Assessing the Preparedness of the Australian Health Care System Infrastructure for an Alzheimer’s Disease-Modifying Therapy

SUMMARY AND KEY FINDINGS

- Disease-modifying therapies to prevent or delay the progression of Alzheimer’s disease (AD) are under clinical investigation. AD is the leading cause of dementia, and over 800,000 Australians with mild cognitive impairment in 2018 could potentially benefit from a therapy that reduces the risk of progression to dementia.

- The delivery of a therapy to people with early-stage disease presents potential infrastructure challenges in diagnosing and treating a large population. The objective of this analysis is to illustrate the magnitude of capacity challenges for the Australian health care system if a hypothetical therapy becomes available in 2023.

- We use a simulation model to compare the expected number of patients with the capacity of the Australian health care system and assess three possible constraints: visits to dementia specialists, biomarker testing and infusion delivery. We make many assumptions, including those related to specifications of a hypothetical therapy, patient uptake rates and projected capacity growth trends.

- If capacity follows historical growth trends, our analysis suggests that Australians could wait over ten months in the initial year. We find that the most pressing constraint is the availability...
Introduction

An estimated 376,000 Australians live with dementia as of 2018 (Australian Institute of Health and Welfare [AIHW], 2018). Since 2013, dementia has been the second leading overall cause of death in Australia and accounted for 13,729 deaths in 2017 (Australian Bureau of Statistics [ABS], 2018c). Rates of dementia differ among subpopulations; for example, dementia prevalence among Aboriginal and Torres Strait Islanders is estimated to be two to five times that of nonindigenous Australians (AIHW, 2018).

Alzheimer’s dementia is the most common type of dementia. Alzheimer’s Disease International (2009) estimates 50 to 75 percent of dementia is due to Alzheimer’s disease (AD). AD is a progressive neurodegenerative disorder characterised by changes in the brain including the accumulation of beta-amyloid plaques and tau tangles. These changes accumulate over many years, progressing through stages of cognitive impairment and eventually leading to irreversible neurological degeneration and Alzheimer’s dementia (Perl, 2010). Although AD is the most common cause of dementia, people often exhibit mixed dementia in which more than one type of dementia occurs, such as Alzheimer’s dementia in combination with vascular dementia or Lewy body dementia (Dementia Australia, n.d.b). Risk factors for AD include age, genetics and lifestyle; while there are nonpharmacological approaches to reducing risk and managing symptoms, there is currently no way to prevent AD (Dementia Australia, n.d.a).

At present, no disease-modifying therapy (DMT) is available for AD; however, 83 DMT agents have been evaluated in more than 200 clinical trials from 2002 to 2012 (Cummings, Morstorf and Zhong, 2014). In 2018, there were several DMTs in development (Cummings et al., 2018), most of which target beta-amyloid, tau or both proteins (Cummings, Morstorf and Zhong, 2014; Cummings, Morstorf and Lee, 2016; Cummings et al., 2017; Cummings et al., 2018). Selected candidate therapies currently in phase 2 and phase 3 clinical trials are presented in Table 1.

Although a therapy is not yet available, early facilitation of policy discussions and actions could help minimise future infrastructure issues in which an approved therapy cannot be accessed due to capacity constraints.
Despite incomplete understanding of the disease mechanisms and drug targets, there has been some optimism for future therapies in recent years, particularly for therapies to delay or prevent disease progression in patients in early stages of AD such as mild cognitive impairment (MCI), rather than therapies that aim to cure or reverse Alzheimer’s dementia after manifest dementia occurs (Aisen, 2017; Lancet Neurology, 2015). However, the future availability of an Alzheimer’s DMT remains uncertain, and phase 3 trials for two leading amyloid candidates were discontinued in early 2019 (Biogen, 2019; F. Hoffman-La Roche Ltd, 2019).

Although a therapy is not yet available, early facilitation of policy discussions and actions could help minimise future infrastructure issues in which an approved therapy cannot be accessed due to capacity constraints. If a DMT becomes available, one of the infrastructure challenges that health systems would face is how to diagnose and treat a large number of people with early-stage AD.

**TABLE 1**

Selected Alzheimer’s Disease-Modifying Therapy Candidates in Phase 2 and Phase 3 Clinical Trials, as of April 2019

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Sponsor</th>
<th>Clinical Trial Phase</th>
<th>Expected Primary Completion Date</th>
<th>National Clinical Trial Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-beta-amyloid antibodies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Hoffmann-La Roche</td>
<td>Phase 3</td>
<td>May 2022</td>
<td>NCT03443973, NCT03444870</td>
</tr>
<tr>
<td>BAN2401</td>
<td>Eisai/Biogen</td>
<td>Phase 3</td>
<td>March 2024</td>
<td>NCT03887455</td>
</tr>
<tr>
<td>LY3002813&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Eli Lilly</td>
<td>Phase 2</td>
<td>October 2020</td>
<td>NCT03367403</td>
</tr>
<tr>
<td><strong>Anti-tau antibodies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABBV-8E12</td>
<td>AbbVie</td>
<td>Phase 2</td>
<td>April 2021</td>
<td>NCT02880956</td>
</tr>
<tr>
<td>RO7105705</td>
<td>Genentech</td>
<td>Phase 2</td>
<td>September 2020</td>
<td>NCT03289143</td>
</tr>
<tr>
<td><strong>BACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elenbecestat (E2609)</td>
<td>Eisai/Biogen</td>
<td>Phase 3</td>
<td>June 2021</td>
<td>NCT03036280</td>
</tr>
<tr>
<td>CNP520</td>
<td>Novartis/Amgen/Banner Alzheimer’s Institute</td>
<td>Phase 2/3</td>
<td>July 2024</td>
<td>NCT03131453</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD106 (anti-beta amyloid)</td>
<td>Novartis</td>
<td>Phase 2/3</td>
<td>August 2024</td>
<td>NCT02565511</td>
</tr>
<tr>
<td>AADvac1 (anti-tau)</td>
<td>Axon Neuroscience</td>
<td>Phase 2</td>
<td>June 2019</td>
<td>NCT02579252</td>
</tr>
</tbody>
</table>

