
Assessing the Preparedness of the Taiwanese Healthcare System Infrastructure for an Alzheimer's Treatment

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Key Findings

- » Potential disease-modifying therapies that are currently in clinical trials or under regulatory review could prevent or delay the progression of early-stage Alzheimer's disease to manifest dementia.
- » The complexity of identifying and evaluating treatment-eligible patients combined with the high prevalence of the disease might overwhelm the capacity of healthcare systems without advance planning and preparation.
- » We use a simulation model to assess the preparedness of Taiwan's healthcare system infrastructure to diagnose and treat people with mild cognitive impairment due to Alzheimer's disease if a future therapy becomes available.
- » If a therapy becomes available in 2022, we estimate that average annual wait times for diagnosis and treatment in Taiwan could peak at 24 months and persist beyond 2050 in the absence of practices to leverage scarce dementia specialists' capacity more efficiently and increase capacity for biomarker testing and treatment delivery.
- » Depending on policies, we estimate that 118,000 to 357,000 Taiwanese could progress from mild cognitive impairment due to Alzheimer's disease to Alzheimer's dementia while on wait lists.
- » Although efforts have been made to strengthen the health system's capacity for dementia care, such as building up community-based and integrated care models, next steps to ensure the delivery of disease-modifying therapy must address the pressing challenges of specialist capacity and the feasibility of introducing new diagnostic and screening technologies.

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Introduction

Alzheimer's disease is a chronic neurodegenerative disorder that leads to cognitive and functional decline, dementia, and premature death. Like many of its Asian neighbors, Taiwan's rapidly aging population is particularly exposed to the growing burden of this disease on patients and their caregivers, as well as health care and long-term care resources. Approximately 270,000 Taiwanese were estimated to have dementia as of 2017, with Alzheimer's being the most frequent cause and the Taiwanese government further estimates that the number of people living with dementia will more than triple to 850,000 by 2061 (Ministry of Health and Welfare, 2018) The Taiwan Alzheimer's Disease Association reported that the economic burden of dementia on Taiwan was an estimated US\$ 6,990 million on dementia in 2015, with US\$ 412 million spent on medical costs, US\$ 3,326 million spent on non-medical costs, and US\$ 3,252 million in lost productivity of family caregivers (Alzheimer's Disease International, 2014).

On August 7, 2020, Biogen and Eisai announced that the U.S. Food and Drug Administration accepted aducanumab's Biologics License Application with a Prescription Drug User Fee Act (PDUFA) action date on June 7, 2021, raising the possibility of the first treatment to slow or halt the progression to dementia becoming available as early as this year. **Table 1** summarizes additional Alzheimer's disease-modifying therapies currently in Phase 2 and Phase 3 clinical trials. These therapies target beta-amyloid and tau, the hallmark proteins that accumulate in the brain and are assumed to cause Alzheimer's disease, as well as other targets.

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TABLE 1. ALZHEIMER'S DISEASE-MODIFYING THERAPY CANDIDATES IN PHASE 2 AND PHASE 3 CLINICAL TRIALS, AS OF FEBRUARY 2021

CANDIDATE	SPONSOR	CLINICAL TRIAL PHASE	EXPECTED PRIMARY COMPLETION DATE	NATIONAL CLINICAL TRIAL IDENTIFIER
Anti-beta-amyloid antibodies				
Gantenerumab	Hoffman-La Roche	Phase 3	September 2022	NCT03443973, NCT03444870
BAN2401	Eisai/Biogen	Phase 3	June 2022	NCT03887455
Donanemab#	Eli Lilly	Phase 2	January 2021	NCT03367403
Anti-tau antibodies				
BIB092	Biogen	Phase 2	March 2024	NCT03352557
RO7105705	Genentech	Phase 2	July 2020	NCT03289143
LY3303560	Eli Lilly	Phase 2	August 2021	NCT03518073
TRx0237	TauRx Therapeutics	Phase 3	June 2022	NCT03446001
Vaccines				
AADvac1 (anti-tau)	Axon Neuroscience	Phase 2	June 2019	NCT02579252
Other Mechanisms				
PQ912	Vivoryon Therapeutics	Phase 2	December-2022	NCT03919162, NCT04498650
PTI-125	Cassava Science	Phase 2	March 2022	NCT04388254, NCT04079803

SOURCE: : Author's review of ClinicalTrials.gov website as of February 3, 2021.

*Phase 2 has been completed with positive results presented at the AAT-Alzheimer's disease/PD 2020 conference.

Eli Lilly announced positive Phase 2 results on January 11, 2021

NOTES: Anti-beta-amyloid and anti-tau antibodies are monoclonal antibodies that are typically administered by intravenous infusions or subcutaneous injections. Alzheimer's vaccines are injections of antigens or antibodies with the aim of triggering antibody responses. Other mechanisms include glutaminyl cyclase inhibitors and a receptor for advanced glycation end-products (RAGE) inhibitor where glutaminyl cyclase enzymes and RAGE are found at unusually high levels of the brain in Alzheimer's patients. Aducanumab is omitted from the table as it has completed its clinical trial program.

However, making such a treatment available creates an unprecedented challenge for healthcare systems because of the combination of a complex evaluation process to determine treatment eligibility and the prevalence of the disease. As many as 700,000 Taiwanese aged 65 and over may live with Mild Cognitive Impairment (MCI), which is the stage at which the disease ought to be treated, today (Yang, 2016) and many may have not been evaluated and diagnosed because of the limited symptoms and treatment options. In previous studies, we have analyzed the preparedness of the healthcare systems in the United States, Australia, Canada, Japan, South Korea and six European countries (Germany, France, Italy, Spain, Sweden, and the United Kingdom), and predicted substantial obstacles to access in all of them, resulting

in wait times and potentially avoidable disease progression (Hlávka, Mattke, & Liu, 2018; Liu et al., 2019; Liu, Hlávka, Hillestad, & Mattke, 2017; Hlávka, Yoong, Wang, & Goto, 2019).

This report presents an analysis of the preparedness of the Taiwanese healthcare system to treat people with early-stage Alzheimer's disease (MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease) when a disease-modifying therapy becomes available. Following our earlier studies, we draw on publicly available data and expert insights to refine a simulation model that quantifies the capacity of the healthcare system to diagnose and treat people with early-stage Alzheimer's disease. We present projections for several scenarios under high-level assumptions; none of the scenarios are meant to provide precise predictions of the future given uncertainties related to the profile of a new therapy, patient uptake, and future capacity growth. Our goal is to demonstrate the magnitude of the potential capacity challenges in order to inform strategies for expanding capacity.

