MSAC Application 1784

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment

PICO Set

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Population

Describe the population in which the proposed health technology is intended to be used:

Disease overview

Dementia is a broad term used to describe a group of symptoms affecting cognitive and social abilities severely enough to interfere with daily functioning. The most prevalent form of dementia is Alzheimer's Disease (AD), which accounts for 60-80% of all dementia cases (Alzheimer's Association 2023; Gauthier S 2022; Tahami Monfared et al. 2022a). AD typically presents with memory loss, but there are many associated cognitive, behavioural and neuropsychiatric features (Knopman et al. 2021). These become more profound as the disease progresses, advancing from more subtle symptoms (such as ability to manage personal finances) to eventually impacting one's ability to perform basic activities of daily living (ADLs), such as cooking and dressing (Alzheimer's research UK 2024). Alzheimer's patients are particularly vulnerable as they commonly wander, get lost and sadly may no longer recognise faces (Alzheimer's research UK 2024; Knopman et al. 2021). The disease therefore not only has a devastating impact on the individuals themselves but has wider implications for family and friends who they become increasingly dependent upon (Alzheimer's research UK 2024).

AD is an age-related progressive neurodegenerative disease, characterised by the accumulation of beta-amyloid (Aß) protein plaques and neurofibrillary tangles (NFTs) in the brain (Breijyeh and Karaman 2020a; Demattos et al. 2012b; Knopman et al. 2021). Aß deposition occurs early in the disease process, preceding tau protein aggregation and other pathologies and is believed to initiate the neurodegeneration cascade, clinically manifesting as cognitive and functional impairment (DeMattos et al. 2012a) The accumulation of Aß protein plaques and NFTs in the brain begins with proteolytic fragmentation of the transmembrane amyloid precursor protein, generating Aß peptides (Bloom 2014). Soluble Aß peptides accumulate outside neurons, becoming insoluble plaques. The deposition of Aß plaques initiates hyperphosphorylation of tau protein, resulting in misfolding of the protein and the formation of NFTs (Abeysinghe et al. 2020), which block the transport of molecules (e.g. glucose) needed for normal neuronal function and survival(Alzheimer's Association 2024a) (Alzheimer's Association 2022). The formation of Aß fibrils and NFTs result in synaptic damage and destruction, impacting the neural circuits responsible for memory and cognition. The loss of synapses can result from the incapacity of live neurons to maintain function and lead to neuronal death (DeTure and Dickson 2019).

The onset of Aß pathology, the key pathophysiological process of AD, can occur up to 20 years before the clinical onset of AD (Bateman et al. 2012; Busche and Hyman 2020; Jack Jr et al. 2018) in what is referred to as the preclinical phase of the disease. The earliest clinical manifestations of AD can be a subjective decline in mental abilities which does not impact performance on objective cognitive tests (Knopman et al. 2021) but as the disease progresses, people living with AD show more advanced symptoms with changes that negatively impact memory and eventually daily functioning, becoming less independent (Alzheimer's Association, 2023)(Knopman et al. 2021; Weller and Budson 2018) AD is therefore regarded as a continuum (Jack et al, 2018). There are three broad phases on the continuum, with no sharp demarcation between them: Preclinical AD, MCI due to AD, and dementia due to AD (see Figure 1). Dementia due to AD is usually further categorised by severity into mild, moderate, and severe.

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Figure 1 Staging and clinical continuum of Alzheimer's disease
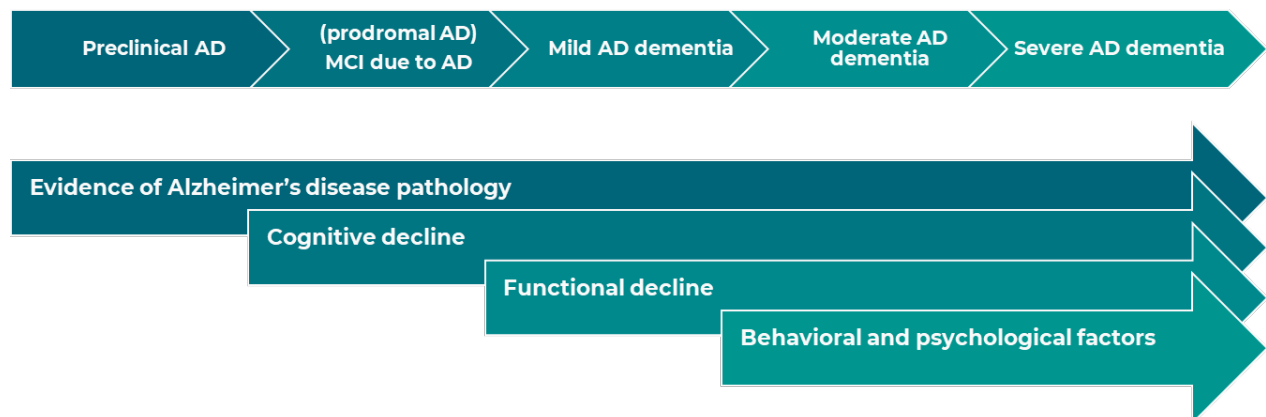
In most cases, onset of AD symptoms typically occurs in people aged ≥65 years. Occurrence of AD at an earlier age (<65 years) is much less frequent and accounts for only 5–10% of AD cases (Ayodele et al. 2021). MCI is the earliest symptomatic stage of cognitive impairment in which single, or potentially multiple, cognitive domains are at least mildly impaired, whilst functional capacities are relatively preserved (Knopman et al. 2021). The presence of amyloid plaques early in AD increases the likelihood of progression from MCI to dementia AD(Mintun et al. 2021) (Mintun et al. 2021), highlighting the importance of detecting amyloid plaques in the early stages of the disease.

Several genes have been shown to increase the risk of AD, with the apolipoprotein E (*APOE*) gene the most characterised. Apolipoprotein E (ApoE) is a lipid-transport protein that plays a role in the regulation of lipids and lipoprotein levels in the blood. The ApoE protein is encoded by the *APOE* gene and interacts with lipids resulting in lipoproteins. Several major isoforms of *APOE* can be distinguished which are ε2, ε3, and ε4 and characterised by two single nucleotide polymorphisms (SNPs) at amino acid positions 112 and 158 (Giau et al. 2015). *APOE* ε4 carriers have an increased risk of AD compared to other isoforms, however, it is not guaranteed that they will develop AD (Alzheimer's Association 2023). The causes of AD are not completely understood and multifaceted (Breijyeh and Karaman 2020a). *APOE* ε4 just one of the many risk factors associated with AD. Homozygous *APOE* ε4 carriers (individuals who possess two copies of the *APOE* ε4 gene variant) have the greatest risk of developing AD, and the lowest average age of onset (Porsteinsson et al. 2021b; Raskin et al. 2015). While *APOE* ε4 is not a defining characteristic required for AD diagnosis, *APOE* status will influence treatment eligibility for donanemab. Evidence from the TRAILBLAZER-ALZ 2 trial (the pivotal phase 3 trial which comprises the key clinical trial to be presented in the PBAC submission), found that *APOE* ε4 homozygotes experienced greater ARIA adverse events with donanemab treatment compared to *APOE* ε4 heterozygotes and non-carriers. Redacted.

In summary, patients with a clinical diagnosis of MCI due to AD, or mild AD are the population of interest in this application for the co-dependent technology, *APOE* genotyping followed by testing for Aß pathology if suitable, to determine eligibility for PBS-subsidised treatment with donanemab.

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Disease and economic burden

AD has a substantial impact on the quality of life of people living with the disease, their families and caregivers, and is associated with a significant humanistic and economic burden (Knopman et al., 2021). Despite being earlier in the disease, patients with MCI due to AD or mild AD experience a range of symptoms, related to memory, mood and emotions, decreased social activity, and reductions in functional activities such as ADLs (DiBenedetti et al. 2020; Tahami Monfared et al. 2022b). As symptoms progress, patients are less able to engage and function in daily activities and this can have a negative impact on psychological and physical health (Knopman et al., 2021). As AD affects functions like memory and cognition, it becomes more difficult to make decisions, engage in activities and socialise. This can make a person with AD feel lonely and isolated and can have a dramatic effect on a person's quality of life (Alzheimer's research UK 2024). The quality of life of caregivers can be impacted in all stages of disease, with caregivers of patients with AD with mild dementia reporting greater physical burden, feelings of missing out on life, and increased anxiety and depression compared with caregivers of patients with MCI. As the severity of the patients' neuropsychiatric symptoms increases, the burden and emotional distress for the caregiver also increases (Ruiz-Fernández et al. 2019).

The economic cost of AD is associated with both direct costs to the healthcare system and indirect societal costs, some of which result from costs due to informal care requirements, and costs due to reduced productivity. In 2022, The National Centre for Social and Economic Modelling assessed the economic and societal cost of AD in Australia for 2021-2041 (Brown et al. 2022). The report assessed the impact of AD on direct costs related to hospital care, out of hospital health services, and formal aged care, the report also assessed indirect costs associated with the provision of informal care, lost productivity, and the disability support pension. In the current AD landscape, the cost of AD dementia in 2021 was estimated to be nearly $15.5 billion, with indirect costs accounting for 63% of total costs, and direct costs accounting for the remaining 37%. The cost of AD dementia is expected to rise by more than 70% over the next 20 years to around $26.6bn in 2041.

Epidemiology

The epidemiology of AD is entangled with that of all-cause dementia (Knopman et al. 2021). By 2025, it is estimated that more than 433,350 Australians will be living with various forms of dementia (Dementia Australia 2024). According to the estimates by the Australian Institutes of Health and Welfare (AIHW), this equates to 15 individuals with dementia per 1,000 Australians, rising to 84 per 1,000 among Australians aged 65 and over (Australian Institute of Health and Welfare 2023; Dementia Australia 2024). Based on current AIHW derived prevalence rates, it is estimated that the number of people with dementia will almost double to 849,300 by 2058, due to the ageing population. However, MCI due to AD and mild AD dementia cases, which is the population of interest for this application, make up a small proportion of the overall dementia cases.

Based on AIHW data, 55% of dementia cases are estimated to be at the mild stage (AIHW, 2023). As previously discussed, it is estimated that between 60-80% of dementia cases are due to AD (Alzheimer's Association 2023; Gauthier S 2022; Tahami Monfared et al. 2022a). This is supported by data from the Australian Dementia Network (ADNeT) Registry which captures data on people newly diagnosed with dementia or MCI in Australia (Ward SA and Arsenova V 2023). The 2022 Annual Report demonstrated that of people diagnosed with dementia, 75% were diagnosed with Alzheimer's Disease.