**SOURCE:** RAND analysis of company websites and ClinicalTrials.gov website as of April 4, 2019.

**NOTES:** Anti-beta-amyloid and anti-tau antibodies are monoclonal antibodies that are typically administered by intravenous or subcutaneous infusions. Beta-secretase (BACE) inhibitors are oral drugs that block BACE, a beta-site amyloid precursor protein-cleaving enzyme thought to prevent the accumulation of beta-amyloid. Alzheimer’s vaccines are injections of antigens or preformed antibodies with the aim of triggering antibody responses.

<sup>a</sup> LY3002813 is being evaluated alone and in combination with LY3202626, a BACE inhibitor.
The concept of a simplified clinical pathway in which people move through screening, diagnosis and treatment within the health system if a DMT for AD was available. People in the normal cognition and untreated MCI states go through the screening and diagnosis clinical phases. Within the MCI state, people may have undiagnosed/untreated MCI, MCI due to causes other than AD, untreated MCI due to AD or treated MCI due to AD depending on what step they are in within the clinical pathway. People are considered to have treated MCI due to AD after undergoing the treatment clinical phase. Untreated and treated MCI due to AD progress to Alzheimer’s dementia at different rates.

### Conceptual Framework and Simulation Model

#### Conceptual Framework

Figure 1 shows the conceptual framework that is the basis for our simulation model. There are two major components to the framework: the disease trajectory (depicted in the grey boxes) and the clinical pathway (depicted in the white boxes). The framework has a trajectory through disease states—normal cognition, MCI and Alzheimer’s dementia—overlaid with a simplified clinical pathway in which people move through screening, diagnosis and treatment within the health system if a DMT for AD was available. People in the normal cognition and untreated MCI states go through the screening and diagnosis clinical phases. Within the MCI state, people may have undiagnosed/untreated MCI, MCI due to causes other than AD, untreated MCI due to AD or treated MCI due to AD depending on what step they are in within the clinical pathway. People are considered to have treated MCI due to AD after undergoing the treatment clinical phase. Untreated and treated MCI due to AD progress to Alzheimer’s dementia at different rates.

Within the normal cognition and MCI states, the Screening Phase includes cognitive assessment of older adults that could occur in primary care settings via an assessment of functional deficits and a
short instrument such as the Folstein Mini-Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975) or the General Practitioner Assessment of Cognition (2016; see also Brodaty et al., 2002). These assessments are not specific for MCI or dementia and are a general screen for mental function that a provider can administer in approximately less than 15 minutes. Those who exhibit cognitive impairment might be evaluated for reversible and treatable causes (i.e., hematologic, metabolic, mood or pharmacological causes).

If no other treatable or reversible features are detected and the impairment is consistent with a potential diagnosis of AD, an individual would likely be referred to a dementia specialist for further evaluation (Diagnostic Phase). The further evaluation may include additional cognitive and functional assessments. After further evaluation, a dementia specialist may refer people for testing of amyloid and/or tau biomarkers to determine if the MCI is likely due to AD. A dementia specialist would then determine whether treatment is indicated for individuals who have a positive biomarker test.

If indicated, patients could be treated with a therapy that would reduce the risk of progression from MCI to Alzheimer’s dementia (Treatment Phase). While people have untreated MCI due to AD, the disease continues to progress. Relative to treated MCI patients, untreated MCI patients have a higher risk of progressing from MCI to a later stage of the disease with manifest dementia, at which point we assume a DMT would no longer be effective.

We model three capacity constraints: availability of dementia specialists, biomarker testing and treatment delivery.

**Simulation Model**

Our simulation model consists of two parts that reflect the disease trajectory and clinical pathway in the framework. First, a Markov model simulates annual transitions between disease states. Individuals move through the disease states—from no cognitive impairment (i.e., no MCI and no Alzheimer’s dementia) to MCI to Alzheimer’s dementia—according to transition probabilities derived from the literature (see Table A.1 in the Appendix). In each state, a share of individuals also exits the model each year based on age-adjusted all-cause mortality rates.

