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# **Assessing the Preparedness of the Japanese Health Care System Infrastructure for an Alzheimer's Treatment**

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## Key Findings

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- » Potential disease-modifying therapies that are currently tested in clinical trials 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 Japan'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 Japan could peak at 14 months and persist until 2041 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 60,000 to 644,000 Japanese could progress from mild cognitive impairment due to Alzheimer's disease to Alzheimer's dementia while on wait lists.
- » Japan also faces the challenge of higher rates of elderly residents in rural areas with limited access to specialty care.
- » Expanding capacity would require coordinated efforts among multiple stakeholders to increase awareness and investment, and to implement policies that ensure adequate capacity to deliver a future Alzheimer's therapy.
- » Several efforts are under way in Japan that could be leveraged for this objective, such as a National Dementia Plan, cognitive screening as part of driver's license renewal for elderly drivers and training of community-based geriatric and dementia support physicians.

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## Introduction

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Alzheimer's disease is a chronic neurodegenerative disorder that leads to cognitive and functional decline, dementia, and premature death. As the most aged country among the G7 countries due to the unique combination of long life expectancy and low birth rates, Japan 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 5.5 million Japanese currently have dementia as of 2018, of which about two-thirds have dementia due to Alzheimer's disease and the Japanese government estimates that dementia prevalence will increase to 8 million by 2050 (Ninomiya, Yutaka, Tomoyuki, & Koji, 2014).

Against this background, the recent announcement by Biogen and Eisai that the U.S. Food and Drug Administration has accepted aducanumab's Biologics License Application with a priority review, with a Prescription Drug User Fee Act (PDUFA) action date of March 7, 2021 is of particular relevance to Japan, because aducanumab would be the first treatment that slows the progression of cognitive decline in

patients with MCI due to Alzheimer's disease. Several other disease-modifying therapies are currently in varying stages of clinical trials and there is optimism that a treatment to slow or halt the progression to dementia could become available soon (Aisen, 2017). Table 1 summarizes 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 believed to contribute to the disease process.

**TABLE 1. ALZHEIMER'S DISEASE-MODIFYING THERAPY CANDIDATES IN PHASE 2 AND PHASE 3 CLINICAL TRIALS, AS OF AUGUST 2020**

CANDIDATE	SPONSOR	CLINICAL TRIAL PHASE	EXPECTED PRIMARY COMPLETION DATE	NATIONAL CLINICAL TRIAL IDENTIFIER
<b>Anti-beta-amyloid antibodies</b>				
Gantenerumab	Hoffman-La Roche	Phase 3	May 2022	NCT03443973, NCT03444870
BAN2401	Eisai/Biogen	Phase 3	February 2022	NCT03887455
<b>Anti-tau antibodies</b>				
BiIB092	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	December 2021	NCT03446001
<b>Vaccines</b>				
AADvac1 (anti-tau)	Axon Neuroscience	Phase 2	June 2019	NCT02579252
<b>Other Mechanisms</b>				
PQ912	Vivoryon Therapeutics	Phase 2	December 2023	NCT03919162, NCT04498650
PTI-125	Cassava Science	Phase 2	September 2021	NCT04388254, NCT04079803
Azeliragon	vTv Therapeutics	Phase 2/3	April 2023	NCT03980730

SOURCE: Authors' review of ClinicalTrials.gov website as of August 27, 2020.

\*Phase 2 has been completed with positive results presented at the AAT-AD/PD 2020 conference.

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 with the aim of triggering antibody responses against Alzheimer's proteins. Other mechanisms include a glutaminyl cyclase inhibitor, a molecule targeting filamin A proteins, and an inhibitor receptor for advanced glycation end-products (RAGE). 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 7 million Japanese may live with MCI today (Petersen et al., 2018)<sup>1</sup>, and most of them 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 U.S., Australia, Canada and six European countries (Germany, France, Italy, Spain, Sweden, and the U.K.) and predicted substantial obstacles to access in all of them, resulting in wait times and potentially avoidable disease progression (Hlávka, Mattke, & Liu, 2018; Liu, Hlávka, Hillestad, & Mattke, 2017).

This report presents an analysis of the preparedness of the Japanese healthcare system to treat people with early-stage Alzheimer's disease (MCI due to AD 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

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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.