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AIHW data does not capture prevalence of MCI, and it is noted that estimates of the prevalence of MCI have been found to vary widely in the literature based on differences in the underlying patient population, diagnostic criteria and study methods ((Sachdev et al. 2015; Ward et al. 2012) Sachdev, Lipnicki *et al* (2015) estimated that the age and sex standardised prevalence rate of patients with amnestic MCI (aMCI) was 2.0%. Notably, amnestic MCI (which involves episodic memory impairment, with or without impairment in other cognitive domains) is considered more likely to progress to AD, than non-amnestic MCI (which involves impairment of cognitive domains other than memory) (Petersen 2004). The same publication also reports prevalence estimates from two Australian studies, i.e. the Sydney Memory and Ageing Study (MAS) (3.6%; Sachdev et al. (2010)), and the Personality and Total Health Through Life Project (PATH) (1.0%,Anstey et al. (2012)). It is important to recognise that not all patients with MCI will have an aetiology of AD. For example, in a study from the USA (N=10,713) that examined aetiologic diagnoses of AD in MCI, it was found that 75% of subjects with MCI had an aetiology of AD, while the remainder had aetiologies such as cardiovascular disease and Lewy body dementia (Knopman et al, 2016). This is similar to the ADNeT 2022 report estimated that 72% of MCI cases were due to AD (Ward SA and Arsenova V 2023).

Up to 25% of the population and approximately 60-75% of AD patients in clinical studies are *APOE* ε4 carriers (Matsuda et al. 2019). The frequency of *APOE* ε4 homozygosity within the Australian population has previously been observed to be lower than seen in international cohorts. Data from the *Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing* (AIBL) demonstrated the frequency of *APOE* ε4 homozygosity to be 6.0% in patients with MCI and 5.6% in patients with severe AD (Heffernan et al. 2016).

Additionally, it is not expected that all patients with mild AD or MCI due to AD will access *APOE* ε4 genotyping, and subsequently, Aß testing, as a proportion of patients are likely to remain undiagnosed. Notably, in a report assessing the preparedness of the Australian health care system infrastructure for an AD modifying therapy, it was estimated that 36% of mild AD and MCI due to AD patients would access Aß testing (Baxi et al. 2019).

As such, the patient population anticipated to access testing for Aß pathology will represent a small proportion of the overall patients with AD. Those considered eligible for treatment with donanemab will represent a smaller subset still, as eligibility for treatment with donanemab will require evidence of Aß pathology.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

The underlying cause of pathological changes in AD (Aß, NFTs, and synaptic loss) is still unknown, but the disease has been associated with several risk factors including age, genetic factors, head injuries, vascular diseases, infections, and environmental factors (Breijyeh and Karaman 2020a). Age is the strongest risk factor for AD, with other demographic risk factors for AD including gender, race and socio-economic status (Armstrong 2019). While several genes have been shown to increase the risk of AD, carrying the APOE ε4 allele increases the risk of AD compared with other alleles, although it does not guarantee an individual will develop the disease (Alzheimer's Association, 2023).

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Both MCI due to AD and mild AD are characterised by objective evidence of cognitive impairment. The main difference between these stages is that in mild dementia due to AD, more than one cognitive domain is involved and there is evidence of substantial interference with daily life that compromises independence Knopman and Petersen (2014). While individuals with MCI due to AD have evidence of lower performance in at least one cognitive domain that is greater than would be expected based on age and educational level, they generally maintain independent functioning in daily life, with minimal assistance and in a way that is largely indistinguishable from the past (Albert et al. 2011; Knopman and Petersen 2014). Some complex functional tasks such as paying bills, cooking, and shopping may begin to be affected in MCI due to AD, and individuals may be less efficient and make more errors than previously (Albert et al. 2011; Cohen et al. 2022; Jack et al. 2018). Table 1 describes the clinical manifestation of each stage in the AD continuum.

Early signs of MCI or AD can be subtle and vary from person to person. Assessment of patients for MCI or AD is often initiated following an expression of concern from family or carers who are often better positioned to identify early changes in a patient's behaviour and cognition (Bunn et al. 2012). Primary care providers are usually the first to evaluate patients for neurocognitive disorders and there is no single test to diagnose dementia or MCI. Assessments undertaken by the primary care provider vary but may include taking a clinical history (including cognitive, behavioural and psychological symptoms), cognitive screening tests, physical examination and blood tests (Guideline Adaptation Committee 2016). If a diagnosis of dementia is suspected, patients will be referred for specialist evaluation.

Within Australia, specialists with expertise in memory disorders include geriatricians, neurologists, and psychogeriatricians. Memory assessment services may be multidisciplinary and include other medical, nursing and allied health staff. These physicians will conduct further specialist assessments to confirm a diagnosis of a subtype of dementia, a clinical diagnosis of MCI, or AD diagnosis with staging. It is expected with the availability of donanemab, the same specialists will carry out assessments for treatment eligibility, which include referral for *APOE* and Aß testing as necessary. Commercial *APOE* tests are available privately in Australia. Although not required for the diagnosis of AD, some patients such as those with a family history, may have already received testing and are aware of their *APOE* status prior to an assessment of treatment suitability. *APOE* genotyping is anticipated to be only required once. If a patient is not excluded from treatment following *APOE* testing and other appropriate assessments, then they will be referred for Aß testing, continuing the assessment for donanemab suitability.

Existing treatment options for AD include non-drug and symptomatic treatments. Currently available symptomatic treatments for AD, including acetylcholinesterase inhibitors (AChEIs) and the N methyl-D-aspartate (NMDA) receptor antagonist memantine, can stabilise the symptoms of AD for a limited time, however, there is no evidence to suggest that these technologies alter the underlying pathology of AD or alter the course of AD progression (Breijyeh and Karaman 2020a; Tan et al. 2018). As presented in Table 2, there are no pharmaceutical treatments indicated for patients with MCI due to AD, and instead these patients may be recommended non-pharmaceutical strategies aimed at optimising brain health including encouragement of physical activity, social engagement, maintenance of cognitive stimulation and good nutrition. For patients with a clinical diagnosis of mild AD, treatment with an AChEI may be indicated in addition to the aforementioned brain health optimisation strategies.

Given the enormous burden on individual patients, their care partners, and health and social care systems of AD, there is an urgent need to make disease modifying therapies available which directly target the underlying pathology of the disease. This codependent application requests MBS listing of two investigative technologies to identify Aß pathology in patients with MCI due to AD, or mild AD, to inform patient access to treatment with donanemab. Donanemab is a humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody, which targets ß-amyloid plaques in the brain of patients with AD with MCI or AD with mild dementia. Positive results have been reported from the TRAILBLAZER-ALZ 2 phase III trial, with donanemab meeting the primary and all secondary efficacy endpoints measuring slowing cognitive and functional decline (Sims et al, 2023).

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Table 1   Signs and symptoms across different stages of Alzheimer's disease

Disease stage	Signs and symptoms
MCI	
Cognition and behaviour	Early symptoms of memory loss Problems with language and thinking abilities Other cognitive ability loss: Struggling to find appropriate words Forgetting recent conversations (episodic memory) Difficulties completing familiar tasks (executive function) Getting lost in familiar surroundings (visuospatial function) Changes are not enough to affect relationships
Function	Able to continue with day -to-day activities More complex activities of daily living may be affected
Dependence	Independent
Mild dementia due to AD	
Cognition and behaviour	Memory loss of recent events Difficulty with problem solving, complex tasks, and sound judgements Difficulty organising and expressing thoughts; finding the right words to describe objects or clearly express ideas becomes increasingly challenging Getting lost or misplacing belongings Some evidence of apathy and depression Subtle changes in personality (e.g. may be subdued or withdrawn, especially in challenging social situations; uncharacteristic irritability or anger; reduced motivation to complete tasks)
Function	Evident functional impact on daily life
Dependence	Mostly independent Most will continue to drive, work, and participate in hobbies May need help with more challenging activities (e.g. handling money or paying bills)
Moderate dementia due to AD	
Cognition and behaviour	Greater memory loss (e.g. may forget details of personal history; repeat favourite stories or make up stories to fill gaps in memory) Greater problems with memory and language; often confuse words and have difficulties expressing thoughts Show increasingly poor judgement and deepening confusion (lose track of where they are, day of the week or season; may confuse family members or mistake strangers for family) May wander Significant changes in personality and behaviour (e.g. may develop unfounded suspicions, or see/hear things that are not there) May grow restless or agitated, especially at the end of the day Exhibit unexpected behaviours and may have outbursts of aggressive behaviour and exhibit frustration and anger
Function	Extensive functional impact Difficulties completing multistep tasks without assistance (e.g. bathing and dressing) Episodes of urinary and faecal incontinence
Dependence	No longer independent; require assistance with many tasks
Severe dementia due to AD	
Cognition	No longer able to respond to environment or and communicate coherently
Function	Changes in physical abilities Problems with walking and sitting; may be unable to hold head up without support Muscles may become rigid and reflexes abnormal Swallowing difficulties, which can lead to aspiration pneumonia Incontinence Eventually become bed bound increasing the risk of blood clots, skin infections, and sepsis
Dependence	Completely dependent and require constant care

Source: Alzheimer's Association (2024b); Jack et al. (2018); Porsteinsson et al. (2021a)

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Table 2 Symptomatic treatments for Alzheimer's Disease (AD)

	Acetylcholinesterase Inhibitors (AChEI)		NMDA Antagonists
Molecule	donepezil, rivastigmine	galantamine	memantine
TGA indication	For the treatment of mild, moderate and severe AD	For the treatment of mild to moderately severe AD	Treatment of symptoms of moderately severe to severe AD
PBS restriction	For the treatment of mild to moderately severe AD		For the treatment of moderately severe AD

Provide a rationale for the specifics of the eligible population:

The TRAILBLAZER-ALZ 2 trial, a phase 3, double-blind placebo-controlled study which evaluated the safety and efficacy of donanemab in patients with early symptomatic AD, provides the pivotal evidence for the codependent component of this application. Eligibility criteria of TRAILBLAZER-ALZ 2 reflect the known characteristics of patients with early symptomatic AD. Eligible patients had a gradual, progressive change in memory function reported by the participant or informant for ≥6 months and a Mini-mental state examination (MMSE) score of 20–28 (inclusive) at screening. This MMSE range corresponds to MCI due to AD stage and mild AD stage as described by the International Working Group (IWG) and the National Institute on Aging–Alzheimer's Association (NIA-AA) (Mild dementia due to AD, MMSE 20–26; MCI, MMSE ≥27) (Perneczky et al. 2006). Patients enrolled in the TRAILBLAZER-ALZ 2 trial were required to have confirmed presence of elevated brain amyloid plaque (≥37 CL) assessed by positron emission tomography (PET) scan and elevated tau levels by PET scan (Sims et al. 2023).