Second, a systems dynamic model simulates health care system capacity constraints within the MCI state. Within the MCI state, people are diagnosed (for MCI due to AD) and treated, and the outflows from these steps are constrained by infrastructure capacity. We model three capacity constraints: availability of dementia specialists, biomarker testing and treatment delivery. The model includes two dementia specialist visits in the diagnostic phase. The allocation of capacity between these two visits is optimised such that specialists do not take on a new patient for an initial visit if they do not have the capacity to provide confirmatory visits for existing patients in the same year. As with the annual transitions between disease state in the stylised model, the clinical pathway for screening, diagnosis and treatment is also modelled as an annual step (i.e., individuals may progress through these phases in one year if capacity allows). We have applied this model to assess the preparedness of the health care systems in the United States (Liu et al., 2017), six European countries (Hlávka, Mattke and Liu, 2018) and Canada (Liu et al., 2019). See the model overview in the Appendix for additional details.

For this analysis, we incorporate Australian data on the population, disease prevalence, mortality and historical workforce and infrastructure into the model. See Table A-1 for model parameter values and their respective sources.
Model Assumptions

In this analysis of a hypothetical future therapy, we incorporate many simplifying assumptions. These assumptions include the year of approval, approved indication, age eligibility to receive treatment, treatment modality, treatment dosage and duration, treatment effectiveness and the treatment safety profile. Our assumptions about patient uptake, contraindications, treatment delivery and effectiveness are generally consistent with those used in our prior United States, European and Canadian studies that were informed by expert input (Liu et al., 2017; Hlávka, Mattke and Liu, 2018; Liu et al., 2019). We apply the same assumptions for this analysis of the Australian health care system unless otherwise noted. To inform our assumptions for the Australian context, we reviewed the literature and consulted two experts familiar with clinical practice and care delivery in Australia.

The key assumptions in our analysis are as follows:

- A DMT for patients with MCI due to AD becomes available in 2023. We assume the therapy would be delivered through a course of intravenous infusions, based on the route of administration for anti-beta-amyloid monoclonal antibody therapies that are the furthest along in clinical trials.
- We assume that individuals age 50 and older are eligible for annual cognitive screening. We model the population 50 years and older because later-stage clinical trials include ages as young as 50 (e.g., U.S. National Library of Medicine, 2019a; 2019b). Screening starts in the year prior (2022) as patients and providers anticipate approval of the therapy in 2023. General practitioners could conduct cognitive assessments, whether through annual screenings or assessments when early symptoms of cognitive impairment are suspected. We assume the capacity to conduct preliminary cognitive and functional assessments would be unconstrained. We assume that 80 percent of individuals age 50 and older would be screened each year starting in the year prior to the availability of a DMT (based on expert input collected in the original development of the model in Liu et al., 2017).
- The number of individuals with MCI is derived from MCI prevalence estimates from a meta-analysis of 20 studies (Petersen et al., 2018). Of those who screen positive for MCI, we assume 50 percent would follow up with a dementia specialist referral to seek further evaluation (based on expert input collected in Liu et al., 2017).
- We assume that dementia specialists would conduct further evaluation of people with MCI that could be due to AD. In Australia, the specialists who are likely to be involved in diagnosing MCI due to AD are geriatricians, neurologists and old-age or neuropsychiatrists. We assume approximately 15 percent of all psychiatrists practice old-age psychiatry or neuropsychiatry, based on a national survey of the psychiatry workforce in Australia (Royal Australian and New Zealand College of Psychiatrists [RANZCP], 2014). If the evaluation confirms MCI and does not find an alternative explanation for MCI (e.g., prior stroke) or a reason to not pursue treatment (e.g., presence of another life-limiting disease), specialists would refer individuals for biomarker testing. Of those with confirmed MCI possibly due to AD, we assume that 90 percent of patients would be referred and consent to biomarker testing, based on expert input in the original development of the model (Liu et al., 2017).
- We assume that biomarker testing may be performed with a positron emission tomography (PET) scan for amyloid deposits in the brain or with lumbar puncture to retrieve cerebrospinal fluid (CSF) for assessment of amyloid and/or tau proteins. The relative use of these biomarker tests in the future with a DMT is uncertain and would depend on factors such as reimbursement levels, costs and patient preferences. Based on our assessment of the literature and input from Australian experts, we selected a base-case assumption that 80 percent of tests would be performed using PET and 20 percent would be performed...
using CSF. Last, we assume that 45 percent of people with MCI have clinically relevant biomarker levels, based on published biomarker studies (Doraiswamy et al., 2014; Ong et al., 2015).

- If an individual’s biomarker level is clinically relevant, she or he returns to a dementia specialist who determines whether treatment is indicated. The individual is referred for treatment if there are no contraindications and the individual consents. Of people with MCI who test above a certain biomarker level, we assume that 80 percent would be eligible for and seek treatment (based on expert input) (Liu et al., 2017).

- We assume that the therapy would be delivered by intravenous infusion every four weeks for one year, following protocols for a typical immunotherapy. We further assume that treatment reduces the relative risk of progression from MCI due to AD to Alzheimer’s dementia by 50 percent relative to untreated MCI due to AD.

**Limitations**

As with our previous studies, this analysis has limitations. First, our model is based on a stylised disease trajectory and clinical pathway that includes the many simplifying assumptions outlined above. The disease trajectory consists of three states (normal cognition, MCI and Alzheimer’s dementia); the model does not allow for reversion of MCI back to normal cognition. This reversion has been observed at fairly high rates but occurs at lower rates in clinic-based studies than community-based studies (Malek-Ahmadi, 2016). Although reversions occur, individuals who revert are at higher risk for retransitioning to MCI (Koepsell and Monsell, 2012). In addition, the definition of MCI has varied considerably over time and across studies.