The following sections present our conceptual framework, simulation model, and projections. We discuss the design of the model and show historical and projected capacity trends that affect case finding, diagnosis and treatment. We show the impact of capacity constraints on wait lists, waiting times, and the number of people progressing from MCI due to Alzheimer's disease to full-blown dementia due to Alzheimer's disease. It is our hope that the analysis will facilitate dialogue among stakeholders and help ensure timely access in the era when a disease-modifying therapy becomes available.

Patient Journey and Simulation Model

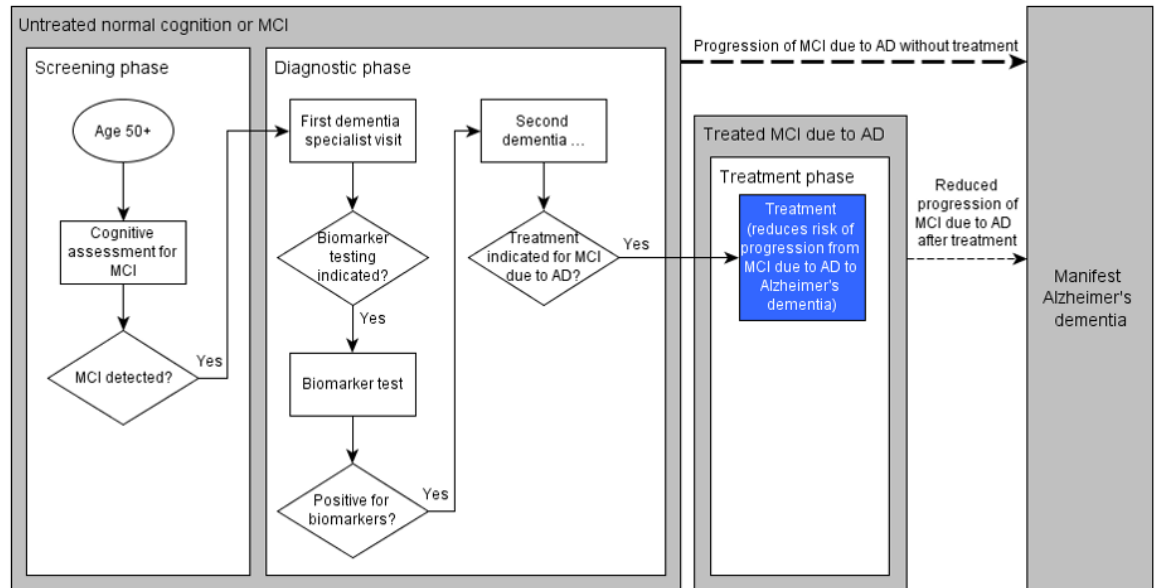
PATIENT JOURNEY

We used a stylized patient journey of the path to a disease-modifying therapy as the basis for our simulation model (Figure 1). We assume that patients will enter this pathway at the stage of mild cognitive impairment, either because they sought medical advice for a memory complaint or because screening suggested early cognitive decline, our Screening Phase. They will then undergo evaluation for the etiology of the cognitive decline, our Diagnostic Phase, and finally be treated if shown to be eligible, our Treatment Phase. The disease continues to progress while patients are passing through the steps of this journey.

In this patient journey, older adults would undergo cognitive assessment with a short instrument such as the Folstein Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Modified Mini-Mental State Examination (Tombaugh, McDowell, Kristjansson, & Hubley, 1996), or the Montreal Cognitive Assessment (Ciesielska et al., 2016) and an assessment of functional deficits in primary care settings. Next, people who exhibit MCI, but no manifest dementia, would be further evaluated to ensure no other treatable causes exist, such as depression, substance use or hypothyroidism.

Having ruled out other treatable or reversible etiologies for MCI, patients would be referred to a dementia specialist for further evaluation, including additional cognitive and functional assessments, and possible referral to testing for the presence of amyloid and/or tau biomarkers to determine if the MCI is likely to be due to Alzheimer's disease (Diagnostic Phase). After a positive biomarker test, a dementia specialist would determine whether treatment was indicated. If indicated, patients could be treated with a therapy that would reduce the risk of progression from MCI to dementia due to Alzheimer's disease (Treatment Phase). For people with untreated MCI due to Alzheimer's disease, the disease would continue to progress. Compared to treated MCI patients, untreated MCI patients have a higher risk of progressing to a later stage of the disease with manifest dementia, at which point the assumed treatment would no longer be effective.

FIGURE 1. STYLIZED PATIENT JOURNEY



SIMULATION MODEL

Our simulation model is a Markov model that simulates transitions between disease states and a systems dynamic model that simulates healthcare system capacity constraints within the MCI state, as used in our previous analyses. In this model, individuals move through the disease states—from no cognitive impairment (i.e., no MCI and no dementia due to Alzheimer’s disease) to MCI to dementia due to Alzheimer’s disease—according to transition probabilities derived from the literature (see Appendix Table A-1). Within the MCI state, people are diagnosed (for MCI due to Alzheimer’s disease) and treated based on a system dynamics model with outflows constrained by infrastructure capacity. We model three capacity constraints: dementia specialists, biomarker testing facilities, and treatment delivery facilities. For the two dementia specialist visits in the diagnostic phase of our framework, the model is optimized 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.

We use Taiwanese data on the population, disease prevalence, mortality, and historical workforce and infrastructure in the model. See Appendix Table A-1 for the parameter values and their respective sources.

MODEL ASSUMPTIONS

As no actual disease-modifying therapy for Alzheimer’s disease exists today, we are using expert-guided assumptions to model a hypothetical therapy in the future. For this analysis of the Taiwanese health care system, we start with the same assumptions for treatment effectiveness, uptake, and disease transitions as in our prior studies, but modify them to the Taiwanese context as noted.