Donanemab is a IgG1 monoclonal antibody which targets and removes amyloid plaques, the key pathological hallmark of AD, via microglial-mediated clearance. The therapy targets early symptomatic AD patients with an existing brain amyloid load. This strategy is based on the amyloid hypothesis of AD, which postulates that the production and deposition of Aß is an early event in the pathogenesis of AD (Selkoe 2000). Accumulation of extracellular Aß plaques act as a pathological trigger for a cascade of events including mitochondrial damage, unstable homeostasis, and synaptic dysfunction (Barage and Sonawane 2015; Fan et al. 2019). Early in the progression of AD, the presence of brain amyloid appears to increase the risk of conversion from MCI to AD dementia (Doraiswamy et al. 2012).

Safety data from the TRAILBLAZER-ALZ 2 trial showed that *APOE* ε4 homozygotes who received donanemab had an increased frequency of experiencing amyloid-related imaging abnormalities (ARIA) adverse events compared to *APOE* ε4 heterozygotes and non-carriers(Sims et al. 2023). Redacted.

This codependent application requests an MBS listing for *APOE* genotyping, Aß PET and CSF AD biomarker immunoassay. Following *APOE* testing, if suitable, either Aß PET or CSF AD could be used to assess Aß pathology in patients with MCI due to AD, or mild AD to determine eligibility for donanemab. The use of blood-based *APOE* genotyping and Aß PET to confirm Aß pathology is consistent with the TRAILBLAZER-ALZ 2 trial. While CSF immunoassay was not utilised as a diagnostic measure in the TRAILBLAZER-ALZ 2 trial, a recent study has demonstrated that approved CSF assays are non-inferior to Aß-PET in identifying patients with AD pathology in a donanemab intended use population (Burnham SC) and the concordance of CSF immunoassays with Aß PET has been further confirmed by a systematic literature review performed by Eli Lilly which is summarised subsequently in Table 3.

An additional MBS item for Aß PET is requested for the purposes of assessing amyloid clearance in patients treated with donanemab. In the TRAILBLAZER-ALZ 2 trial patients were allowed to switch to placebo in a blinded manner if they achieved amyloid plaque clearance, as assessed via Aß at 24, 52 and 76 weeks (Sims et al. 2023). In Australian clinical practice, it is expected that donanemab treatment will continue up to a maximum treatment duration of 18 months, with a potential for earlier treatment completion if amyloid plaque clearance can be assessed and is achieved. A limited duration of therapy based on amyloid clearance has the potential to decrease disease burden, costs, and unnecessary treatments.

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Are there any prerequisite tests?
Yes

Are the prerequisite tests MBS funded?
Yes

Provide details to fund the prerequisite tests:
Donanemab is currently under evaluation by the TGA for the treatment of MCI due to AD and mild AD and as such the TGA label and the need for any prerequisite tests (prior to testing for Aß pathology) have not yet been finalised. This application proposes that testing for Aß pathology occur after a clinical diagnosis of MCI due to AD or mild AD has been made. There is no single test which can provide a diagnosis of AD; a diagnosis is made from clinical assessment and a comprehensive medical evaluation, encompassing:

- Family history
- Cognitive assessment
- Medication review
- Blood and urine testing
- Physical assessment
- Structural imaging (CT or MRI) to exclude other possible underlying cerebral pathologies

MRI

It is anticipated that a recent MRI (performed within the last year) will be required to initiate treatment with donanemab. At a recent advisory board conducted by Eli Lilly in February 2024, key opinion leaders in the diagnosis and management of people with AD noted that the majority of patients will have a MRI completed as part of the diagnostic work-up for AD, to exclude other possible underlying cerebral pathologies and that MBS items exist for MRI of the head which would be suitable for use (e.g. MBS item 63004). This application proposes that, while a recent MRI may be a prerequisite for donanemab initiation, the majority of people with AD will have a MBS-subsidised MRI completed as part of the diagnostic process to confirm AD.

FDG-PET

There currently exists MBS funding via item 61560 for fluorodeoxyglucose (FDG) PET which is indicated for the diagnosis of AD where clinical evaluation is inconclusive. FDG-PET is a non-specific marker which measures cerebral metabolic rates of glucose as a proxy for neuronal activity, as opposed to a specific test for AD Aß pathology (Mosconi 2013). However, FDG-PET should not be considered a prerequisite test for access to Aß PET, and CSF AD biomarker immunoassay. FDG PET has lower sensitivity for the diagnosis of AD (Rabinovici et al. 2011), and use of FDG PET as a prerequisite test could exclude patients who would be otherwise eligible for treatment with donanemab. This is consistent with advice from PASC from the ratified PICO confirmation for application 1643 which requested MBS listing of two testing options for determining eligibility for access to PBS subsidised aducanumab in patients with early-stage AD. PASC agreed that FDG-PET should not be a prerequisite for Aß PET or CSF AD biomarker testing to inform access to the codependent drug.

Intervention

Name of the proposed health technology:
A test to determine *APOE* genotype, and two testing options to assess Aß pathology in patients with a clinical diagnosis of MCI due to AD or mild AD, to determine eligibility for PBS-subsidised donanemab.

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Describe the key components and clinical steps involved in delivering the proposed health technology:

APOE genotyping

Blood-based *APOE* genotyping tests are commercially available in Australia and offered by private pathology providers for a non-rebated fee of approximately $150 (Sonic Genetics 2023). Testing may have already been considered by clinicians in the management of a patient presenting to a specialist memory clinic, and hence not required again. For majority of patients who require testing for an assessment of treatment eligibility, around 4ml sample of blood is required for testing with results available within 10 business days (Sonic Genetics 2023).

Proposed testing of Aß pathology

The key components and clinical steps involved in determining Aß pathology (via either Aß PET or CSF biomarker immunoassay) in early symptomatic AD have already been considered by PASC at the December 2020 and April 2021 meetings in the evaluation of Application 1643 - *Two testing options for determining eligibility for access to Pharmaceutical Benefits Schedule-subsidised aducanumab in patients with early stage Alzheimer Disease.* Similarly, Application 1738 has also requested funding for Aß PET or CSF biomarker immunoassay to assess Aß pathology and determine eligibility for PBS-Subsidised lecanemab, and notably has bypassed PASC. As such, a summary of the key components and clinical steps involved in delivering Aß PET or CSF biomarker immunoassay is provided below.

Aß PET

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European association of Nuclear Medicine (EANM) procedure standard and practice guideline for Aß PET imaging of the brain provides advice to nuclear medicine practitioners in recommending, performing, interpreting, and reporting results of Aß PET. Appropriate use criteria for amyloid imaging are currently being updated by SNMMI, and existing guidelines and standard procedures were developed prior to amyloid targeting therapies (ATT) therapies being available. The criteria emphasise that Aß PET is currently most likely to be helpful when the patient has objectively confirmed cognitive impairment, when the cause of cognitive impairment remains uncertain after a comprehensive evaluation by a dementia expert, when the differential diagnosis includes AD dementia, and when the knowledge of the presence or absence of Aß pathology is expected to increase diagnostic certainty or alter patient management (Johnson et al. 2013; Minoshima et al. 2016). This is consistent with the indications proposed for Aß PET in this application, as imaging in this setting will alter patient management by informing a patient's eligibility for treatment with donanemab.

In Australia, there are currently, no radiopharmaceuticals for Aß PET approved by the TGA. The Applicant understands that radiotracers for Aß PET scanning do not currently require TGA approval under "extemporaneous compounding" exemption. Internationally, the FDA and the European Medicines Agency (EMA) has approved ^{18}F-Florbetaben (Neuraceq), ^{18}F-Florbetapir (Amyvid), and ^{18}F-Flutemetamol (Vizamyl) for amyloid imaging. Another radiopharmaceutical, ^{18}F-Flutafuranol (NAV4694), is currently used for research purposes and is understood to be under development for wider commercial use. All amyloid radiotracers share a common imaging target, and concordance between radiotracers has previously been demonstrated, with no marked differences in diagnostic accuracy having been observed (Morris et al. 2016). This application does not propose the use of a specific Aß PET radiopharmaceutical for assessing Aß pathology and a tracer agnostic MBS item was supported by key opinion leaders in the diagnosis and management of AD patients in Australia at an advisory board conducted by Eli Lilly in February 2024. In particular, a tracer agnostic MBS item was noted to allow for more equitable access to amyloid PET tracers as only NAV4694 is available on the west coast and the two hour half-life of F-18 tracers making supply of amyloid tracers from the east coast not feasible.

The steps involved in performing Aß PET are generally consistent across the radiotracers. During the procedure, radiotracers are injected through a short intravenous catheter, and during image acquisition the patient is in a supine position, with their head supported and secured to minimise movement. The recommended dose, waiting period and acquisition time will differ depending on the Aß radiotracer selected.

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The specific criteria for Aß PET image interpretation also differ among available radiotracers, as such, image interpreters should be appropriately trained to interpret according to the appropriate criteria specific to the radiotracer. Aß PET image interpretation can be performed via visual reading, but can also be quantified which is generally performed using a standardised uptake value ratio (SUVr) (Pegueroles et al. 2021). Generally, negative Aß PET scans show nonspecific white matter uptake and little to no binding in the grey matter. In patients with significant Aß deposition in the brain, radiotracer uptake in grey matter blurs the distinction of the grey-white junction. Aß positive patients will therefore exhibit a loss of grey-white matter contrast, with radiotracer uptake extending to the edge of the cerebral cortex and forming a smooth, regular boundary.

Quantitative assessment of amyloid images is sensitive to experimental variables, including the tissue being assessed, choice of analysis techniques, and scanner reconstruction effects (Schmidt et al. 2015). The Centiloid Project was initiated to derive a standardised quantitative amyloid imaging measurement scale, based upon normalisation of data from the 18F-tracers to that of Pittsburgh compound B (PiB). In this linear scale, young controls (≤ 45 years) have a mean of zero Centiloid units (CL) and typical mild to moderate AD patients score on average 100 CL (Klunk et al. 2015).

In the TRAILBLAZER-ALZ 2, patients' amyloid burden was reported as standardised uptake value ratio (SUVR) reported in CL units, and patients were required to have to evidence of amyloid pathology (≥37 CL on Aß PET scan) to be enrolled in the trial.