In the clinical pathway, we make assumptions about the availability and specifications of the therapy, which are dependent on clinical trial results. We also make assumptions around provider and patient uptake, which would be dependent on factors such as the therapeutic profile, effectiveness, outreach and awareness and public reimbursement of a DMT in Australia. As the safety profile and possible adverse reactions are unknown with a hypothetical therapy, the model does not account for specific treatment monitoring.

Although our model focuses on three key capacity constraints, there would likely be other capacity challenges. For example, with screening, the capacity of general practitioners to conduct cognitive assessments may be limited given competing needs with ageing populations. On the other hand, behavioural issues such as awareness of screening availability or stigma associated with a positive screen for predementia may reduce patient uptake for screening.

Our model evaluates the capacity in Australia as a whole. We do not examine capacity issues at the state and territory level or for different populations. There would be additional capacity challenges and access issues in rural and remote areas and in closing the health status gap between the general population and Aboriginal and Torres Strait Islander people (Smith et al., 2008; Eades et al., 2010; AIHW, 2018; Australian Government Department of the Prime Minister and Cabinet, 2019). Moreover, while we model national capacity, the actual expansion of diagnostic and treatment delivery capacity would depend on national, state and territory decisions on priorities, reimbursement, capital investment and clinical guidelines.

With these limitations in mind, our analysis is meant to convey the magnitude of potential capacity challenges in hypothetical scenarios to inform policy and planning decisions, not to predict future outcomes.
workforce data from the Medical Board of Australia (2018). For the projected workforce, we use projections from the *Health Workforce 2025 Medical Specialties Volume 3* report (AFHW, 2012) for neurologists and geriatricians through 2025 and projections from the *Australia’s Future Health Workforce—Psychiatry* report (Department of Health, 2016) for psychiatrists through 2030. Beyond the available published projections (after 2025 for neurologists and geriatricians and after 2030 for psychiatrists), we apply the population growth rates for the population aged 50 and older, in effect assuming that the number of specialists per capita remains steady in future years (Beckett and Morrison, 2007; Tsai, Eliasziw and Chen, 2012) to meet the population’s demand (Hara et al., 2018); this assumption appears reasonable as the historical and published workforce projection trends are similar to population growth trends (Medical Board of Australia, 2018; AFHW, 2012; 2016; ABS, 2018e).

Table 2 shows the projected number of specialists, which we estimate will increase from 5,695 in 2022 to 7,147 in 2035, or by about 25 percent.

Although further evaluation would typically be conducted by these three types of specialists, not all geriatricians, neurologists and psychiatrists would conduct cognitive evaluations of people with MCI. Geriatricians typically see older patients, who have higher prevalence of early-stage AD and also later-stage AD and possibly manifest dementia. Neurologists

<table>
<thead>
<tr>
<th>Year</th>
<th>Neurologists</th>
<th>Geriatricians</th>
<th>Psychiatrists</th>
</tr>
</thead>
<tbody>
<tr>
<td>2022</td>
<td>694</td>
<td>882</td>
<td>4,119</td>
</tr>
<tr>
<td>2025</td>
<td>734</td>
<td>955</td>
<td>4,236</td>
</tr>
<tr>
<td>2030</td>
<td>787</td>
<td>1,024</td>
<td>4,809</td>
</tr>
<tr>
<td>2035</td>
<td>850</td>
<td>1,106</td>
<td>5,191</td>
</tr>
</tbody>
</table>

Sources: Historical data are from the Medical Board of Australia (2018). Published workforce projections for geriatricians and neurologists (AFHW, 2012) and psychiatrists (AFHW, 2016) were applied through 2025 and 2030, respectively. After 2025 (geriatricians and neurologists) and 2030 (psychiatrists), projections are based on the population growth rate from the ABS (2018e) Series B projections.

Note: The full psychiatrist workforce is displayed in this table. For this analysis, we assume 15 percent of all psychiatrists in Australia would be involved in diagnosing Alzheimer’s pathology in people with MCI.
Although current clinical trial protocols typically require an amyloid PET scan to identify amyloid deposits in trial participants, reimbursement and access to technology will dictate the use of diagnostic modalities in routine clinical practice. Increasing PET scanner capacity would require substantial capital investment in equipment, staff and building upgrades. There has been a marked increase in the number of PET scanners over the last several years, and there are currently 82 PET scanners in Australia, including a new scanner in the Northern Territory (AFHW, 2018; Fyles, 2018; Organisation for Economic Co-operation and Development [OECD], 2018c). Access to the radioactive tracer is another constraint; cyclotrons produce the radioactive tracers used in PET imaging and are generally located near PET facilities due to the short half-life of the tracers. Aside from a new PET scanner and cyclotron in the Northern Territory, most scanners and cyclotrons are based in the eastern and southern coasts of Australia, leaving individuals in the northern and western coasts without ready access to this technology.