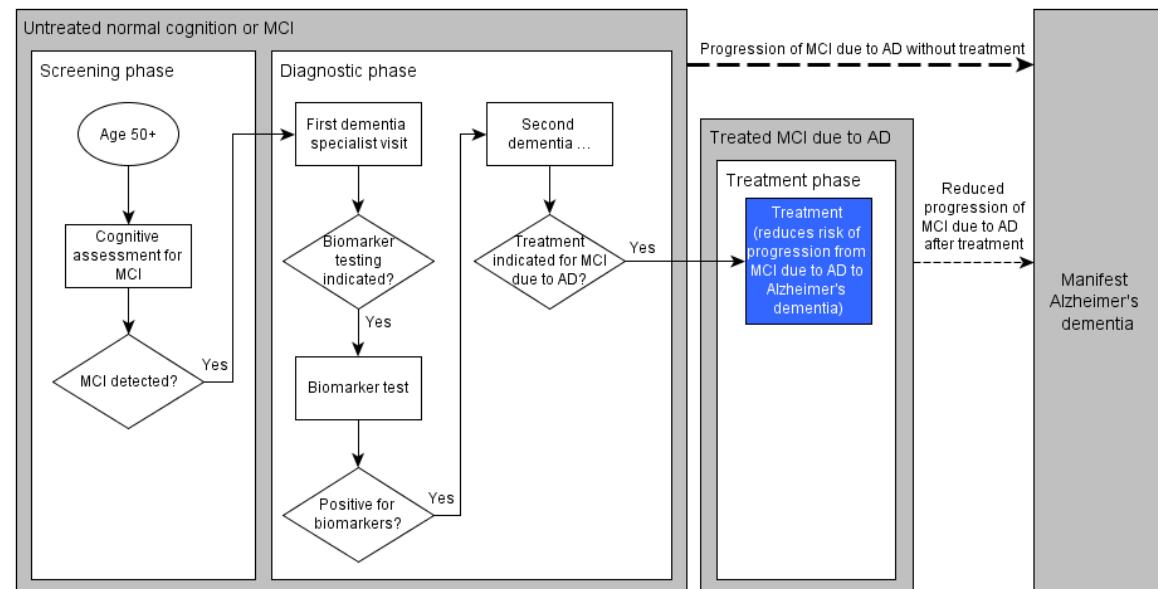
In this patient journey, older adults would undergo cognitive assessment with a short instrument such as the Folstein Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Modified Mini-Mental State Examination (Tombaugh, McDowell, Kristjansson, & Hubley, 1996), or the Montreal Cognitive 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

<sup>1</sup> The exact prevalence of MCI is difficult to determine, as it will depend on which diagnostic criteria and which cutoff values of cognitive tests are used. As for our previous studies, we used the consensus estimates for MCI prevalence by age bracket from Petersen et al. (Petersen et al., 2018), but note that the studies behind this estimate reported MCI prevalence estimates from 3.2 percent to 42.0 percent depending on instrument, age group and cutoff. Similarly, a previous study conducted for the Japanese government had estimated around 4 million cases in 2012 (Asada, 2012).

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**



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### 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 Japanese 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 Japanese 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 Japanese context as noted.

To adapt assumptions for Japan, we consulted with several experts familiar with clinical practice, care delivery, patient needs, and the policy environment in Japan. 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.<sup>2</sup> 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).<sup>3</sup> 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 60 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, whom we assume to include 80 percent of neurologists, 40 percent of geriatricians and 100 percent of geriatric psychiatrists, who represent 40 percent of all 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 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 Japan, we assume that biomarker testing may be performed with a Positron Emission Tomography (PET) scan for amyloid deposits in the brain, or with a cerebrospinal fluid (CSF) test.<sup>4</sup> Based on

<sup>2</sup> Our U.S. and European analyses, which were published in 2017 and 2018, assumed that a therapy would become available in 2020.

<sup>3</sup> Our U.S. and European analyses assumed that the age eligibility would be 55 and older. For this analysis, similar to our analysis of Canada, we lowered the age range to 50 as the later stage clinical trials tend to target earlier age groups and some trials targeting later age groups have been terminated (e.g., Phase 3 trial of BAN2401, NCT03887455).

<sup>4</sup> 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.

input from Japanese experts regarding the potential availability of PET scanners and patient preferences, our assumption is that 90 percent of tests would be performed using PET and 10 percent would be performed using CSF. 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 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. We estimate that there would be 7.7 million Japanese who would either be known to have or screen positive for MCI in 2021. Of those, 3.9 million patients would seek evaluation by a specialist, 3.5 million would undergo biomarker testing, 1.5 million would test positive for amyloid pathology and 1.2 million patients would be determined eligible for treatment.