Cerebrospinal fluid Alzheimer's disease biomarker immunoassay
As previously described in Applications 1643 and 1738, there are a number of CSF immunoassays commercially available outside of Australia. In Australia, three CSF biomarker testing kits have been TGA approved (considered class 3 IVDs), and comprise:

- Elecsys® CSF AD ß-Amyloid (1-42) CSF

- Elecsys® Phospho-Tau (181P) CSF

- Elecsys® Total -Tau CSF

Roche Diagnostics is the manufacturer of the Elecsys® AD CSF portfolio. Currently, CSF immunoassay for AD testing is conducted in at least one National Association of Testing Authorities Australia (NATA)/ International Laboratory Accreditation Cooperation (ILAC) accredited diagnostic laboratory using the Elecsys® immunoassays; the National Dementia Diagnostics Laboratory at The Florey in Melbourne. It is expected that following the introduction of amyloid targeting therapies, and the requirement for Aß testing, there will be an increase in accredited pathology testing laboratories offering this service.

CSF samples are collected by lumbar puncture, and it is important that specimen collection and pre-analytical handling follow a highly standardised procedure as specified by the analysing laboratory or as recommended by the manufacturer of the assay kit being used. Assay procedures should follow manufacturer specifications. Levels of specific biomarkers (Aß 42 peptides, total tau and phosphorylated tau) in the sample are then quantified by in vitro immunoassay methods, and amyloid positivity or negativity determined by cut-offs which have been validated against Aß PET.

Mechanism of action and treatment with co-dependent drug intervention donanemab (KISUNLA®)
Donanemab, a humanised IgG1 antibody (mAb), targets a reduction in Aß plaques by specifically binding to the N-terminal pyroglutamate Aß epitope on the plaques. It works by inducing microglial-mediated clearance of existing Aß plaques with the intent of slowing the progressive decline in cognitive function associated with AD. The TRAILBLAZER-ALZ 2 trial demonstrated the efficacy and safety of donanemab in patients with early symptomatic AD (Sims et al. 2023). Donanemab is currently being evaluated by the TGA, the TGA delegates overview is expected redacted.

Eligibility for donanemab for patients with MCI due to AD, or mild AD will require confirmation of evidence of Aß pathology using a validated test where today the tests available are brain Aß PET or CSF AD biomarker testing. Redacted.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Treatment with donanemab should be maintained until amyloid plaques are cleared as confirmed using a validated method up to a maximum of 18 months, redacted. Currently the only method available to assess amyloid clearance is Aß PET, and a separate MBS item is proposed to assess amyloid clearance in patients treated with donanemab. Redacted.

Identify how the proposed technology achieves the intended patient outcomes:

The mechanism of action of donanemab antibody is to target and remove deposited amyloid plaque, a key pathological hallmark of AD, via microglial-mediated clearance. The clinical strategy for donanemab identifies early symptomatic AD patients with existing brain amyloid load and have a reduced risk of experiencing ARIA events. Clinically diagnosed patients will receive an *APOE* screen to assess risk and determine whether they are excluded from treatment. Following eligibility from *APOE* testing, Aß PET and CSF AD biomarker testing can be used to confirm presence of Aß pathology.

APOE genotyping test

Blood-based *APOE* genotyping identifies the exact genetic sequence of the *APOE* gene to determine which *APOE* ε variant/s are present. The ε4 variant is the clinically significant allele of interest which informs treatment eligibility. Redacted. Redacted.

Amyloid PET

PET scanning allows the visualisation of proteins associated with AD pathophysiology in the brains of affected individuals. Aß PET uses tracers that specifically bind to Aß located within amyloid plaques (Porsteinsson et al. 2021a). A positive amyloid PET scan will show increased cortical retention of the tracer in regions of Aß deposition within the brain and allows direct quantification of amyloid pathophysiology.

CSF AD biomarker test

Various proteins, including important diagnostic biomarkers for AD, are secreted from the brain extracellular space to the CSF on account of the proximity of the CSF to brain functional tissue (Blennow and Zetterberg 2018). The CSF is accessible by lumbar puncture for the analysis of these fluid biomarkers. CSF immunoassay for AD is an in vitro diagnostic test which allows for the quantitative determination of biomarker protein levels in patient CSF fluid. Levels of specific biomarkers (including Aß 42 peptides, total tau and phosphorylated tau) are utilised, either as single values or as ratios, to determine Aß positivity. In a systematic literature review, performed by Eli Lilly, CSF biomarkers, namely ratios P-tau181/Aß42, T-tau/Aß42, and Aß42/Aß40, were demonstrated to have high concordance with Aß PET. These results are summarised in Table 3, and will be presented in detail in the ADAR. Additionally, a recent study has demonstrated that approved CSF assays are non-inferior to Aß-PET in identifying patients with AD pathology in a donanemab intended use population (Burnham SC).

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Table 3 Summary of concordance (%) results of CSF biomarkers versus amyloid PET from a systematic literature review performed by Eli Lilly

CSF biomarker	Concordance with amyloid PET	Supporting publications
Aβ42	76%–96%	(Bucci et al. 2021; Carandini et al. 2019; de Wilde et al. 2019; Doecke et al. 2018; Doecke et al. 2020; Jung et al. 2020; Kaplow et al. 2020; Lee et al. 2020; Mattsson-Carlgren et al. 2020; Nojima et al. 2022; Palmqvist et al. 2014; Sacchi et al. 2022; Schipke et al. 2017; Shaw et al. 2018; Spallazzi et al. 2019; Tijms et al. 2018; Weston et al. 2015; Willemse et al. 2021)
p-tau181	78% and 79%	(Doecke et al. 2020; Nojima et al. 2022) C
t-tau	75%–87%	(Doecke et al. 2020; Kaplow et al. 2020; Nojima et al. 2022; Weston et al. 2015)
p-tau181/Aβ42	83%–96%	(Doecke et al. 2018; Doecke et al. 2020; Nojima et al. 2022; Shaw et al. 2018; Willemse et al. 2021)
t-tau/Aβ42	84%–96%	(Alvarez et al. 2018; de Wilde et al. 2019; Doecke et al. 2018; Doecke et al. 2020; Kaplow et al. 2020; Nojima et al. 2022; Shaw et al. 2018; Weston et al. 2015; Willemse et al. 2021)
Aβ42/Aβ40	79%–100%	(Doecke et al. 2018; Doecke et al. 2020; Janelidze et al. 2021; Lombardi et al. 2020; Nojima et al. 2022; Pannee et al. 2016; Sacchi et al. 2022; Weston et al. 2015; Willemse et al. 2021)

Abbreviations: Aβ, Amyloid beta; CSF, Cerebrospinal fluid; PET, Positron Emission Tomography; p-tau, Phosphorylated tau; t-tau, Total tau

The use of Aß and tau protein biomarkers for AD diagnosis is recommended in diagnostic guidelines for AD from the National Institute on Aging-Alzheimer's Association(Albert et al. 2011; McKhann et al. 2011; Sperling et al. 2011) and international working group (Dubois et al. 2014; Dubois et al. 2021)

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes

APOE genotyping, Aß PET, and CSF AD biomarker immunoassay are non-branded terms describing interventions which are not trademarked, however, the specific technologies which are used for these tests are branded with associated trademarks.

The co-dependent treatment donanemab is currently under evaluation by the TGA with the registered brand name KISUNLA®.

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
It is not essential to have a trademark component for any testing technologies proposed by this application as Aß radiotracers have demonstrated high intra-rated concordance. MSAC guidelines (p.44) note MSAC prefer technology-agnostic language for item descriptors, and given the demonstrated concordance between Aß radiotracers, which will be substantiated further in the ADAR, this application requests a tracer agnostic item description for Aß PET.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

The two TGA approved and National Association of Testing Authorities (NATA)/International Laboratory Accreditation Cooperation (ILAC) accredited immunoassay kits for clinical diagnostic use in Australia, the Fujirebio Innotest and the Roche Elecsys CSF AD biomarker assay kit quantify the same biomarkers, and have also demonstrated concordance, with high inter and intra-laboratory variability (Dakterzada et al. 2021). This application requests a test assay agnostic listing for CSF AD biomarker immunoassay, as it is anticipated that analysis will be conducted using a TGA registered immunoassay in a NATA accredited laboratory setting. Thus, it is not necessary to specify a specific immunoassay. Concordance between the evidentiary standard and CSF testing will be explored in the ADAR.

This application also requests an assay-agnostic MBS item for blood-based *APOE* PCR genotyping. Available PCR testing in Australia is the same as the clinical utility standard used for *APOE* genotyping in the pivotal TRAILBLAZER-ALZ 2 trial. Additionally, *APOE* genotyping is conducted in NATA-accredited laboratories. As the clinical utility standard is directly applicable to the method of testing in Australian clinical practice, the TRAILBLAZER-ALZ 2 trial provides direct evidence of the performance and accuracy of *APOE* genotyping using PCR. As such, an assessment of the performance and accuracy of *APOE* genotyping using PCR is not presented in this submission.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes

Provide details and explain:

Test frequency
Patients referred for *APOE* testing are eligible only once as *APOE* genotype will not change throughout a patient's lifetime. If a patient's *APOE* status is already known prior to the assessment of donanemab suitability, further *APOE* testing is not required.

Patients with a clinical diagnosis of MCI due to AD, or mild AD (meeting clinical criteria for treatment with donanemab) and other eligibility assessments (redacted) will be eligible for testing with one of the proposed technologies: Aß PET or CSF AD biomarker immunoassay, to confirm Aß pathology, and thus determine eligibility for treatment with PBS-subsidised donanemab. If a patient is determined to be negative for Aß pathology, the implication would be that any current cognitive impairment is as a result of something other than AD, however, it is noted that this would not preclude the possibility of AD dementia in the future. As such, a patient may be eligible for future testing for Aß pathology. Limitations on the number of tests for assessing Aß pathology have not been proposed in this application but will be discussed in the ADAR.

Assessment of amyloid clearance

In Australian clinical practice, it is expected that donanemab treatment will continue up to a maximum treatment duration of 18 months, with a potential for earlier treatment completion if amyloid plaque clearance can be assessed and is achieved. At present, Aß PET is the only method for assessing amyloid clearance in AD patients.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

In the TRAILBLAZER-ALZ 2 clinical trial, amyloid clearance was defined as achieving amyloid plaque levels <24.1 CL (Navitsky et al, 2018). In the TRAILBLAZER-ALZ 2 trial, patients received donanemab every 4 weeks for up to 18 months. If amyloid plaque level (assessed at 24, 52 and 76 weeks) was <11 CL on a single PET scan or was ≥11 CL but <25 CL on two consecutive PET scans, patients switched from donanemab treatment to placebo in a blinded manner. However, it should be noted that <25 CL is the operational rule and not the scientific definition of amyloid clearance; <25 CL represents the nearest integer covering the quantitative value of <24.1 CL for amyloid plaque clearance, which converts the negative SUVR to CL. For trial implementation, the requirement for <25 CL on two consecutive scans increased the certainty that participants would have amyloid levels <24.1 CL and not >25 CL due to measurement errors or variations on a subsequent scan, but in real-world healthcare-constrained, clinical practice, a single Aß PET scan showing amyloid plaque levels <24.1 CL may support an opportunity to consider stopping treatment with donanemab.