There is not a standard way of diagnosing MCI due to AD in clinical practice; rather, a diagnosis is made only after careful and thorough clinical consultation. Although current clinical trial protocols typically require an amyloid PET scan to identify amyloid deposits in trial participants, reimbursement and access to technology will dictate the use of diagnostic modalities in routine clinical practice. Increasing PET scanner capacity would require substantial capital investment in equipment, staff and building upgrades. There has been a marked increase in the number of PET scanners over the last several years, and there are currently 82 PET scanners in Australia, including a new scanner in the Northern Territory (AFHW, 2018; Fyles, 2018; Organisation for Economic Co-operation and Development [OECD], 2018c). Access to the radioactive tracer is another constraint; cyclotrons produce the radioactive tracers used in PET imaging and are generally located near PET facilities due to the short half-life of the tracers. Aside from a new PET scanner and cyclotron in the Northern Territory, most scanners and cyclotrons are based in the eastern and southern coasts of Australia, leaving individuals in the northern and western coasts without ready access to this technology.

Measurement of liquid biomarkers in CSF is less costly than PET scans, and lumbar punctures to retrieve CSF could be performed in many facilities. However, only one laboratory, the National Association of Testing Authorities / International Laboratory Accreditation Cooperation, is currently accredited to conduct CSF diagnostic testing in Australia (National Dementia Diagnostics...
Laboratory, 2019). Although standardisation of thresholds and laboratory assays has been a challenge in the use of CSF biomarkers, there has been significant progress in validating CSF biomarkers as an alternative to PET (Bjerke and Engelborghs, 2018; Hansson et al., 2018). While using CSF could result in lower costs relative to PET, quality control of laboratory measurements would need to be established.

Given that current PET and laboratory capacity for biomarker testing to diagnose MCI due to AD is limited to research and specialised clinical settings in the absence of a DMT, investment in one or both methods would be required in order to expand diagnostic capacity for early-stage Alzheimer’s patients. Given the uncertainty over reimbursement levels and which method would be preferred in Australia in the future, we analyse scenarios with the following two sets of assumptions:

- **Base-case biomarker testing assumption:** 80 percent of biomarker testing performed using PET and 20 percent using CSF. This assumes that PET would be the primary method used. We assume that capacity growth in PET scanners and cyclotrons, including capital and personnel training, would be similar to recent growth rates in Australia (see Figure A-2 in the Appendix).

- **Alternative biomarker testing assumption:** 50 percent of biomarker testing performed using PET and 50 percent using CSF. This assumes that there would be investment in CSF testing, which could include establishing protocols for lumbar punctures and laboratory measurements, in addition to continued growth in PET capacity similar to recent growth rates. Although CSF would be less costly than PET, we assume that there would still be investment in PET, particularly in urban areas and for people who are unable to undergo a lumbar puncture due to anatomical reasons or contraindications, or who have an aversion to the procedure.

In this analysis, we do not model capacity constraints for CSF testing. In theory, physicians are capable of performing lumbar punctures, although some may need retraining and support to become more comfortable with the procedure. Currently, lumbar punctures are typically performed in hospital settings by physicians. However, lumbar punctures could be done with only a procedure room and a postprocedure recovery room if needed.

In contrast, we assume that access to PET scans would be limited by the capacity of scanners and cyclotrons required for amyloid PET scanning. Cyclotrons produce the radioactive tracers that bind to beta-amyloid and are typically located within approximately 320 kilometres of PET sites or within four hours transit time (Giamis, 2012) because the half-life of radiopharmaceutical containing the fluorine-18 (¹⁸F) isotope is relatively short. There are two registered entries for FDG tracers in Australia: 2-deoxy-2-¹⁸F fluoro-D-glucose and FDGen (fludeoxyglucose [¹⁸F] injection), though only the former lists neurological disorders as an indication (MSAC, 2015a). There are at least seven sites, including two commercial entities that produce radiolabelled-FDG (MSAC, 2015a). Figure 3 shows the locations of current PET scanners in Australia. Cyclotron coverage area is greatest across the eastern and southern coastal areas where most of the population resides, and tracers are generally flown from cyclotrons to sites with PET scanners but no cyclotron. However, there are still relatively few PET scanners to accommodate the expected number of people with MCI who could seek PET imaging, and only one scanner in the Northern Territory.

**Infusion Delivery**

We assume that a DMT would be delivered intravenously through a course of infusions, typically taking place in hospital outpatient clinics. Many infusion therapies currently in development would be delivered every few weeks for a period of 12 to 24 months. While other modalities and treatment durations may eventually be adopted in clinical practice, we model a hypothetical therapy that would be administered approximately every four weeks over the course of one year for a total of 14 infusions per patient. In an alternative scenario, we also assess when infusion delivery is not a barrier, modelling expanded capacity
Simulation Results Under Selected Capacity Scenarios

Base-Case Scenario

The base-case scenario reflects historical capacity trends projected forward and our assumptions related to specialist availability, biomarker testing performed and infusion capacity.

Figure 4 shows the wait lists under these assumptions. Initially, the main constraint is the availability of specialists to evaluate patients who screen positive for MCI. We estimate that the specialists’ capacity for visits would be 314,000 visits in 2022, or 65 percent of the projected 486,000 people with MCI who may seek evaluation by a specialist and who would need two visits in our model. The backlog of patients due to
barriers to diagnosis and treatment of people with MCI due to AD. The key assumptions for each of the three alternate scenarios are shown in Table 3.