To adapt assumptions for Taiwan, we consulted with several experts familiar with clinical practice, care delivery, patient needs, and the policy environment in Taiwan. The experts were identified by a targeted search of the literature and websites of academic institutions and by snowball sampling in which interviewees recommended other experts for our recruitment process. We selected interviewees based on their clinical specialty, expertise, and contributions to the field. The interview questions were related to

the following domains: clinical pathway, detection, and diagnosis, treatment and monitoring, data, and policies and practices. These assumptions include the types of specialists involved in the diagnosis of MCI due to Alzheimer's disease, and the relative role of PET and CSF to measure biomarkers.

The key assumptions in our analysis are as follows:

- » A disease-modifying therapy for patients with MCI due to Alzheimer's disease becomes available in 2022.¹ Our analyses are based upon an anti-beta-amyloid monoclonal antibody therapy. We further assume that the therapy would be delivered by intravenous administration.
- » We assume that individuals age 50 and older are eligible for annual cognitive screening, unless they have been diagnosed with MCI or manifest dementia. We modeled the population 50 years and older because most later-stage clinical trials include ages as low as 50 (e.g., a Phase 3 trial of BAN2401, NCT03887455).² Screening starts in 2021 as patients and providers anticipate the approval of the therapy. Annual screenings may be conducted by general practitioners. We assume their capacity to conduct cognitive screening and functional assessments would be unconstrained. We assume that 50 percent of individuals age 50 and older would consent to screening each year. Of those who screen positive for MCI or are known to have MCI, we assume 50 percent would seek further evaluation from a dementia specialist. These proportions are based upon expert input collected in the original development of the model.
- » Further evaluation would be conducted by a dementia specialist. Based on expert input we assume that this would include 90 percent of hospital-based neurologists and 60 percent of hospital-based psychiatrists.
- » Individuals would be referred to testing for biomarkers if the evaluation confirmed MCI and did not find an alternative explanation for MCI (e.g., severe depression) or a reason to not pursue treatment (e.g., presence of another life-limiting disease). Of those with confirmed MCI that is possibly due to Alzheimer's disease, we assume that 90 percent of patients would seek biomarker testing, based on expert input in the original development of the model.
- » In Taiwan, we assume that biomarker testing is likely to be performed with a Positron Emission Tomography (PET) scan for amyloid deposits in the brain or with a cerebrospinal fluid test (CSF).³ Based on input from Taiwanese experts regarding the potential availability of PET scanners and patient preferences, our assumption is that there is a strong preference for tests to be performed using PET rather than performed using CSF, and hence 90 percent of tests are conducted by PET. We assume that 45 percent of people with MCI have clinically relevant biomarker levels that warrant anti-beta-amyloid monoclonal antibody therapy (Ong et al., 2015; Doraiswamy et al., 2014).
- » If an individual's amyloid level is clinically relevant, she or he returns to a dementia specialist who determines whether treatment is indicated. If there are no contraindications and the individual consents, the individual is referred for treatment. Of people with MCI who test above a certain

¹ Our United States and European analyses, which were published in 2017 and 2018, assumed that a therapy would become available in 2020.

² Our United States and European analyses assumed that the age eligibility would be 55 and older. For this analysis, similar to our analysis of Canada, Japan and Korea, we lowered the age range to 50 as current clinical trials tend to start enrolling at that age (e.g., Phase 3 trial of BAN2401, NCT03887455) and some trials targeting later age groups have been terminated.

³ We applied the same assumption in our prior analysis in Korea, but a different assumption 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.

amyloid level, we assume that 80 percent would have no contraindications for treatment (based on expert input).

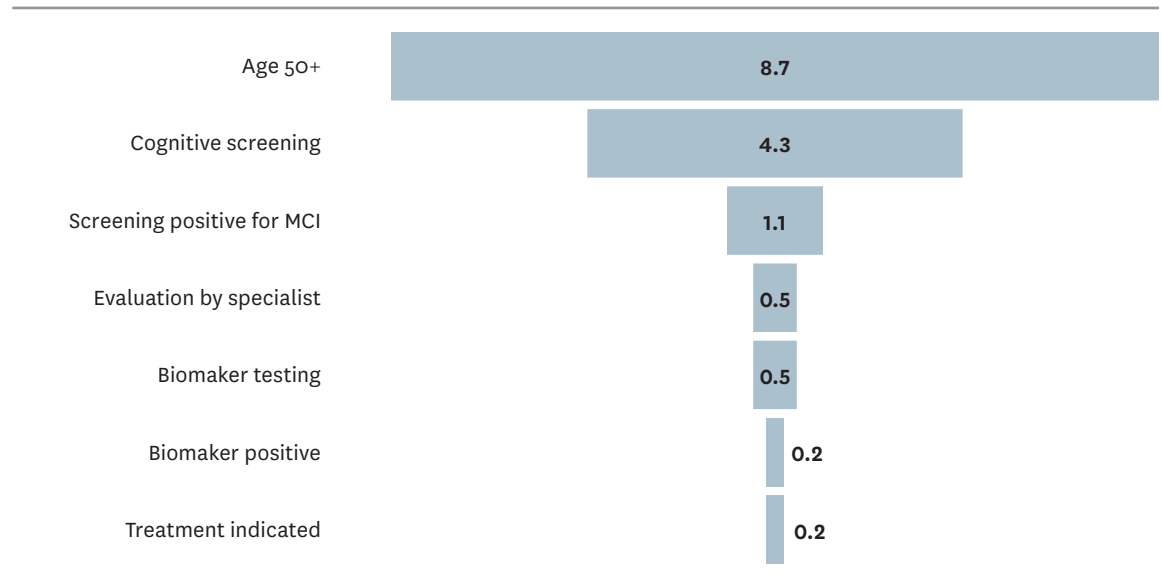
- » We assume that the therapy would be delivered by intravenous infusion every four weeks for 18 months, following the protocol for aducanumab. We further assume that treatment reduces the relative risk of progression from MCI due to Alzheimer’s disease to dementia due to Alzheimer’s disease by 30 percent after treatment.

Current Patient Demand and Capacity Estimates

PATIENT DEMAND

Figure 2 shows the expected patient demand in the screening and diagnostic phases of the clinical pathway. Of the 8.7 million Taiwanese in the population aged 50+ overall, we estimate 1.1 million Taiwanese would either be known to have or screen positive for MCI in 2022. Of those, based on the assumptions outlined above, 0.54 million patients would seek evaluation by a specialist, 0.49 million would undergo biomarker testing, 0.22 million would test positive for amyloid pathology and 0.18 million patients would be determined eligible for treatment.