In the overall population in the TRAILBLAZER-ALZ 2 trial, amyloid clearance was reached in 29.7% (95% CI, 26.56%-33.04%) of participants at 24 weeks, 66.1% of participants at week 52, and 76.4% (95% CI, 72.87%-79.57%) at 76 weeks of donanemab-treated participants compared with 0.2% (95% CI, 0.07%-0.90%) at 24 weeks and 0.3% (95% CI, 0.08%-1.05%) at 76 weeks of placebo-treated participants (Sims et al. 2023). Thus, a limited duration of therapy based on amyloid clearance has the potential to decrease disease burden, costs, and unnecessary treatments.

A separate MBS item is proposed to assess amyloid clearance in patients treated with donanemab. Currently, a maximum of three uses of this MBS item is proposed with a requirement to be utilized within 18 months of donanemab treatment initiation, which aligns with the Aß PET monitoring schedule within the TRAILBLAZER-ALZ 2 trial. Alternative Aß PET monitoring schedules will be explored in the ADAR. Redacted.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

An *APOE* test requires a blood sample collected in EDTA, which should be collected by a suitably qualified and trained professional to carry out blood collection. PCR genotyping will be carried out in a NATA accredited laboratory.

Aß PET examinations should be performed by, or under the supervision of, a physician specialized in nuclear medicine and certified by accrediting boards, or a registered or certified nuclear medicine technologist. Aß PET results should be interpreted by specialists who have completed the appropriate training programs provided by the manufacturers of the radiotracers.

CSF collection, via lumbar puncture is usually performed by a medical officer with relevant training. In some circumstances, a nurse practitioner may also perform a lumbar puncture. CSF AD immunoassay must be performed at a NATA accredited laboratory.

Donanemab will be prescribed, based on the results of amyloid pathology testing, by a specialist with expertise in memory disorders, this includes geriatricians, neurologists, and psychogeriatricians. Donanemab is administered by intravenous infusion, and this may occur in an infusion clinic, hospital or private clinic setting under the supervision of a registered nurse, or medical officer.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Patients eligible for the proposed health technologies for testing to determine *APOE* status and assess Aß pathology and determine eligibility for treatment with PBS subsidised donanemab must have a diagnosis of MCI due to AD, or mild AD. This diagnosis is made by a specialist with expertise in memory disorders, this includes geriatricians, neurologists, and psychogeriatricians.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:
APOE testing

Any blood-based *APOE* PCR genotyping to inform access to donanemab will occur at NATA accredited laboratories. It is expected that pathologist training and quality assurance programs would be developed to accompany implementation of the test.

Aß PET

As per note IN.0.17 for Group I4 – Nuclear Medicine Imaging, Category 5 – diagnostic imaging services on the MBS, PET services must be:

- performed by or under the personal supervision of:
  - specialist or consultant physician credentialled under the Joint Nuclear Medicine Specialist Credentialling Program for the Recognition of the Credentials of Nuclear Medicine Specialists for Positron Emission Tomography overseen by the Joint Nuclear Medicine Credentialling and Accreditation Committee of the RACP and RANZCR; or
  - practitioner who is a Fellow of either the RACP or RANZCR, and who, prior to 1 November 2011, reported 400 or more studies forming part of PET services for which a Medicare benefit was payable, and who holds a current license from the relevant State radiation licensing body to prescribe and administer the intended PET radiopharmaceuticals to humans;

It is noted that specific criteria for interpretation of Aß PET scans may vary across available radiotracers. As such, it is expected that nuclear medicine specialists who would interpret Aß PET scans would complete the appropriate training programs provided by the manufacturers of the radiotracers.

CSF AD biomarker immunoassay

Any CSF AD biomarker immunoassay to inform access to donanemab will occur at NATA accredited laboratories. It is expected that pathologist training and quality assurance programs would be developed to accompany implementation of the test.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
☒ Consulting rooms
☒ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

It is anticipated that Aß PET services may be provided in both an inpatient and outpatient setting. *APOE* genotyping and CSF AD biomarker immunoassay would be undertaken in a laboratory setting, but specimen collection and some pre-analytical handling of the specimen could take place in multiple admitted and non-admitted patient settings. Infusion of donanemab may occur in an infusion clinic, hospital or private clinic setting.

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the <u>Australian healthcare system)</u>. This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:
This application is requesting the following MBS items for use in patients with a clinical diagnosis of MCI due to AD, or mild AD to inform PBS subsidised access to donanemab.

    i.   *APOE* genotyping to assess treatment suitability

    ii.   *a)* Aß PET testing and b) CSF AD biomarker immunoassay to assess Aß pathology

The appropriate comparator for APOE genotyping is 'no *APOE* genotyping'.

The appropriate comparator for Aß PET testing is 'no testing for Aß pathology'.

The appropriate comparators for CSF biomarker testing are 'no testing for Aß pathology' and Aß PET

The appropriate comparator for donanemab is standard of care, which for patients with a clinical diagnosis of MCI due to AD or mild AD, is instigation of non-pharmaceutical interventions (including encouragement of physical activity, social engagement, maintenance of cognitive stimulation and good nutrition), and for patients with mild AD may also include treatment with AChEI therapy.

List any existing MBS item numbers that are relevant for the nominated comparators:
N/A

Provide a rationale for why this is a comparator:
APOE genotyping is not required in the diagnosis of AD and is not currently MBS subsidised in Australia, hence, there is no appropriate comparator.

There are no amyloid targeting therapies currently available in Australia, and as such there is currently no requirement to assess patients who have received a clinical diagnosis of AD for evidence of Aß pathology. There are no MBS subsidised technologies to assess for evidence of Aß pathology. As such, the appropriate comparator for Aß PET testing, and CSF biomarker testing is 'no testing for Aß pathology'.

The pathological hallmark of AD, Aß, can be reliably detected by Aß PET and CSF AD biomarker immunoassay. Eligible patients in the TRAILBLAZER-ALZ 2 trial had evidence of amyloid pathology (≥37 CL) assessed by Aß PET. Patients in the trial were not assessed using CSF AD biomarker immunoassay. To assess the clinical validity of CSF AD biomarker immunoassay, to quantify Aß burden in patients with AD, the concordance between Aß PET and CSF AD biomarker immunoassay will be considered. As such, a second comparator for CSF AD biomarker immunoassay is Aß PET.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

As previously presented in Table 2, there are no pharmaceutical treatments available (TGA registered or PBS-listed) for the treatment of MCI due to AD, and instead patients may be treated with non-pharmaceutical interventions aimed at optimising brain health, which may include encouragement of physical activity, social engagement, maintenance of cognitive stimulation and good nutrition. Patients with a clinical diagnosis of mild AD are eligible for PBS listed AChEIs, in addition to non-pharmaceutical interventions previously described.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☒ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

Currently, patients who receive a clinical diagnosis of MCI due to AD or mild AD are not required to have *APOE* testing or evidence of Aß pathology assessed and *APOE* testing, Aß PET and CSF testing are not currently reimbursed for the diagnosis of AD. This application proposes the use of *APOE* testing, Aß PET and CSF testing in patients with MCI due to AD or mild AD to determine eligibility for treatment with PBS-subsidised donanemab. As such, it is proposed that patients considered for these services must also meet specific PBS eligibility criteria for treatment with donanemab other than the criterion relating to amyloid pathology. Thus, *APOE* genotyping and testing for Aß pathology in these patients is anticipated to entirely replace the comparator, no testing, except in circumstances where treatment with donanemab may be contraindicated. The variable uptake of Aß PET compared with CSF AD biomarker immunoassay will be addressed in the ADAR.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☐ Resources
☐ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

There are currently no amyloid targeting therapies available in Australia for the treatment of AD. Outcomes assessed in the ADAR will assess the validity of the proposed testing options to inform access to PBS subsidised donanemab. Clinical evidence for the treatment efficacy of donanemab is based on data from the Phase III TRAILBLAZER-ALZ 2 clinical trial. In the TRAILBLAZER-ALZ 2 clinical trial patients were eligible for treatment with donanemab with confirmed presence of Aß pathology (≥37 CL) assessed with Aß PET. Subsequently, Aß PET conducted in the TRAILBLAZER-ALZ 2 clinical trial is the evidentiary standard for this submission.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Test accuracy outcomes

Positive and negative concordance between Aß PET and the evidentiary standard ([18]florbetapir and [18]florbetaben)

Positive and negative concordance between CSF AD biomarker immunoassay and the evidentiary standard.

Positive and negative concordance between commercially available CSF AD biomarker immunoassays

Longitudinal accuracy between CSF AD biomarker immunoassay and the evidentiary standard (if available)

Test related adverse events

Safety associated with Aß PET and CSF AD biomarker immunoassay including:

- Safety of exposure to radiation during Aß PET
- Adverse events (AE's) related to lumbar puncture for CSF testing

Yield of testing

Outcomes related to the therapeutic component

Health outcomes

Clinical effectiveness of the intervention

Cognitive and functional evaluation, assessed using:

- Integrated Alzheimer's Disease Rating Scale (iADRS)
- Clinical Dementia Ratings Scale – Sum of Boxes (CDR-SB)
- Alzheimer's Disease Assessment – Cognitive subscale (ADAS-Cog$_{13}$)
- Clinical Dementia Ratings Scale – Global Score (CDR-G)
- Alzheimer's Disease Cooperative Study - Activities of Daily Living for Mild Cognitive Impairment (ADCS-iADL)
- Amyloid Clearance
- MMSE

Safety

Treatment emergent adverse events: Treatment-related amyloid-related imaging abnormality-(o)edema (ARIA-E) and amyloid-related imaging abnormality haemorrhage (ARIA-H) events.

Healthcare system

Utilisation

Healthcare costs

Cost effectiveness analysis between Aß PET and CSF AD biomarker immunoassay

Total cost to MBS and PBS

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

Donanemab is a novel therapy for the treatment of patients with MCI due to AD, and mild AD. There are currently no amyloid targeting therapies available in Australia. A clinical diagnosis of AD is made through a comprehensive medical evaluation, and there is currently no requirement for patients to be screened for *APOE* ε4 or investigated for Aß pathology. As such, tests for APOE genotyping and assessing presence of Aß pathology are not currently MBS funded.