In alternative scenario 1, we assume that use of CSF biomarker testing would be expanded such that 50 percent of biomarker testing is conducted using PET and 50 percent using CSF. Capacity for CSF testing could rapidly be expanded if planning, policies, regulations and reimbursements encourage the establishment of protocols training for lumbar punctures (e.g., in outpatient settings) as needed and developing standard laboratory procedures for the assays. If CSF can be used for 50 percent of the biomarker testing, we estimate that the waits for biomarker testing would be eliminated (Figure 6). Thus, the extent to which PET and CSF biomarker testing are used in Australia would affect patients’ access to the therapy. However, even in this scenario with investment in

limited specialist capacity would continue until 2025, at which point the backlog of patients would have been seen and only incident cases would require evaluation going forward. As the backlog of patients moves past the specialist wait lists, the waits for biomarker testing and then infusion treatments increase. The wait lists for biomarker testing are relatively short and are eliminated by 2026. The wait lists for infusion treatment extend longer and would continue until 2034.

Figure 5 illustrates average waiting times while patients are on the wait lists for diagnosis and treatment. With PET as the predominant biomarker test in the base case, we estimate that biomarker testing would initially result in average wait times of about two to three months in each year. The average waiting times for infusions are also relatively short, with a maximum of two months, but the waits would be sustained until 2034.

Alternative Scenarios
We now assess alternative scenarios that reflect concerted efforts to expand capacity and eliminate barriers to diagnosis and treatment of people with MCI due to AD. The key assumptions for each of the three alternate scenarios are shown in Table 3.
TABLE 3
Capacity Assumptions Across Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Specialists</th>
<th>Biomarker Testing</th>
<th>Infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
<td>Neurologists, geriatricians, and 15% of psychiatrists with 5% excess capacity for visits</td>
<td>80% PET with historical capacity projected forward, 20% CSF with no capacity constraint</td>
<td>Level estimated using a general health care capacity index, with current capacity projected forward</td>
</tr>
<tr>
<td><strong>Alternative 1:</strong></td>
<td>Investment in CSF</td>
<td>Same as base case</td>
<td>Same as base case</td>
</tr>
<tr>
<td></td>
<td>Same as base case</td>
<td>50% PET with historical capacity projected forward, 50% CSF with no capacity constraint</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative 2:</strong></td>
<td>Investment in CSF and infusion delivery (or nonintravenous administration)</td>
<td>Same as base case</td>
<td>No capacity constraint</td>
</tr>
<tr>
<td></td>
<td>Same as base case</td>
<td>50% PET with historical capacity projected forward, 50% CSF with no capacity constraint</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative 3:</strong></td>
<td>No capacity constraint</td>
<td>No capacity constraint</td>
<td>No capacity constraint</td>
</tr>
</tbody>
</table>

FIGURE 6
Projected Wait Lists and Times for Alzheimer’s Disease Diagnosis, Testing and Treatment Under Alternative Scenario 1

CSF, delays in access would still extend through 2033 due to waits for specialists and infusions.

In alternative scenario 2, the elimination of the infusion delivery constraint could reflect adequate capacity growth of infusion services or a nonintravenous therapy modality (i.e., subcutaneous or oral administration). Assuming infusions would be delivered approximately every 4 weeks over 52 weeks for a total of 14 doses, 2.1 million infusions would need to be administered to treat the approximately 147,000 Australians with MCI due to AD estimated to be eligible for treatment as of 2023. Eliminating the infusion constraint may be accomplished if building additional infusion centre capacity becomes a priority and/or if home infusions can be utilised widely.
Table 4 shows a comparison of the projected wait times in each scenario. In alternative scenario 3, we present the case in which all three capacity constraints and the associated wait times are eliminated. Key assumptions leading to this scenario include adequate training and task shifting such that health care providers could evaluate all patients seeking diagnosis, as well as adequate expansion of PET and/or CSF capacity and infusion services. Taking into account the extensive time and resources required to train a significant number of specialists as well as challenges in shifting tasks and preparing a broad workforce to evaluate MCI patients with diagnostic criteria currently used only in research and specialised clinical settings, this outcome is unlikely. However, this scenario demonstrates an upper bound of Alzheimer’s dementia cases that could be avoided if all capacity constraints were overcome. Whether these constraints could be fully addressed is subject to future policies, technological advances and drug development.

In addition to the alternative scenarios, we conducted sensitivity analysis around our capacity projections. In the Appendix, we present low and high projected capacity scenarios for specialist visits, PET scanners and infusions (Figures A.1–A.6). Under the high projected capacity scenario, wait lists would be eliminated by 2028. However, under the low projected capacity scenario, the wait times would extend beyond 2050 due to the limited dementia specialist visits to accommodate patient demand.