FIGURE 2. EXPECTED PATIENT DEMAND IN SCREENING AND DIAGNOSTIC PHASES IN 2022 (MILLIONS)



SPECIALIST WORKFORCE

Based on expert input, we expect that two categories of specialist physicians will be involved in Alzheimer’s diagnosis in Taiwan: neurologists and psychiatrists. We use specialist data from the Taiwanese Medical Association 2020 for the number of practicing neurologists and psychiatrists. We project future workforce pool using historical trends of the physician workforce and use population forecasts from the Population Projections for the R.O.C. (Taiwan): 2018-2065 (National Development Council of Taiwan, 2020). Based on expert input, we assume that 90 percent of hospital-based neurologists and 60 percent of hospital-based psychiatrists would be able to evaluate patients with suspected Alzheimer’s disease (Table 2). Of note, geriatrics is a new specialty in Taiwan with only a few physicians trained in it.

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TABLE 2. PROJECTED WORKFORCE OF SPECIALISTS THAT MAY DIAGNOSE EARLY ALZHEIMER'S DISEASE

YEAR	NEUROLOGISTS	PSYCHIATRISTS
2020	876	506
2030	1,149	634
2040	1,473	761
2050	1,798	889

SOURCE: Taiwanese Medical Association 2019 (https://www.tma.tw/stats/index_NYearInfo.asp?/2019.html).

NOTE: SOURCE: Taiwanese Medical Association 2019 (https://www.tma.tw/stats/index_NYearInfo.asp?/2019.html)

NOTE: We assume that 90 percent of hospital-based neurologists and 60 percent of hospital-based psychiatrists would

be able to evaluate patients with suspected Alzheimer's disease in Taiwan.

DIAGNOSTIC TECHNOLOGY

A diagnosis of Alzheimer's disease requires confirmation of its biologic hallmarks based on biomarkers (beta-amyloid and/or tau) (Portet et al., 2006), which can be obtained with two diagnostic technologies: PET scans with tracers that bind to beta-amyloid in the brain, and CSF measurement of beta-amyloid and tau levels (Moore et al., 2014; Okamura et al., 2018). Currently, while available, both technologies are predominantly used for research and clinical trials in Taiwan and PET scans are not reimbursed by the National Health Insurance scheme (NHI), leading to extremely low utilization. NHI records for patients diagnosed with dementia show that CT scans were the most commonly utilized with MRI scans being the second most common procedure, while fewer than 1 percent of patients had ever received a PET or SPECT scan (Hung et al., 2016).

In our model, we assume that 90 percent of biomarker test-eligible patients will undergo a PET scan, as experts advised us that Taiwanese are highly reluctant to undergo lumbar punctures. We assume that the remaining 10 percent of patients will undergo a cerebrospinal fluid (CSF) test that reports both amyloid beta and tau biomarker levels. Our model does not apply any constraint on CSF tests, while capacity is constrained for PET scans (given limited excess capacity and relatively slow increase in the number of facilities). There are currently 56 PET scanners (Statistics of Medical Care Institution's Status & Hospital Utilization 2019) and a reported 12 cyclotrons in Taiwan (IAEA, 2020)

INFUSION DELIVERY

Our base case assumption is that a disease-modifying therapy would be delivered intravenously, since many Alzheimer's disease treatments in clinical trials are delivered as intravenous drugs. As such therapies are delivered every few weeks for a period of 12 to 24 months, we model a therapy that would be administered every four weeks for a total of 19 infusions per patient over the course of 18 months. We recognize that other modalities and treatment durations may eventually be adopted in clinical practice. We explore an alternative scenario in which infusion delivery is not a barrier, as some candidate treatments are delivered subcutaneously or orally.

Given the lack of publicly available infusion data in Taiwan, we use an index approach consistent with our prior European, Canadian, Japanese, and Korean analyses. Our estimates of the capacity to deliver

infusions are based on the relative capacity of the Taiwanese health care system based on four indicators: hospital beds, active nurses, magnetic resonance imaging (MRI) scanners, and PET scanners (see Appendix Table A-2). We use Organisation for Economic Co-operation and Development (OECD) data to develop a capacity index for Taiwan relative to the United States (OECD, 2018), which we use to scale the per-capita infusion capacity projected for the United States and assume the same relative rate of growth in infusion capacity as in the United States. As in our prior analyses, we assume that existing infusion clinics can expand capacity by 10 percent to accommodate new patients, while 80 percent of the capacity in new infusion clinics would be dedicated to administering the Alzheimer’s therapy.

Simulation Results under Selected Capacity Scenarios

BASE CASE SCENARIO

Figure 3 shows the projected wait times for receipt of a disease-modifying therapy, assuming such a treatment becomes available in 2022. We estimate average peak wait times of approximately two years initially, mostly because of capacity limitation for specialist visits. Over time, however, as more people will have been seen by specialists, this constraint is no longer a binding issue. Capacity for biomarker testing will become the main constraint, resulting in wait times that remain close to 10 months even in 2050.