Costs associated with A*POE* genotyping

APOE tests are available at private pathology providers at a cost of around $150 (Sonic Genetics 2023).

Costs associated with Aß PET

Generally, the cost components of performing Aß PET include the Aß PET ligand, PET scan and Aß PET interpretation. To date, all MBS-subsidised PET imaging of the brain has utilised F-18 fluorodeoxyglucose (FDG), e.g. MBS Item 61559 - FDG PET study of the brain, performed for the evaluation of refractory epilepsy which is being evaluated for surgery (fee: $918) or MBS Item 61560 - FDG PET study of the brain, performed for the diagnosis of Alzheimer's disease (fee: $605.05).

Notably, all amyloid tracers are owned by commercial companies, in contrast to F-18 FDG which is in the public domain. While current MBS items for FDG-PET may provide comparable costs for performing and interpreting the PET scan, the MBS fee for Aß PET will need to also incorporate the price of the Aß PET ligand which is currently unknown.

Costs associated with Aß CSF immunoassay

The costs components involved with performing Aß CSF immunoassay have previously been assessed by PASC during evaluation of Application 1643 and include the following:

- Costs associated with performing the lumbar puncture: Currently reimbursed on the MBS via items 21945, 39000 and 23010, representing a total MBS fee of $213.65.

- Day private hospital charge (if necessary) for the performance of lumbar puncture (includes costs of use of fluoroscopic or CT guided procedure): Consistent with Application 1738, this is currently assumed to be $521.00 based on cost of Minor Medical Procedures ($788; NHCDC Round 24 Tier 2; 1013) excluding the pathology cost ($267; NHCDC Round 24; 3005) (Independent Health and Aged Care Pricing Authority 2019/20) :

- Cost of the CSF test assay. At present, Aß CSF immunoassay is performed at The National Dementia Diagnostics Laboratory (NDDL), located at The Florey in Melbourne for a non-rebated fee of $400 ([National Dementia Diagnostics Laboratory | Scientific facilities and research services | The Florey](#)).

Costs associated with donanemab administration

Infusion

Donanemab is administered via intravenous infusion. Redacted. In the ratified PICO for Application 1643, it is noted that "The Department confirmed that a new MBS item is not required for intravenous infusion of aducanumab; this service should be included as part of a consultation with a specialist".(MSAC application 1643 Second PASC consideration-Ratified PICO Confirmation 2021) As such, this application assumes that a separate MBS item for infusion of donanemab is not required and that MBS items relating to specialist consultation (i.e. MBS items 104 and 105) will be utilised as appropriate.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

MRI monitoring

Patients treated with donanemab are anticipated to require MRI monitoring for detection of ARIA. As donanemab is currently under evaluation by the TGA, the MRI monitoring schedule has not yet been finalised.

The Applicant wishes to clarify whether the use of existing MBS items for MRI scans of the head (e.g. MBS item 63004) would be appropriate for use for MRI monitoring of patients treated with donanemab, or whether a new MBS item would need to be created. Should a new MBS item, the current MBS fee for a MRI scan of the head of $426.50 is assumed to be appropriate.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

Proposed item details

Table 4   Amyloid beta positron emission tomography to confirm and quantify amyloid pathology.

MBS item number (where used as a template for the proposed item)	MBS item 61560 used as a template for the proposed item descriptor
Category number	5
Category description	Diagnostic Imaging Services
Proposed item descriptor	Beta-amyloid positron emission tomography (PET) study of the brain, with or without quantitative assessment, for the evaluation of patients with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease, requested by the specialist or consultant physician, to determine if the requirements related to amyloid pathology for access to treatment with donanemab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. The patient considered for this service must also meet specific PBS eligibility criteria for treatment with donanemab other than the criterion relating to amyloid pathology. Applicable not more than X per lifetime
Proposed MBS fee	TBD
Indicate the overall cost per patient of providing the proposed health technology	TBD
Please specify any anticipated out of pocket expenses	No additional out of pocket costs are expected
Provide any further details and explain	N/A

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Table 5 Amyloid beta positron emission tomography to assess patients response to treatment with donanemab

MBS item number (where used as a template for the proposed item)	MBS item 61560 used as a template for the proposed item descriptor
Category number	5
Category description	Diagnostic Imaging Services
Proposed item descriptor	Beta-amyloid positron emission tomography (PET) study of the brain, with or without quantitative assessment, for the evaluation of patients with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease, requested by the specialist or consultant physician, for assessing response to treatment with donanemab under the Pharmaceutical Benefits Scheme (PBS) Test must be performed within 18 months of initiating treatment with PBS subsidised donanemab, testing limited to 3 per patient.
Proposed MBS fee	TBD
Indicate the overall cost per patient of providing the proposed health technology	TBD
Please specify any anticipated out of pocket expenses	No additional out of pocket costs are expected
Provide any further details and explain	N/A

Table 6 Cerebrospinal fluid Alzheimer disease biomarker immunoassay for confirmation of amyloid pathology

MBS item number (where used as a template for the proposed item)	MBS item 71139 used as a template for the proposed item descriptor
Category number	6
Category description	Pathology Services
Proposed item descriptor	Quantification by immunoassay of ß-amyloid and tau protein concentration in a sample of cerebrospinal fluid from a patient with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease, requested by the specialist or consultant physician, to determine if the requirements related to amyloid pathology for access to treatment with donanemab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. The patient considered for this service must also meet specific PBS eligibility criteria for treatment with donanemab other than the criterion relating to amyloid pathology. Applicable not more than X per lifetime
Proposed MBS fee	TBD
Indicate the overall cost per patient of providing the proposed health technology	TBD
Please specify any anticipated out of pocket expenses	No additional out of pocket costs are expected
Provide any further details and explain	N/A

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the <u>proposed health technology</u>:

As previously described, AD is a continuum, which is normally characterised in clinical stages MCI, mild AD, moderate AD and severe AD. Early signs of MCI or AD can be subtle and vary from person to person. Assessment of patients for MCI or AD is often initiated following an expression of concern from family or carers who are often better positioned to identify early changes in a patient's behaviour and cognition (Bunn et al. 2012). Primary care providers are usually the first to evaluate patients for neurocognitive disorders. Assessments undertaken by the primary care provider vary but may include taking a clinical history (including cognitive, behavioural and psychological symptoms), cognitive screening tests, physical examination and blood tests (Guideline Adaptation Committee 2016). If a diagnosis of dementia is suspected, patients will be referred for specialist evaluation.

Within Australia, specialists with expertise in memory disorders include geriatricians, neurologists, and psychogeriatricians. Memory assessment services may be multidisciplinary and include other medical, nursing and allied health staff. These physicians will conduct further specialist assessments to confirm a diagnosis of a subtype of dementia, a clinical diagnosis of MCI, or AD diagnosis with staging.

There is no single test to diagnose dementia or MCI. Due to the nonspecific presentation of symptoms. physicians will undertake a wide range of initial assessments including taking patient and carer history, medication review, blood and urine testing and physical assessment to determine if a different condition is producing dementia like-symptoms. Structural imaging, including CT and MRI, are useful for the differential diagnosis of dementia pathologies and to exclude other cerebral pathologies. Notably, at an advisory board conducted by Eli Lilly in February 2024, key opinion leaders in the diagnosis and management of patients with AD, noted that the majority of their patients will have a MRI completed as part of the diagnostic work up for AD.

If no additional cause is identified which explains a patient's loss of cognitive functioning, physicians will perform a clinical cognitive assessment of patient's memory, orientation and executive function. There are a suite of validated cognitive assessment tools available to clinicians to assess patients' cognitive functioning. Commonly used tools in Australia include the MMSE, Montreal Cognitive assessment, the Kimberly Indigenous Cognitive assessment tool (KICA-Cog), and Rowland Universal Dementia Assessment Scale (RUDAS). The choice of assessment tool will depend on the cultural sensitivities, language and education of the patients, clinicians should also consider the age, prior level of functioning, aphasia, hearing or visual impairments, psychiatric illness or physical/neurological problems when interpreting patient scores on these tests (Guideline Adaptation Committee 2016). The KICA-Cog and RUDAS are both short mental status tests that have been developed in Australia for use in specific subpopulations. The KICA-Cog is recommended for use with Aboriginal and Torres Strait Islander peoples (LoGiudice et al. 2006), while the RUDAS tool is recommended for use with people from culturally and linguistically diverse backgrounds (Storey et al. 2004).

Where initial and specialist assessments are inconclusive, and AD is suspected, there are two tests available on the MBS which may provide additional certainty. MBS item 61402 for cerebral perfusion study, with single photon emission tomography (SPECT) may be useful for the differential diagnosis of suspected dementia (Harvey et al. 2013). However, at an advisory board conducted by Eli Lilly in February 2023, key opinion leaders in the diagnosis and management of AD noted that SPECT is rarely performed during the diagnosis of AD. The second available test is MBS item 61560 for fluorodeoxyglucose PET. FDG PET shows distinct spatial patterns of glucose metabolism in the brain, and it is indicated for the diagnosis of AD where clinical evaluation is inconclusive.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Based on the outcome of the clinical assessment, patients may be diagnosed with a clinical diagnosis of MCI, of unknown cause or due to AD; or mild, moderate or severe AD. This application proposes that patients with a diagnosis of MCI due to AD, or mild AD will be eligible for *APOE* genotyping, and if suitable, followed by Aß PET or CSF biomarker testing to assess Aß pathology, and inform PBS subsidised access to donanemab.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

To access *APOE* genotyping, and Aß PET or CSF AD biomarker immunoassay to assess Aß pathology, and inform access to PBS subsidised donanemab, patients must have an existing diagnosis of MCI due to AD, or mild AD. The proposed technologies are not intended to be used to diagnose AD. Notably, while a recent (within one year) MRI is expected to be required to initiate treatment with donanemab, it has been highlighted through discussions with key opinion leaders in the diagnosis and management of AD, that the majority of AD patients will have a MRI completed as part of the diagnostic work up to exclude other cerebral pathologies. As such, no differences are expected in the clinical management algorithm prior to the usage of the proposed tests versus the comparator, which is no testing for Aß pathology.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

APOE screening (including analysis of the ε2, ε3, and ε4 variants) conducted via a blood test is offered for a non-rebated fee of approximately $150 (Sonic Genetics 2023). MBS item 73928 applies to the collection of blood sample in EDTA, which is obtained using standard blood collection procedures.