Alzheimer’s Dementia Cases Avoided in the Base and Alternative Scenarios

Figure 7 shows the cumulative incident Alzheimer’s dementia cases between 2023 and 2033 in the base-case and alternative scenarios. In the base-case scenario with historical capacity trends projected forward, we estimate that 344,000 people with MCI due to AD would not develop to Alzheimer’s dementia due to treatment between 2023 and 2033. These results are contingent on the assumed treatment effectiveness of a 50 percent relative risk reduction in the progression of MCI due to AD to Alzheimer’s dementia after treatment. Progression to Alzheimer’s dementia occurs at a higher rate for people who are on wait lists during this period.

The alternative scenarios depict expanded capacity that reduce wait lists. Relative to the base-case scenario, alternative scenario 1 (investment in CSF) would lead to 5,000 additional avoided dementia cases and alternative scenario 2 (investment in CSF and infusion delivery (or nonintravenous administration)) would lead to an additional 19,000 avoided cases. In alternative scenario 3, in which all capacity constraints are alleviated, we estimate an additional 54,000 cases of dementia would be avoided relative to the base-case scenario. In total, we estimate that 398,000 cases of Alzheimer’s dementia cases could be avoided if a treatment was available and all constraints were addressed between 2023 and 2033.

See Figure A.9 for the cumulative Alzheimer’s dementia cases avoided under the sensitivity
DMT becomes available in 2023. People with MCI due to AD who are not diagnosed and treated in a timely fashion would be at higher risk of progressing to Alzheimer's dementia when their dementia could potentially be avoided. If a treatment becomes available in 2023 and assuming the capacity of the health system follows historical trends, Australians could wait over ten months to undergo diagnosis and biomarker testing in the initial year, and wait lists could extend through 2033. If a hypothetical therapy reduces relative risk of progression by 50 percent and all of the capacity constraints are overcome, 398,000 Alzheimer's dementia cases could be avoided between 2023 and 2033.

As in other countries, there are several different policy and planning solutions that may help address these capacity constraints (Liu et al., 2017; Hlávka, Mattke and Liu, 2018; Liu et al., 2019).

Discussion

A DMT would be a breakthrough innovation to reduce the progression of early-stage AD to Alzheimer's dementia. Alzheimer's dementia exacts a substantial burden on patient and caregiver health, as well as significant costs to health systems and individuals as the estimated total direct costs of dementia were $8.8 billion AUD in 2016 (Brown, Hansnata, and La, 2017). Although the future availability of an Alzheimer's DMT is uncertain, particularly in light of recent discontinued trials, there are currently still several therapies under investigation in clinical trials. If a therapy becomes available, the large number of people who could benefit from diagnosis and treatment would present health system challenges that would require timely attention to address.

The objective of this analysis is to examine the magnitude of potential capacity challenges if a DMT becomes available in 2023. People with MCI due to AD who are not diagnosed and treated in a timely fashion would be at higher risk of progressing to Alzheimer's dementia when their dementia could potentially be avoided. If a treatment becomes available in 2023 and assuming the capacity of the health system follows historical trends, Australians could wait over ten months to undergo diagnosis and biomarker testing in the initial year, and wait lists could extend through 2033. If a hypothetical therapy reduces relative risk of progression by 50 percent and all of the capacity constraints are overcome, 398,000 Alzheimer's dementia cases could be avoided between 2023 and 2033.

As in other countries, there are several different policy and planning solutions that may help address these capacity constraints (Liu et al., 2017; Hlávka, Mattke and Liu, 2018; Liu et al., 2019).

The initial bottleneck in the clinical pathway would be specialist visits to evaluate and diagnose early stage Alzheimer's dementia. In Australia, access to specialists and some technologies would likely be more problematic in rural and remote areas. One consideration is that a greater share of the population aged 50 or older lives outside of major cities.
The availability of inexpensive biomarker testing could reduce the need for PET and CSF biomarkers to confirm diagnosis of MCI due to AD as well as the number of cases needing referral to specialists. Our alternative scenarios illustrate the possibility of reducing waiting times, which could be due to capacity expansion due to infrastructure building or to advances in technology. Alternative scenario 1 results in no constraints on biomarker testing that could be due to investment in CSF biomarkers or the emergence of other diagnostic technology. Alternative scenario 3 reflects a case in which there are no capacity constraints. Blood biomarker tests that could be used for routine screening and diagnosis could help achieve alternative scenario 3 by alleviating both the burden on specialists (e.g., by reducing false positives through increased or routine screening or biomarker tests ordered by nonspecialists) and on PET equipment.

Based on our analyses, biomarker testing is less of a constraint in Australia than in other countries; this may be due to the age of the population and a relatively well-established PET scanner infrastructure. For example, in 2017, 33 percent of Australians were aged 50 or older, compared with 37 percent of Canadians (ABS, 2019a; Statistics Canada, 2018). In 2015, Australia had 2.64 PET scanners per million persons, while the United States had 5.12, France had 1.95 and Canada had 1.31 scanners per million persons (OECD, 2018c). While there are still some expected waits, actual capacity and use will depend on factors such as Medicare and other payer reimbursement policies. Furthermore, access to PET scanners varies across Australia, with most of the scanners available in major cities along the southern and eastern coasts.