FIGURE 3: PROJECTED WAIT TIMES FOR ALZHEIMER’S DISEASE DIAGNOSIS, TESTING, AND TREATMENT

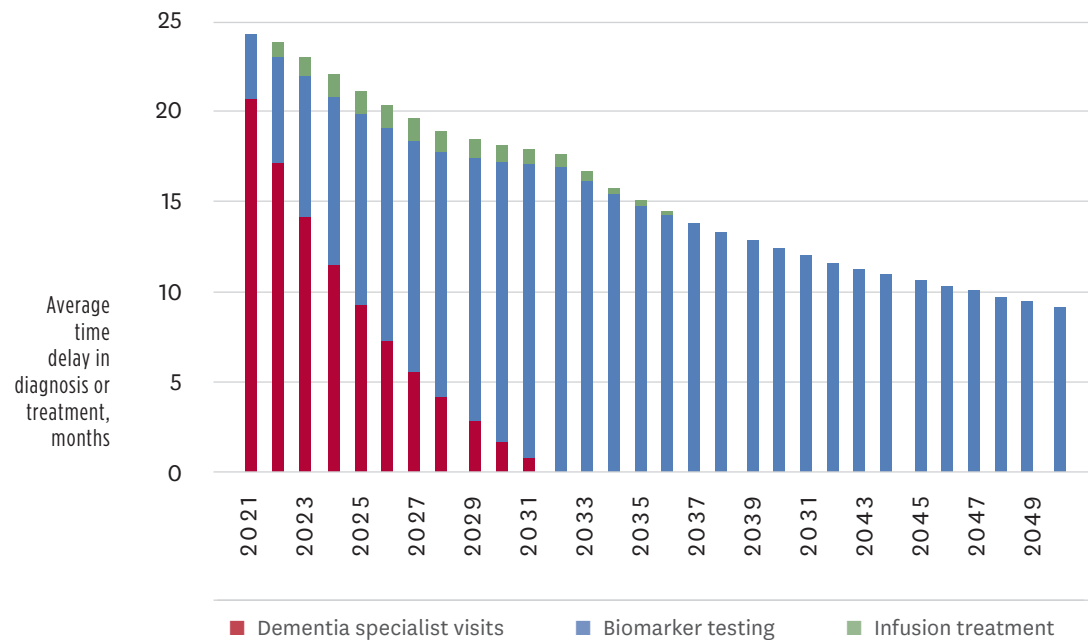
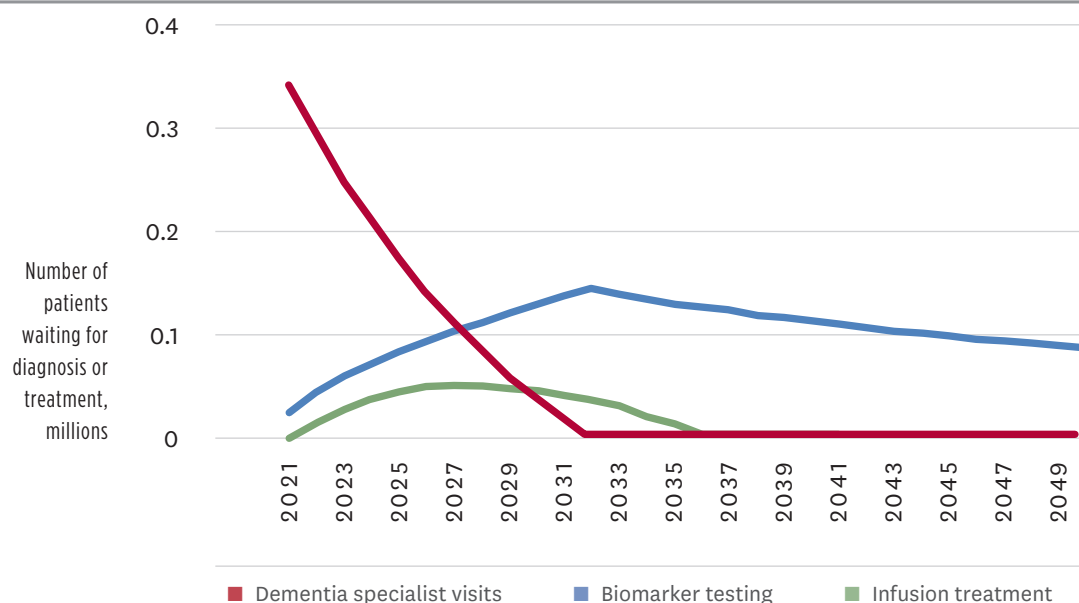


Figure 4 illustrates the effects of the capacity constraints on the number of patients in the respective queues. Initially, over 300,000 Taiwanese patients are estimated to wait for their specialist appointment, but that number persistently declines as the waitlist clears by 2032. However, the number of patients waiting for biomarker testing steadily increases and remains at close to 100,000 even up to 2050.

FIGURE 4: PROJECTED WAIT LISTS FOR ALZHEIMER'S DISEASE DIAGNOSIS, TESTING, AND TREATMENT



ALTERNATIVE SCENARIOS

We assess alternative scenarios that reflect efforts to expand capacity in order to eliminate some of the barriers to diagnosis and treatment of people with MCI due to Alzheimer’s disease. The assumptions for three alternative scenarios are shown in **Table 3**.

TABLE 3. CAPACITY ASSUMPTIONS ACROSS SCENARIOS

SCENARIO	SPECIALISTS	BIOMARKER TESTING	INFUSIONS
Base case	90% of hospital-based neurologists, 60% of hospital-based psychiatrists	90% PET with historical capacity projected forward, 10% CSF with no capacity constraint	Level estimated using a general health care capacity index, with current capacity projected forward
Alternative 1: Increased CSF testing	Same as base case	80% PET with historical capacity projected forward, 20% CSF with no capacity constraint	Same as base case
Alternative 2: Increased CSF testing and blood-based biomarker testing	Same as base case	20% CSF with blood-based biomarkers (equivalent of increasing specialist capacity by 60% and PET scanners by 40%)	Same as base case
Alternative 3: Increased CSF testing and blood-based biomarker testing with expanded infusion capacity	Same as base case	20% CSF with blood-based biomarkers (equivalent of increasing specialist capacity by 60% and PET scanners by 40%)	No capacity constraint

Given the long training times for dementia specialists and our experts' input, net increases in specialist capacity or installation of large numbers of new PET scanners seem unlikely.

Alternatively, shifting towards CSF testing may help relieve capacity constraints, or better triaging of patients earlier in the diagnostic pathway could reduce demand for confirmatory tests. Currently available cognitive tests that are suitable for primary care settings have reasonable sensitivity to detect MCI, but limited specificity for MCI due to Alzheimer's disease. In a recent review (Lam, Hlávka, & Mattke, 2019), we concluded that there was limited potential to improve specificity of simple cognitive tests, because the patterns of early cognitive decline due to different etiologies are not distinct enough to be differentiated with such tools. However, blood-based tests for the biomarkers of Alzheimer's disease might allow identifying patients with cognitive decline due to other etiologies at the primary care level. We estimated that a using an automated blood test for amyloid- β with published performance (Palmqvist et al., 2019) in patients with suspected MCI could eliminate about two-thirds of subsequent specialist visits, and thus reduce initial wait times. (S. Mattke, Cho, Bittner, Hlavka, & Hanson, 2020)

To assess these options, in alternative scenario 1, we therefore model a scenario based on increasing the use of CSF testing rather than PET scans, and in alternative scenario 2, we further introduce the use of a blood-based biomarker (BBBM) test for Alzheimer's disease biomarkers that would allow for identifying patients with MCI due to other causes earlier in the process and thus reducing specialist referrals. We find that introducing the CSF alone reduces wait times significantly in the longer run, although these continue to persist up to 2050. Introducing a BBBM in addition, however, eliminates biomarker testing wait times as early as 2028, resulting in wait times declining to under 3 months after 2030 and finally to zero after 2041.