Aß PET scanning is always performed with a CT (PET/CT) or MRI (PET/MRI) (Herholz and Heiss 2004) for accurate anatomic localisation of the pathology and for attenuation correction purposes. In their assessment of MSAC application 1643 for two testing options for determining eligibility for access to PBS subsidised aducanumab in patients with early-stage AD, PASC noted that MBS item 61505 for CT scan performed at the same time, covering the same body area as PET for the purpose of anatomic localisation or attenuation correction, would be appropriate for use with the new MBS item which would be required for Aß PET. There is no MBS item available for concurrent PET/MRI, however MSAC has indicated that this is rarely performed, and an additional MBS item is therefore unlikely to be required. At the July 2021 meeting, MSAC assessed application 1632, and supported the creation of a new MBS item for prostate-specific membrane antigen (PSMA) PET/CT for informing treatment of patients with prostate cancer. MSAC noted that in current clinical practice, PET is never performed without CT, except for cases in which PET/MRI is used, which were noted to be rare.

For CSF biomarker testing, the CSF sample is obtained by lumbar puncture using a standardised collection procedure. Following assessment of application 1643, PASC indicated that lumbar puncture for CSF sample collection could be covered by MBS item 39000, accompanied by MBS item 23010 for the administration of anaesthesia performed with the procedure. Noting that a lumbar puncture for the collection of CSF fluid for Aß biomarker testing is likely to be performed in a generally older cohort of patients, image guided fluoroscopy or CT may be required. Existing MBS items for CT of the spine (MBS item 56219) and MBS items in the subgroup for fluoroscopic examination may be appropriate for this indication.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Explain what other healthcare resources are used in conjunction with the <u>comparator health technology</u>:
No additional healthcare resources are used in conjunction with the comparator 'no testing for *APOE*' or 'no testing for Aß pathology'.

Describe and explain any differences in the healthcare resources used in conjunction with the <u>proposed health technology</u> vs. the <u>comparator health technology</u>:
Currently in Australia, there is no requirement for patients to be screened for *APOE ε4* or have evidence of Aß pathology confirmed or quantified. Following a clinical diagnosis of MCI due to AD, or mild AD patients are treated with standard of care, encompassing non-pharmacological intervention. For mild AD patients, standard of care may also encompass treatment with a AChEI. Patients accessing the proposed health technologies for Aß testing, and subsequent treatment with donanemab will also be treated with standard of care. As a result, all healthcare resources which will be used in conjunction with the proposed health technology will be an addition to the current treatment algorithm.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the <u>proposed health technology</u>:
This codependent application requests MBS listing for *APOE* screening, Aß PET and CSF AD biomarker immunoassay for the assessment of Aß pathology in patients with a clinical diagnosis of MCI due to AD, or mild AD, to inform access to PBS subsidised donanemab. It is anticipated that patients who access these diagnostic services will have met the PBS eligibility criteria for treatment with donanemab. Redacted.

Donanemab is administered by intravenous infusion Q4W, redacted. It is anticipated that donanemab treatment will be administered in addition to standard of care. That is, for patients with MCI due to AD, donanemab would be administered in addition to non-drug brain health optimisation strategies. For patients diagnosed with mild AD, donanemab may be administered in addition to non-drug brain health optimisation strategies with or without symptomatic treatment with AChEIs.

For patients initiated on donanemab, monitoring with MRI to assess for incidences of ARIA will be required. As donanemab is currently under evaluation by the TGA, the appropriate MRI monitoring schedule has not yet been finalised. This application has proposed the use of existing MBS items for MRI may be used for monitoring of ARIA, but seeks confirmation on whether a standalone MBS item would be required.

In Australian clinical practice, it is expected that donanemab treatment will continue up to a maximum treatment duration of 18 months, with a potential for earlier treatment completion if amyloid plaque clearance can be assessed and is achieved. Where a treat to clearance approach is taken, additional assessment of response to treatment with Aß PET will be required. In the TRAILBLAZER-ALZ 2 trial, amyloid clearance was assessed at 24, 52 and 76 weeks (Sims et al. 2023). Alternative Aß PET monitoring schedules will be explored in the ADAR. A standalone MBS item for the purpose of assessing amyloid clearance via Aß PET for patients treated with donanemab has been proposed within this application.

Testing options to detect amyloid beta pathology and determine *APOE* genotype in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO set

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the <u>comparator health technology</u>:
Where the comparator is 'no *APOE* testing' and 'no testing for Aß pathology', patients are not assessed for evidence of Aß pathology and are treated with the current standard of care as there are no disease modifying therapies for the treatment of AD currently available in Australia. There are limited pharmaceutical options available for the treatment of AD; AChEIs (donepezil, galantamine and rivastigmine) are PBS listed for mild to moderately severe AD, and the NMDA memantine is indicated for moderately severe AD. These medications treat the symptoms of AD, increasing cognitive and neural cell function but do not treat the underlying pathology of AD (Breijyeh and Karaman 2020b). In addition to pharmaceutical intervention, standard treatment for patients with AD involves person-centered care with an integrated care approach focusing on adequate nutrition, promoting functional independence, occupational therapy and exercise, cognitive training and rehabilitation (Guideline Adaptation Committee 2016). These therapies and interventions are only useful in patients with mild to moderate AD, and the efficacy of the interventions is only short term. After patients have progressed to severe disease, the only available intervention is best supportive care.

Describe and explain any differences in the healthcare resources used *after* the <u>proposed health technology</u> vs. the <u>comparator health technology</u>:
As previously described, the proposed health technologies, and codependent access to donanemab are intended to be delivered in conjunction with standard of care. *APOE* genotyping, Aß testing and treatment with donanemab will be used as an addition to the current standard of care.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Figure 2 Current clinical management algorithm

Figure 3 Proposed clinical management algorithm
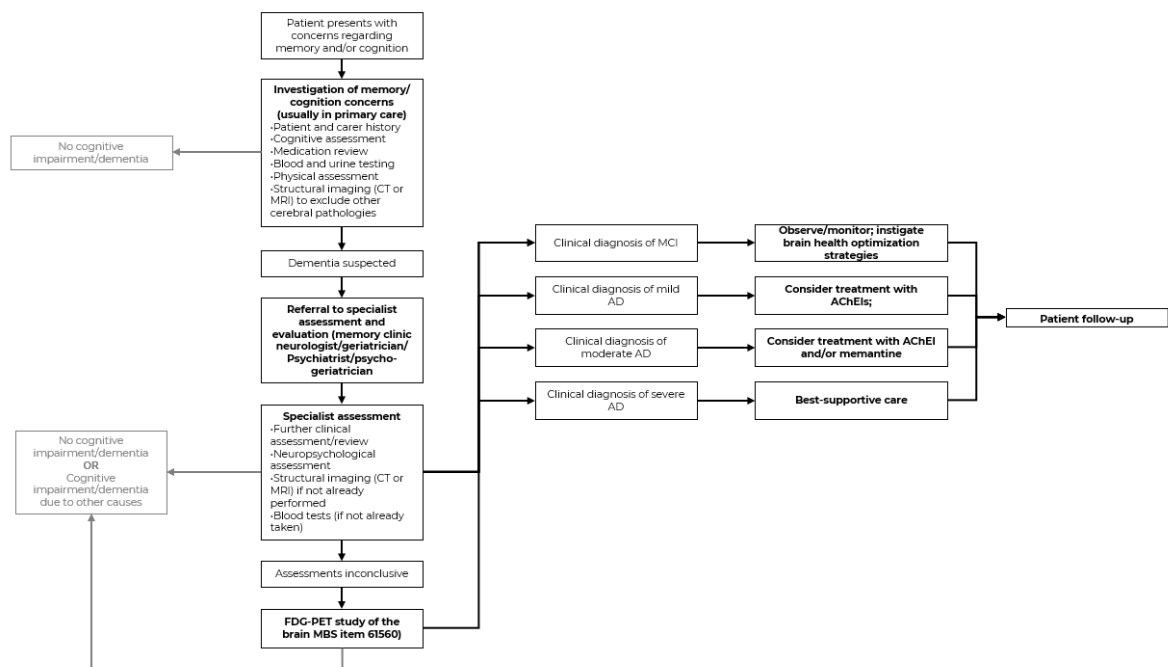
Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

This application proposes that the co-dependent technology, *APOE* genotyping to assess treatment suitability, Aß testing (via either Aß PET or CSF) to assess Aß pathology, followed by therapy with donanemab and standard of care in patients with confirmed evidence of Aß, results in superior health outcomes, and manageable safety outcomes compared to no testing and standard of care in patients with a clinical diagnosis of MCI due to AD, or mild AD.

This clinical claim is justified by acceptable safety and analytical performance of Aß testing (via either Aß PET or CSF), superior efficacy with a manageable safety profile of donanemab treatment compared to standard of care in patients with MCI due to AD or mild AD and confirmed evidence of Aß pathology (as supported by the TRAILBLAZER-ALZ 2 trial), and clinical utility of the co-dependent technology. Redacted. TRAILBLAZER-ALZ 2 was a phase 3, randomised, double-blind study that evaluated the efficacy and safety of donanemab in the treatment of MCI or mild dementia due to AD with presence of amyloid and tau pathology. The primary objective of TRAILBLAZER-ALZ 2 was to assess the efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque. The efficacy and safety of donanemab was assessed in 1,736 patients who were randomised in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 76 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met. *APOE* status was not part of the recruitment criteria for the trial, but subgroup analyses according to *APOE* status were conducted to assess differences in safety and efficacy.

The primary outcome evaluated in TRAILBLAZER-ALZ 2 was the integrated assessment of cognition and daily function, denoted as iADRS. This assessment comprises items from the ADAS-Cog13 and the ADCS-iADL, providing a measure of global AD severity across the continuum (scores range between 0-144, with a lower score indicating greater impairment).

Key secondary outcomes included:

- Clinical Dementia Rating Scale (CDR-SB)

- ADAS-Cog13

- ADCS-iADL

- Biomarker results

- MMSE

- Adverse events

The results from TRAILBLAZER-ALZ 2 trial provided evidence of the benefit of treatment with donanemab in patients with early symptomatic AD, as clinically meaningful slowing of disease progression was demonstrated across all key clinical efficacy measures. A summary of key results is provided below.