Last, infusion capacity will also depend on how quickly capacity could be expanded as well as Medicare reimbursement levels. Such expansion could follow the trends observed in infusion expansion for oncology and multiple sclerosis therapies, including expanded centres or home-based treatments (chemo@home, n.d.; South Australia Health, 2014).
**Conclusions**

A DMT for AD would be a breakthrough to reduce the burden on people with Alzheimer’s, their caregivers and health care systems. Although there is uncertainty in the future of therapies that are in development, it may be useful for policymakers, payers and providers to consider potential challenges in delivering such a therapy to the large population of people with early-stage AD.

We have estimated the magnitude of potential capacity challenges under a number of assumptions if a hypothetical Alzheimer’s DMT became available in 2023. The goal of our analysis is not to provide precise projections, but to facilitate discussions among stakeholders that could help address infrastructure challenges. As we have found in analyses of other countries, delays in access to a therapy in Australia could result in people progressing from early stages of cognitive impairment to full-blown dementia due to capacity limitations. Our analysis suggests that not expanding capacity beyond historical trends could result in approximately 54,000 Australians progressing from MCI due to AD to Alzheimer’s dementia while waiting for diagnosis and treatment between 2023 and 2033. As the development of Alzheimer’s therapies continues, our hope is that discussions on ways to expand capacity and increase awareness also continue.

**Notes**

1. Clinical trials of AD treatments include DMTs and symptom-reducing agents. In 2018, 63 percent of clinical trials were investigating DMTs (either small molecule or immunotherapy) (Cummins et al., 2018).

2. Other cognitive assessments may be used (Cognitive Decline Partnership Centre, 2015), such as the Standardised MMSE (Molloy, 1991) and the Montreal Cognitive Assessment (MoCA) (Ciesielka et al., 2016).

3. Cognitive and functional assessments may involve the Alzheimer’s Disease Assessment Scale Cognitive subscale (ADAS-Cog) (Dementia Australia, 2006; Skinner et al., 2012; Cognitive Decline Partnership Centre, 2015), the Neuropsychiatry Unit Cognitive Screening Tool (NUCOG) (Walterfang, Siu and Velakoulis, 2006; Walterfang and Velakoulis, 2013) or the Clinicians Interview Based Impression of Severity (CIBIS) (Knopman et al., 1994).

4. We assume that a diagnosis of MCI due to AD would need to be confirmed by a specialist for two reasons. First, biomarker tests would likely be ordered and interpreted by a specialist. Second, there is precedent based on symptom-management treatments for Alzheimer’s dementia that require a diagnosis confirmed by a specialist in order to receive Medicare reimbursement (Dementia Australia, 2019).

5. Our U.S. and European analyses, published in 2017 and 2018, assumed that a therapy would become available in 2020. Our Canadian analysis, published in 2019, assumed a therapy would become available in 2021. In March 2019, the leading phase 3 trial for an Alzheimer’s DMT scheduled for trial completion in 2020 was discontinued (Biogen, 2019). As of April 2019, the leading phase 3 trial has a primary completion date in 2022 (U.S. National Library of Medicine, 2019a). Thus, for this current analysis, we selected 2023 as the first year that a DMT would be available.

6. Our U.S. and European analyses assumed that the age eligibility would be 55 and older. For the Canadian analysis and this analysis, we assume eligibility would be ages 50 and older as the later stage clinical trials tend to target earlier age groups and some trials targeting later age groups have been terminated (e.g., U.S. National Library of Medicine, 2019c). The inclusion of ages 50–54 in our analysis has relatively little impact on the results because MCI prevalence is lower among younger ages.

7. There is considerable variation in how MCI has been defined over time and across studies. The meta-analysis conducted by Petersen et al. (2018) includes some studies using narrower definitions to those using broader definitions as well as studies from different countries. Australian studies have reported similar MCI prevalence (Anstey et al., 2013; Brodaty et al., 2017); however, there is variation. By relying on the prevalence estimates by age from the meta-analysis, the implicit assumption is that variation in the underlying prevalence of MCI is greater across studies (and definitions) than across countries.

8. This assumption differs from our prior analysis in the United States, where a PET scan is the only currently FDA-approved modality for clinical use. In our analyses of European countries, we assumed that 90 percent of biomarker testing would be performed by CSF biomarker testing and only 10 percent would be PET imaging for patients with contraindications to lumbar puncture. The 80 percent PET and 20 percent CSF screening assumption is consistent with our analysis in Canada.

9. In alternative scenarios, we assume that 50 percent PET and 50 percent CSF would be used. For more details about this alternative assumption, see the next section.

10. Currently, these scanners are primarily used to diagnose and evaluate oncology indications.

11. Approximately 71 percent of the Australian population resides in major cities (ABS, 2016; 2018b), defined as populations of 100,000 or more, where PET scanners are more likely to be available.

12. Fluorodeoxyglucose (18F) has a half-life of 110 minutes (International Atomic Energy Agency [IAEA], 2012).

13. To assess the validity of our index approach, we examined data from the government’s Pharmaceutical Benefits Scheme and found similar trends.


Heart of Australia, homepage. As of April 29, 2019: https://www.heartofaustralia.com


IAEA—See International Atomic Energy Agency.


MSAC—See Medical Service Advisory Committee.


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About This Report

This report illustrates the magnitude of health care system infrastructure challenges in the diagnosis and treatment of early-stage Alzheimer’s disease with a hypothetical disease-modifying therapy in Australia.

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