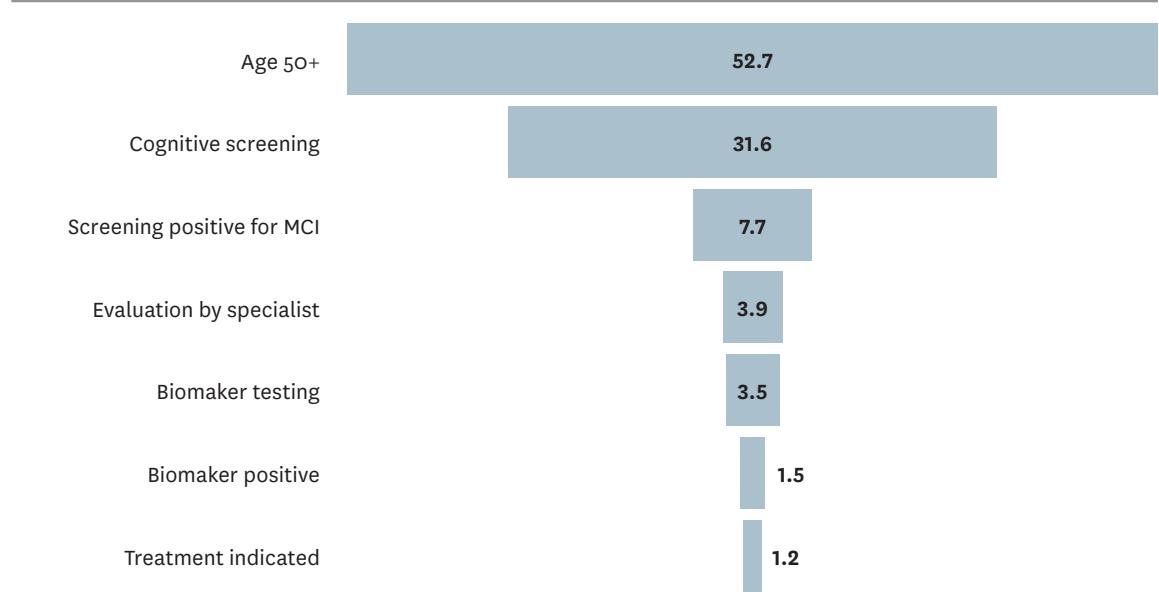
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FIGURE 2: EXPECTED PATIENT DEMAND IN SCREENING AND DIAGNOSTIC PHASES IN 2021 (MILLIONS)



## SPECIALIST WORKFORCE

Based on expert input, we expect that three categories of specialist physicians will be involved in Alzheimer's diagnosis in Japan: neurologists, geriatricians and geriatric psychiatrists. We use data from the Ministry of Health, Labor and Welfare from 2016 for the number of specialists in the country (Ministry of Health, 2016). We project future workforce pool using 2018 physician workforce forecasts from the Ministry (adjusted on a per-capita basis) (Ministry of Health, 2018) and use medium fertility population forecasts from the National Institute of Population and Social Security Research until 2050 (National Institute of Population and Social Security Research, 2017). Based on expert input, we assume that 80 percent of neurologists, 40 percent of geriatricians and 40 percent of psychiatrists would be able to evaluate patients with suspected Alzheimer's disease (Table 2).

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

YEAR	NEUROLOGISTS	GERIATRICIANS	GERIATRIC PSYCHIATRISTS
2020	6,344	499	7,112
2030	6,852	539	7,680
2040	7,189	566	8,059
2050	7,487	589	8,393

SOURCE: *Ministry of Health Labour and Welfare, Japan (2016)*

NOTE: We assume that 80 percent of neurologists, 40 percent of geriatricians and 100 percent of geriatric psychiatrists would be able to evaluate patients with suspected Alzheimer's disease in Japan. Geriatric psychiatrists represent 40% of the specialty.