Finally, in alternative scenario 3, we add to the introduction of a BBBM the elimination of the infusion delivery constraint. This could reflect adequate capacity growth of infusion services, or a therapy that does not require intravenous delivery (i.e., could be administered subcutaneously or orally). Eliminating the infusion constraint may be possible if increasing infusion center capacity becomes a priority, and/or if home or community-based infusions are utilized more widely. In this scenario, wait times could be eliminated altogether before 2030. **Table 4** illustrates projected wait times under the base case and alternative scenarios.

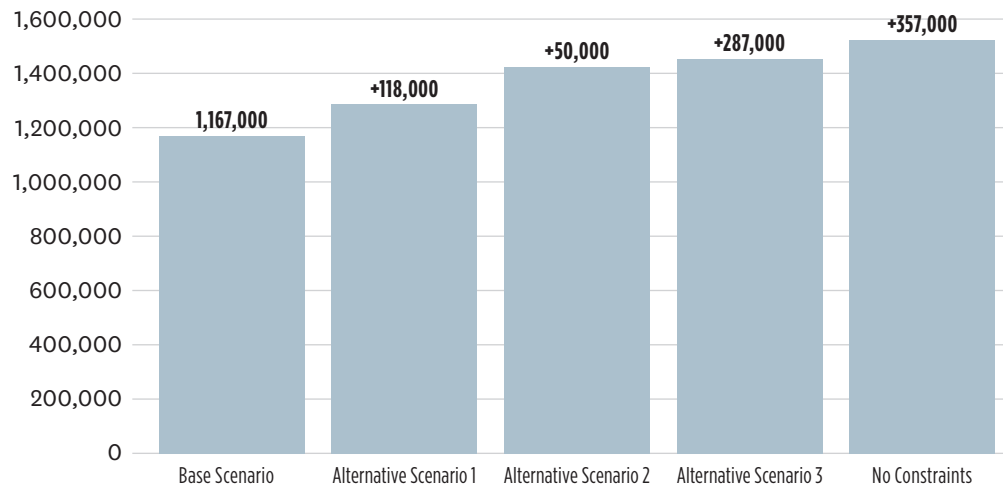
TABLE 4. SUMMARY OF PROJECTED WAIT TIMES FOR ALZHEIMER'S DISEASE DIAGNOSIS, TESTING, AND TREATMENT, BY SCENARIO

SCENARIO	Average Wait Time in Months			
	2021	2030	2040	2050
Base case	24.2	18.1	12.4	9.1
Alternative 1: <i>Expanded CSF</i>	22.5	11.3	4.5	2.0
Alternative 2: <i>Expanded CSF + BBBM</i>	13.5	2.4	0.2	0
Alternative 3: <i>Expanded CSF + BBBM + no infusion capacity constraints</i>	13.5	0	0	0

DEMENTIA DUE TO ALZHEIMER'S DISEASE CASES AVOIDED IN THE BASE AND ALTERNATIVE SCENARIOS

Figure 5 shows the cumulative incident dementia due to Alzheimer's disease cases between 2023 and 2050 in the base case and alternative scenarios. These changes would help to avoid between ten and 31 percent of additional cases of dementia due to Alzheimer's disease. If all constraints were removed, up to 357,000 of dementia cases due to Alzheimer's disease could be averted in Taiwan between 2023-2050, assuming that the treatment reduces the risk of progression from MCI due to Alzheimer's disease to manifest dementia by 30 percent.

FIGURE 5. CUMULATIVE INCIDENT CASES OF DEMENTIA DUE TO ALZHEIMER'S DISEASE CASES AVERTED, 2023-2050



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Limitations

Our analysis has several limitations and our estimates should therefore be seen as illustrative of the magnitude of the problem rather than precise predictions of wait times and disease progression.

We use a stylized clinical pathway that simplifies actual care patterns and make many assumptions about hypothetical scenarios in future states of the world. However, our stylized model is intended to provide a range of estimates to help identify potential capacity constraints if an Alzheimer's disease-modifying therapy becomes available in the near future.

We use assumptions for treatment effectiveness and indications. As the efficacy of a therapy is unknown at this time, we use the assumption of a 30 percent reduction in relative risk of transitioning from MCI to dementia due to Alzheimer's disease. The actual efficacy may be different and might affect patient uptake and the number of dementia due to Alzheimer's disease cases that could be avoided. We assume that the therapy would be indicated for people with MCI due to Alzheimer's disease; we do not include pre-symptomatic individuals and we assume the therapy would not be effective for people who have developed manifest dementia. If the therapy were indicated for pre-symptomatic individuals, the subsequent wait times could be longer. Patient uptake in response to a new disease-modifying therapy would also depend on a variety of factors, such as awareness, efficacy of the therapy, side effects, stigma associated with a MCI or dementia diagnosis, and costs.

On the infrastructure side of the model, we focus on three capacity constraints. We do not model capacity challenges related to cognitive screening, CSF testing, other imaging such as magnetic resonance imaging (MRI), radiologists and nuclear medicine specialists, and treatment monitoring. There will likely be challenges with the capacity considerations that we did not model, and successful delivery of a novel disease-modifying therapy will depend on a host of practitioners and planners to coordinate services. However, we focus on specialists, biomarker testing for diagnosis, and infusion delivery because these are likely to be the most pressing barriers and possibly the most difficult to overcome.

Our estimated capacity of specialists to conduct these visits reflects the theoretical capability and willingness of the specialists to provide the services. Based on our expert input, we recognize that not all neurologists and psychiatrists may choose to provide evaluation and diagnostic services to people with MCI. In addition, these specialists typically see different types of patients. Neurologists tend to see younger patients, and psychiatrists see a range of younger and older patients who have mood and or behavioral issues. Our model does not stratify patients by age, i.e., we consider the entire cohort of people aged 50 and older and assess patients based on average age of the cohort each year and other characteristics such as rates of patient uptake and contraindications. For example, younger people may be less likely to seek further evaluation from a specialist, while older people would more likely to be frail or have comorbidities that could preclude them from the treatment. We use uniform patient uptake assumptions that reflect an average patient. Including age strata would allow for subgroup analysis but would be unlikely to change the overall findings of our study given the uncertainties around the therapeutic profile, efficacy, and patient uptake.

