Rodríguez-Rodríguez, E, Roe, CM, Rot, U, Rowe, CC, Rüther, E, Sabri, O, Sanchez-Juan, P, Santana, I, Sarazin, M, Schröder, J, Schütte, C, Seo, SW, Soetewey, F, Soininen, H, Spiru, L, Struyfs, H, Teunissen, CE, Tsolaki, M, Vandenberghe, R, Verbeek, MM, Villemagne, VL, Vos, SJ, van Waalwijk van Doorn, LJ, Waldemar, G, Wallin, A, Wallin Å, K, Wiltfang, J, Wolk, DA, Zboch, M & Zetterberg, H 2015, 'Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis', *Jama*, vol. 313, no. 19, May 19, pp. 1924-1938.

Khalafi, M, Dartora, WJ, McIntire, LBJ, Butler, TA, Wartchow, KM, Hojjati, SH, Razlighi, QR, Shirbandi, K, Zhou, L, Chen, K, Xi, K, Banerjee, S, Foldi, N, Pahlajani, S, Glodzik, L, Li, Y, de Leon, MJ & Chiang, GC 2025, 'Diagnostic accuracy of phosphorylated tau217 in detecting Alzheimer's disease pathology among cognitively impaired and unimpaired: A systematic review and meta-analysis', *Alzheimer's & Dementia*, vol. 21, no. 2, p. e14458.

Livingston, G, Huntley, J, Liu, KY, Costafreda, SG, Selbaek, G, Alladi, S, Ames, D, Banerjee, S, Burns, A, Brayne, C, Fox, NC, Ferri, CP, Gitlin, LN, Howard, R, Kales, HC, Kivimaki, M, Larson, EB, Nakasujja, N, Rockwood, K, Samus, Q, Shirai, K, Singh-Manoux, A, Schneider, LS, Walsh, S, Yao, Y, Sommerlad, A & Mukadam, N 2024, 'Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission', *Lancet*, vol. 404, no. 10452, Aug 10, pp. 572-628.

Long, JM & Holtzman, DM 2019, 'Alzheimer Disease: An Update on Pathobiology and Treatment Strategies', *Cell*, vol. 179, no. 2, Oct 3, pp. 312-339.

Mallik, A, Drzezga, A & Minoshima, S 2017, 'Clinical Amyloid Imaging', *Semin Nucl Med*, vol. 47, no. 1, Jan, pp. 31-43.

Michaelian, JC, Rowe, CC, Kurrle, SE, Pond, CD, Woodward, M & Naismith, SL 2025, 'Is Australia ready for the rollout of amyloid-targeting therapies for Alzheimer disease? Results from a national survey characterising current infrastructure capability, workforce and training needs of memory and cognition clinics', *Intern Med J*, vol. 55, no. 7, Jul, pp. 1081-1089.

Mitchell, SL 2025, 'Care of patients with advanced dementia', in JL Wilterdink (ed.), *UpToDate [Internet}*, Wolters Kluwer.

Myers, RH, Schaefer, EJ, Wilson, PW, D'Agostino, R, Ordovas, JM, Espino, A, Au, R, White, RF, Knoefel, JE, Cobb, JL, McNulty, KA, Beiser, A & Wolf, PA 1996, 'Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study', *Neurology*, vol. 46, no. 3, Mar, pp. 673-677.

National Institute for Health 2025, *Infographic: Understanding Different Types of Dementia*, viewed 06July 2026, <https://www.nia.nih.gov/health/alzheimers-and-dementia/understanding-different-types-dementia>.

National Institute for Health and Care Excellence 2018, *Dementia: assessment, management and support for people living with dementia and their carers*, viewed July 2026, <https://www.nice.org.uk/guidance/ng97>.

Pagano, J, Fong, JC, Wood, EM, Paul, RA, Goldman, JS & Klee, V 2024, 'Clinical genetic testing for Alzheimer disease and related dementias ', *Practical Neurology*.

QueenslandXRay, *Amyloid PET Scan*, viewed June 2026, <https://www.qldxray.com.au/services/petct-scan/amyloid-pet-scan>.