Testing options to detect amyloid beta pathology in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO Set

Efficacy results

As of the data cut-off on 23 April, the least squares mean (LSM) change in iADRS score at 76 weeks for the combined population (including low/medium and high tau pathology), as analysed using the natural cubic spline model with 2 degrees of freedom (NCS2), was -10.19 (95% CI -11.22 to -9.16) in the donanemab group and -13.11 (95% CI -14.10 to -12.13) in the placebo group (difference 2.92; 95% CI 1.51 to 4.33; p = 0.001), representing a significant 22.3% (95% CI 11.38% to 33.15%) slowing of disease progression (p<0.001). In donanemab-treated participants, a significant difference compared with placebo was observed as early as Week 12 (p<0.001) and this treatment effect widened over time, with a LSM treatment difference of −1.19, −2.27, and −2.92 at Weeks 24, 52, and 76, respectively. In the literature, clinically meaningful benefit of treatment in AD has been considered as >20% slowing of clinical progression (Abushakra et al. 2016; Insel et al. 2019; Petersen et al. 2023; Sims et al. 2023; Vellas et al. 2007)().

Consistent with the primary efficacy endpoint results, donanemab was associated with a significant and clinically meaningful slowing of disease progression compared with placebo as measured by the CDR-SB score in the overall population. In the mixed model for repeated measures (MMRM) analysis, the LSM change from baseline to Week 76 was 1.72 (95% CI 1.53, 1.91) in the donanemab group compared with 2.42 (95% CI 2.24, 2.60) in the placebo group, which represented a 29% (95% CI 18.41, 39.44) slowing of disease progression in donanemab-treated participants (p<0.001) (Sims et al, 2023). A significant separation from placebo occurred as early as Week 12 and the treatment effect continued to increase over time to Week 76, with a LSM difference compared with placebo of −0.31, −0.56, and −0.70 at Weeks 24, 52, and 76, respectively.

In the overall population, the other gated secondary clinical endpoints that measured cognitive and functional decline, the ADAS-Cog$_{13}$ and ADCS-iADL, demonstrated robust, consistent, and clinically meaningful results in favour of donanemab versus placebo. According to the primary analyses (NCS2), donanemab slowed clinical progression relative to placebo by 20% (95% CI 8.23, 30.83) and 28% (13.48, 42.13) as measured by the ADAS-Cog$_{13}$ and ADCS-iADL, respectively.

Biomarker results

Biomarker results show significant amyloid plaque reduction in patients treated with donanemab compared to placebo. In the overall population at week 76, amyloid plaque level decreased by 87.0 CL (95% CI, −88.90 to −85.17) with donanemab treatment and decreased by 0.67 CL (95% CI, −2.45 to 1.11) in the placebo group. A significantly higher proportion of donanemab-treated participants in the overall population achieved amyloid clearance at all time points compared with placebo-treated participants (p<0.001 all time points) (Shcherbinin S 2023). Amyloid plaque clearance was reached in 29.7% (95% CI 26.56, 33.04), 66.1%, and 76.4% (72.87, 79.57) of participants in the donanemab group at Weeks 24, 52, and 76, respectively (Shcherbinin S 2023; Sims et al. 2023) resulting in 29.7%, 36.4%, and 10.3% completing donanemab treatment and switching to blinded placebo at 24, 52, and 76 weeks, respectively.

Biomarker results relating to amyloid clearance are a key outcome of interest due to the growing evidence supporting a correlation between speed and rate of amyloid clearance and cognitive and functional outcomes. In particular, a retrospective analysis has explored the relationship between amyloid plaque reduction and clinical outcomes (using CDR-SB) in studies of amyloid targeting therapies including gantenerumab, lecanemab, aducanumab, and donanemab (Boxer and Sperling 2023)). Boxer and Sperling noted that at trial conclusion, "significant clinical efficacy was strongly related to the amount of amyloid (measured in centiloids) removed from the brain."

Testing options to detect amyloid beta pathology in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO Set

Safety

In TRAILBLAZER-ALZ 2, donanemab was generally well tolerated by patients, and exhibited a safety profile that was consistent with other amyloid targeted therapies. During the 76 weeks, 759 participants (89.0%) in the donanemab group and 718 (82.2%) in the placebo group reported at least one treatment emergent adverse event (TEAE). While a higher frequency of participants died in the donanemab group compared with the placebo group, with 16 (1.9%) and 10 (1.1%) deaths respectively, 3 deaths in the donanemab arm were considered related to treatment. At least one serious adverse event was observed in the donanemab (17.4%) and placebo (15.8%) groups. There was a higher frequency of participants (13.1%) who discontinued study treatment due to AEs in the donanemab group compared with the placebo group (4.3%).

AEs of special interest included amyloid-related imaging abnormalities-oedema/effusions (ARIA-E) and amyloid-related imaging abnormalities haemorrhage/hemosiderin deposition (ARIA-H), macrohaemorrhages, hypersensitivity (including immediate and non-immediate) including infusion-related reactions and anaphylaxis. Of the 52 donanemab-treated participants who experienced symptomatic ARIA-E, approximately 85% had resolution of symptoms associated with ARIA-E during the 76-week period. The incidence of ARIA-H based on MRI or TEAE cluster was higher in the donanemab group (n = 268, 31.4%) compared with the placebo group (n = 119, 13.6%) during the 76-week period. A total of 4 (0.5%) donanemab-treated participants had a serious adverse event (SAE) of ARIA-H, of which 3 (0.4%) participants also had an SAE of ARIA-E. While treatment was associated with a higher risk of ARIA and hypersensitivity reactions, the robust clinical trial design enabled the demonstration of risk mitigation strategies where an intense monitoring arrangement and specific dosing guidance are recommended to aid early detection and management of ARIA events.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

AD progression occurs slowly over a period of years, with not only worsening mental function but eventually also loss of bodily functions, including walking and swallowing. It poses a significant burden to patients, families, healthcare systems, and society, even at the early disease stages, and the burden increases with progression.

There are currently no TGA registered therapies available in Australia for AD which treat the underlying pathophysiology of the disease, and symptomatic treatments for early AD are very limited. As previously discussed, current interventions for patients with MCI due to AD are limited to non-pharmaceutical interventions, while mild AD patients may also be treated with AChEI inhibitors to temporarily ease or stabilise the symptoms of AD (Tan et al. 2018). AChEI inhibitors do not modify disease progression (Breijyeh and Karaman 2020a). Over time, the nerve endings die and the AChEIs are no longer effective (Alzheimer Society Canada 2022; NICE 2011). AChEI agents are associated with side effects including gastrointestinal symptoms and cardiac concerns, and this should be considered in any treatment approach (Petersen et al. 2018). Non-pharmacological interventions such as exercise and nonmedical cognitive intervention have limited evidence supporting their effectiveness (Guideline Adaptation Committee 2016).

Thus, there is a significant unmet need for an intervention that slows the progression of early AD as this would provide clinical and humanistic benefits for the patient in addition to delaying or avoiding the costs associated with severe disease. The key benefit of treatment with donanemab is a clinically meaningful slowing of disease progression. Compared to the comparator, no testing for *APOE* or Aß pathology, and treatment with standard of care, *APOE* screening and Aß testing to inform treatment with donanemab provides patients with an opportunity to access a disease modifying treatment with demonstrated evidence to slow AD progression.

Identify how the proposed technology achieves the intended patient outcomes:

This codependent application request MBS listing for *APOE* genotyping, Aß PET and CSF AD biomarker immunoassay for the confirmation of Aß pathology, to inform access to treatment with PBS subsidised donanemab.

Testing options to detect amyloid beta pathology in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO Set

Donanemab is an IgG1 monoclonal antibody directed against insoluble, modified, N-terminal truncated form of Aß (N3pG Aß) present only in brain amyloid plaques (Bridel et al, 2017). Donanemab binds to the deposited amyloid plaque and aides its removal through microglial-mediated phagocytosis (DeMattos et al, 2012). The accumulation of Aß plaque in the brain is one of the defining pathophysiological features of AD (Jack et al, 2018). Treatment with donanemab will require patients to have evidence of Aß pathology.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome?   Yes

Other benefits?   No

Please provide a rationale, and information on other benefits if relevant:
Patients who redacted and determined to be Aß positive, after testing with either Aß PET or Aß CSF immunoassay, would be eligible to receive treatment with donanemab (subject to meeting any other clinical criteria for treatment). Positive results have been reported from the TRAILBLAZER-ALZ 2 phase 3 trial, with donanemab meeting the primary and all secondary efficacy endpoints measuring slowing cognitive and functional decline (Sims et al, 2023).

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?
☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
The comparator for *APOE* screening and Aß testing proposed in this application is no *APOE* screening and no testing for Aß. In Australia, there is currently no requirement for patients with MCI due to AD or mild AD to undergo *APOE* screening or testing to confirm Aß pathology. The landscape of AD treatment and diagnosis is currently evolving, with the introduction of amyloid targeting therapies into the clinical management algorithm, *APOE* screening and characterisation of patients Aß pathology will now inform change in treatment management. As such, introduction of the proposed technology will be associated with an increased cost, compared to the comparator, no *APOE* screening or Aß testing.

Testing options to detect amyloid beta pathology in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO Set

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Phase 3 RCT: Multicenter (277 medical research centres/hospitals in 8 countries), randomised, double-blind, placebo-controlled, 18-month study	Donanemab in Early Symptomatic Alzheimer Disease TRAILBLAZER-ALZ 2 ClinicalTrials.gov Identifier: NCT04437511	The primary objective of TRAILBLAZER-ALZ 2 was to assess the efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque. The efficacy and safety of donanemab was assessed in 1736 patients who were randomised in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 76 weeks	https://jamanetwork.com/journals/jama/fullarticle/2807533	July 17, 2023
2.	Phase 2 RCT: Multicenter, randomised, double-blind, placebo-controlled study	Donanemab in Early Alzheimer's Disease TRAILBLAZER-ALZ trial ClinicalTrials.gov Identifier: NCT03367403	Trial of donanemab in patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on positron emission tomography (PET). Patients were randomly assigned in a 1:1 ratio to receive donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo intravenously every 4 weeks for up to 72 weeks	https://www.nejm.org/doi/10.1056/NEJMoa2100708	May 6, 2021

Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

Testing options to detect amyloid beta pathology in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO Set

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Phase 3 RCT: Multicenter, randomised, double-blind, placebo-controlled, 18-month study	Donanemab in Early Symptomatic Alzheimer Disease TRAILBLAZER-ALZ 5 ClinicalTrials.gov Identifier: NCT05508789	The primary objective of TRAILBLAZER-ALZ 5 is to evaluate the safety and efficacy of donanemab in participants with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology.	A Study of Donanemab (LY3002813) in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 5) - Full Text View - ClinicalTrials.gov	*Estimated study completion date is April 2027*

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

Testing options to detect amyloid beta pathology in patients with mild cognitive impairment due to Alzheimer's disease, or mild Alzheimer's disease, to determine eligibility for PBS subsidised donanemab treatment – PICO Set

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