The actual expansion of biomarker testing capacity would depend on factors such as the interplay between the regulatory agencies, commercial laboratory companies and imaging providers. Although this is a proxy measure for infusion capacity, future capacity growth is difficult to predict, but it is likely that providers would add infusion capacity, if an intravenous treatment were approved and covered by the National Health Insurance.

Discussion

A disease-modifying therapy for Alzheimer's disease may become available for the first time this year. Such a therapy has the potential to greatly reduce the number of dementia due to Alzheimer's disease cases by delaying or preventing disease progression. However, this preventive paradigm implies that the population impact of a therapy will depend on a country's ability to identify people who would benefit from therapy and to administer it in a timely fashion.

Our analysis suggests that almost 357,000 Taiwanese could progress from MCI due to Alzheimer's disease to dementia between 2022 and 2050 while on wait lists for diagnosis, testing, and treatment if a therapy became available in 2022. The wait times are most pronounced in the first few years, but remain high and will persist for decades.

Peak wait times in Taiwan are projected to be much longer than those in the United States (19 months), Japan (15 months), and Korea (14 months), as well as those in the United Kingdom (14 months) and Germany (11 months), but comparable to Canada (28 months). However, the reliance on PET testing means that queues in Taiwan will clear more slowly than in Canada, which is the G7 country with the longest projected wait times.

Taiwan has embarked on several policy initiatives that can be seen as first steps to reduce wait times for access to a disease-modifying therapy for Alzheimer's diseases.

Efforts to raise awareness, introduce more comprehensive community care and take steps towards integrated models of dementia care were undertaken under the first National Dementia Plan and have been

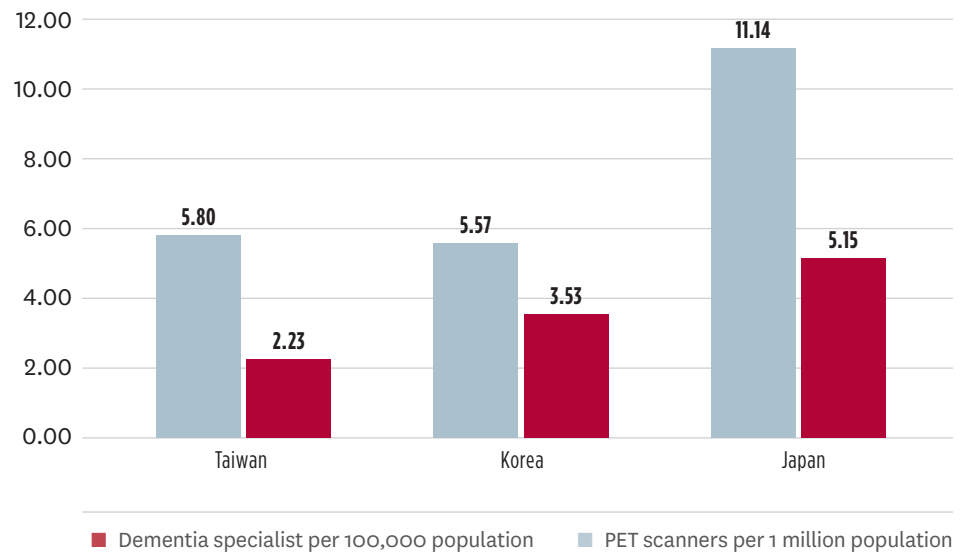
further expanded as the National Dementia Plan 2.0, known formally as the “Taiwan Dementia Policy: A Framework for Prevention and Care 2.0”

Many of these policies have been focused on increasing screening and detection by increasing public awareness and community resources. Under the first Dementia Plan, medical referral services for community members with suspected dementia or cognitive impairment were introduced in community centers. In the second Plan, the government has further launched Integrated community-based Dementia Care Centers, which have an explicit goal to help undiagnosed patients to be diagnosed within 6 months and provide referral services, in addition to other community resources. Other steps towards a national screening program include the proposed integration of dementia screening into the nationwide integrated health screening program which provides subsidized regular cancer screening to all individuals aged 50 and over.

WORKFORCE EXPANSION

As in many other countries, limited capacity of dementia specialists is the most limiting obstacle to evaluating patients with MCI for treatment eligibility in Taiwan. Taiwan has a similar number of dementia specialists per capita as South Korea, but fewer PET scanners, and considerably fewer specialist and PET scanners than Japan.

FIGURE 6. CAPACITY COMPARISON OF TAIWAN TO JAPAN AND KOREA (2020)



Expanding specialty capacity is also the hardest constraint to address, because specialist training takes many years and current training pipelines do not even keep up with the growing needs of ageing populations under established treatment options. One possibility is to expand with suitable incentives and training, the fraction of the specialist workforce engaged in dementia care, especially psychiatrists. An alternative is to qualify other specialists, non-specialist healthcare professionals, such as general practitioners, or physicians in adjacent specialties, such as internal medicine, in the evaluation and diagnosis of memory complaints.

DIAGNOSTIC CAPACITY

The capacity to confirm the Alzheimer’s pathology with biomarkers is the second most pressing constraint in Taiwan, as it is in other countries that we studied. Taiwan has comparable density and utilization of PET scanners to G7 countries, but—in contrast to European countries—would be more reliant on using PET scans rather than CSF tests. There are some specific challenges to implement CSF testing in Taiwan, such as strong patient reluctance to undergo lumbar punctures, particularly among older adults. Installing additional PET scanners in Taiwan, as elsewhere, is likely to be challenging because of the cost and strict building requirements. Thus, the more viable path to increased testing capacity with current technologies could lead to more use of new blood-based biomarker technologies as modeled in our scenarios.

Conclusion

There is cautious optimism that a disease-modifying therapy for Alzheimer’s disease will be available in the coming years. Many jurisdictions do not have sufficient infrastructure to deliver such a therapy to a large population of people with MCI due to Alzheimer’s disease, and Taiwan is no exception. Without efforts to expand existing capacity or augment it with the introduction of new technologies for diagnostics and screening, we estimate that projected wait times for access to treatment could peak at more than 24 months and furthermore could remain at almost a year for decades to come. This is significantly longer than the peak wait times estimated in Japan and Korea, as well as in Europe and the United States. The comparatively low density of dementia specialists and the limited excess capacity of PET scanners, combined with reluctance to use CSF testing, contribute most to those wait times.