Rajič Bumber, J, Rački, V, Mežnarić, S, Pelčić, G & Mršić-Pelčić, J 2025, 'Clinical Significance of APOE4 Genotyping: Potential for Personalized Therapy and Early Diagnosis of Alzheimer's Disease', *J Clin Med*, vol. 14, no. 17, Aug 26.

Renbaum, P & Levy-Lahad, E 1998, 'Monogenic determinants of familial Alzheimer's disease: presenilin-2 mutations', *Cell Mol Life Sci*, vol. 54, no. 9, Sep, pp. 910-919.

Sabbagh, MN, Lue, LF, Fayard, D & Shi, J 2017, 'Increasing Precision of Clinical Diagnosis of Alzheimer's Disease Using a Combined Algorithm Incorporating Clinical and Novel Biomarker Data', *Neurol Ther*, vol. 6, no. Suppl 1, Jul, pp. 83-95.

Sherrington, R, Rogaev, EI, Liang, Y, Rogaeva, EA, Levesque, G, Ikeda, M, Chi, H, Lin, C, Li, G, Holman, K, Tsuda, T, Mar, L, Foncin, JF, Bruni, AC, Montesi, MP, Sorbi, S, Rainero, I, Pinessi, L, Nee, L, Chumakov, I, Pollen, D, Brookes, A, Sanseau, P, Polinsky, RJ, Wasco, W, Da Silva, HA, Haines, JL, Perkicak-Vance, MA, Tanzi, RE, Roses, AD, Fraser, PE, Rommens, JM & St George-Hyslop, PH 1995, 'Cloning of a gene bearing

missense mutations in early-onset familial Alzheimer's disease', *Nature*, vol. 375, no. 6534, Jun 29, pp. 754-760.

Swanson, CJ, Zhang, Y, Dhadda, S, Wang, J, Kaplow, J, Lai, RYK, Lannfelt, L, Bradley, H, Rabe, M, Koyama, A, Reyderman, L, Berry, DA, Berry, S, Gordon, R, Kramer, LD & Cummings, JL 2021, 'A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody', *Alzheimers Res Ther*, vol. 13, no. 1, Apr 17, p. 80.

Therriault, J, Servaes, S, Tissot, C, Rahmouni, N, Ashton, NJ, Benedet, AL, Karikari, TK, Macedo, AC, Lussier, FZ, Stevenson, J, Wang, YT, Fernandez-Arias, J, Stevenson, A, Socualaya, KQ, Haeger, A, Nazneen, T, Aumont, É, Hosseini, A, Rej, S, Vitali, P, Triana-Baltzer, G, Kolb, HC, Soucy, JP, Pascoal, TA, Gauthier, S, Zetterberg, H, Blennow, K & Rosa-Neto, P 2023, 'Equivalence of plasma p-tau217 with cerebrospinal fluid in the diagnosis of Alzheimer's disease', *Alzheimers Dement*, vol. 19, no. 11, Nov, pp. 4967-4977.

van Dyck, CH, Swanson, CJ, Aisen, P, Bateman, RJ, Chen, C, Gee, M, Kanekiyo, M, Li, D, Reyderman, L, Cohen, S, Froelich, L, Katayama, S, Sabbagh, M, Vellas, B, Watson, D, Dhadda, S, Irizarry, M, Kramer, LD & Iwatsubo, T 2023, 'Lecanemab in Early Alzheimer's Disease', *N Engl J Med*, vol. 388, no. 1, Jan 5, pp. 9-21.

Ward, SA, Borodaty, H, Lin, X, Wallis, K, Honardoost, MA & Tsui, A 2023, *The Australian Dementia Network (ADNeT) Registry 2022 Annual Report*, <https://australiandementianetwork.org.au/wp-content/uploads/2023/05/ADNeT22_Report_F1_Web-1.pdf>.

Wolk, DJ & Dickerson, BC 2024, 'Clincal features and diagnosis of Alzheimer disease', in JL Wilterdink (ed.), *UpToDate [Internet]*, Wolters Kluwer.

World Health Organisation 2025, *Dementia*, viewed June 2026, <https://www.who.int/news-room/fact-sheets/detail/dementia>.

Zheng, Q & Wang, X 2025, 'Alzheimer's disease: insights into pathology, molecular mechanisms, and therapy', *Protein Cell*, vol. 16, no. 2, Feb 1, pp. 83-120.