Taiwan has acknowledged the importance of addressing the issue of dementia and undertaken steps under a series of national dementia plans (see Box 1). The focus of these plans to date has been to seek to increase diagnoses and bolster community care resources, which is an important first step. At the same time, these plans do not address the changes necessary to expand capacity for treatment, which will not happen without the concerted and coordinated effort of multiple stakeholders, given the need for increased awareness, capital investment, care model innovation, and changes to regulation and reimbursement.

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Box 1: Priorities for dementia care in Taiwan

Taiwan’s dementia care policy is based on the Dementia Prevention and Care Policy and Action Plan 2.0 (2018-2025) which refers to 19 action plans around seven strategies under the WHO Global Action Plan on the Public Health Response to Dementia 2017-2025. The strategies include action plans to: (1) recognize dementia as a public health priority; (2) raise dementia awareness and friendliness; (3) reduce the risk of dementia; (4) provide dementia diagnosis, treatment, care and support; (5) provide support for dementia caregivers; (6) build information system for dementia; and (7) promote dementia research and innovation (Ministry of Health and Welfare, 2018). As of May 2018, Taiwan has 34 daycare centers that offer dementia care services, and 21 veteran homes and welfare institutions with dementia departments, with 1,012 beds available for dementia care (Department of Long-Term Care, 2018). Moreover, there are also 9 nursing homes and 26 ministry-registered hospitals that provide dementia services, with 997 beds available for dementia care (Department of Long-Term Care, 2018)

The Taiwan government invested US\$ 315.75 million (TW\$ 9 billion) between 2018 and 2019 to actively promote the prevention and care of dementia. About 46 percent of the budget was spent on reducing the risk of dementia, while 41 percent was spent to provide dementia diagnosis, treatment, care and support, 8 percent was spent to promote dementia research and innovation and 4 percent was spent to provide support for dementia caregivers (Taiwan Alzheimer's Disease Association, 2018).

While much of this investment has gone into the expansion of services at the community level, Taiwan has established 72 integrated dementia care centers (IDCCs) as of June 2018, which offer assistance to suspected dementia cases in seeking medical care, raise public awareness and acceptance of dementia, and train dementia caregivers at various locations (Department of Long-Term Care, 2018). Furthermore, Taiwan established 333 Support Centers for People with Dementia and their Families (SPDFs) to promote dementia awareness, organize dementia-alleviating programs, and train home caregivers and support groups for counseling and consultation (Department of Long-Term Care, 2018), as well as 10 dementia friendly communities and 2,400 dementia friendly organizations (HPA, 2019).

Other proposed steps towards a national screening program include the potential integration of dementia screening into the nationwide integrated health screening program which provides subsidized regular cancer screening to all individuals aged 50 and over.

Without these changes, we estimate that up to 357,000 Taiwanese adults could progress from MCI to manifest dementia due to Alzheimer's disease while waiting for treatment between 2023 and 2050. With a disease-modifying therapy for Alzheimer's disease potentially being available within a few years, preciously little time remains for stakeholders to take action and remedy the capacity gap. Failure to do so in a timely and decisive manner will likely result in hundreds of thousands of potentially avoidable cases of dementia due to Alzheimer's disease.

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Box 2: Dementia Therapy Financing under the NHIA

While the National Health Insurance Administration remains fiscally solvent, issues about its sustainability in the face of aging are emerging. Drug reimbursement decisions are supported by a formal process of health technology assessment to evaluate effectiveness and value for new and breakthrough drugs.

With respect to treatment, dementia has been included in the Hospital Patient-centered Integrated Outpatient Service Plan by the NHIA. The corresponding memory clinics in all regional hospitals provide early intervention and treatments for patients at different stages of dementia. Pharmacological treatments covered under this plan include both Western and Chinese medications, and cover both dementia-specific regimens (donepezil, rivastigmine, galantamine, memantine, ergoloid mesylates, and ginkgo), as well as medicines used to manage the common behavioral and psychological symptoms associated with Alzheimer's disease (antipsychotics, antidepressants, antianxiety agents, and hypnotics).

While treatments such as cholinesterase inhibitors and memantine are available in the NHI, their use is subject to strict rules for reimbursement. Patients must be confirmed as having Alzheimer's disease after a complete diagnostic workup performed by a board-certified psychiatrist or neurologist, and meet criteria based on the Mini-Mental Status Examination (MMSE) score and a clinical dementia rating (CDR) grade. These evaluations must be repeated annually. Specific therapies are made available only to patients with severe Alzheimer's disease based on their MMSE score and CDR grade. The requested blood tests include venereal disease research laboratory, thyroid function, complete blood count, fasting sugar, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, blood urea nitrogen, creatinine, serum cobalamin, and folic acid levels. In addition, neuroimaging is required to exclude other causes of dementia. The NHI Administration hires external experts to review the records of the ambulatory care visits, and the in-patient claims to verify the accuracy of the diagnoses (Wan et al. 2018)

Current healthcare utilization may reflect these strict reimbursement guidelines. Hung et al. (2016) observed that in historical NHI records more than 95 percent of dementia patients recorded no usage for cholinesterase inhibitors and NMDA receptor agonists, which they suggest may be due to the fact that cholinesterase inhibitors and NMDA receptor agonists are more restricted by the NHI guidelines than antipsychotics. The majority also did not undergo imaging. Of those who did so the majority received CT or MRI scans. As PET scans are not reimbursed by NHI, less than 1 percent of patients currently received them. These patterns suggest that for any new disease-modifying therapy, reimbursement criteria may have significant consequences for adoption.

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About This Report

This report illustrates the magnitude of healthcare system infrastructure challenges for diagnosis and treatment of early-stage Alzheimer's disease with a future potential disease-modifying therapy in Taiwan. This research was funded by an unrestricted grant of Eisai, Inc. to the University of Southern California. For questions about this report, please contact Dr. Soeren Mattke at mattke@usc.edu

For more information about our data, please see this report's technical appendix at cesr.usc.edu/research/publications

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