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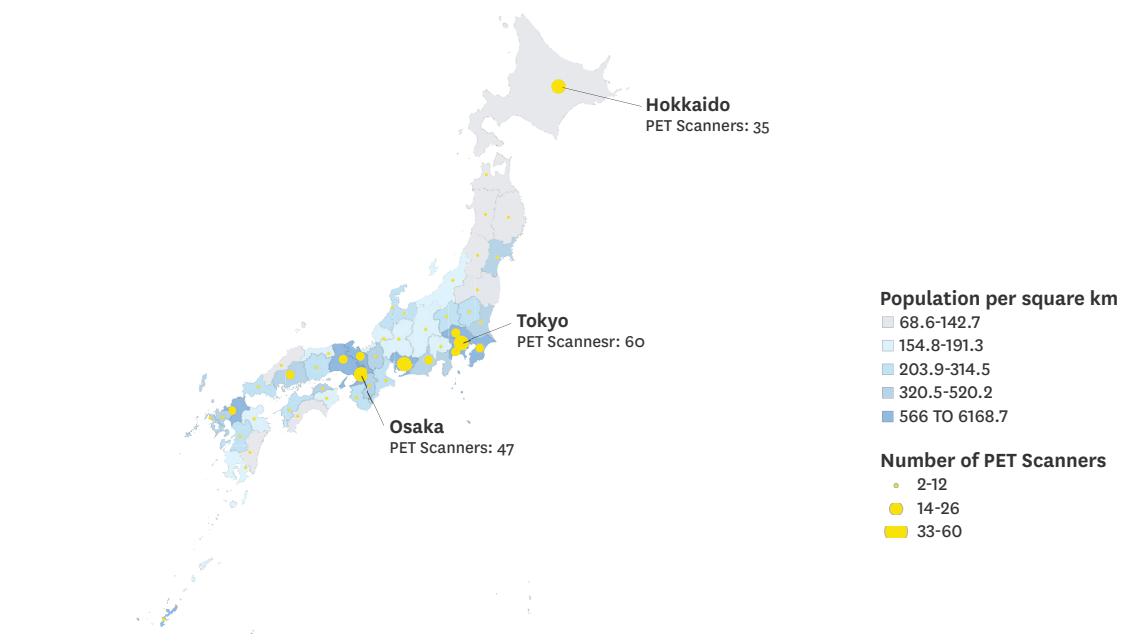
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## DIAGNOSTIC TECHNOLOGY

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, both technologies are predominantly used for research and clinical trials in Japan, while only selected cases with unusual presentation of cognitive impairment, such as early onset dementia, would be tested as part of their clinical evaluation. In our model, we assume that 90 percent of biomarker test-eligible patients will undergo a PET scan. 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).

In Figure 3 and Figure 4, we show the locations of the 586 PET scanners and 208 cyclotrons in Japan.

**FIGURE 3: PET SCANNERS IN JAPAN (AS OF 2018)**



SOURCE: [www.newmed.co.jp/shin-iryo/n1803](http://www.newmed.co.jp/shin-iryo/n1803)

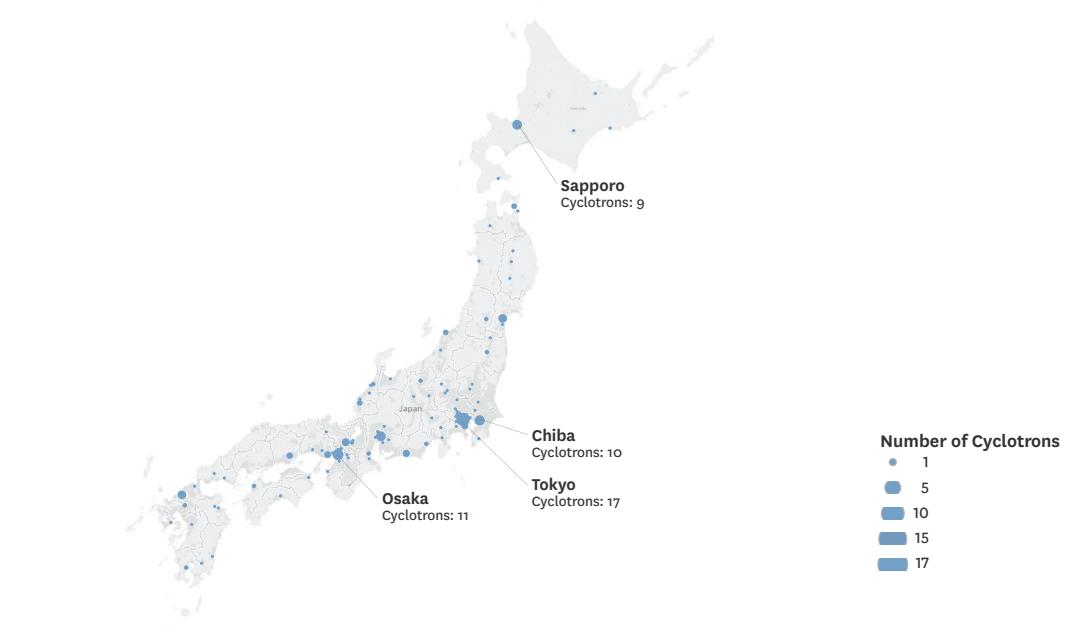
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**FIGURE 4: CYCLOTRONS IN JAPAN (AS OF 2018)**



SOURCE: [www.newmed.co.jp/shin-iryo/n1803](http://www.newmed.co.jp/shin-iryo/n1803)

## **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 4 weeks for a total of 20 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.

Given the lack of publicly available infusion data in Japan, we use an index approach consistent with our prior European and Canadian analyses. Our estimates of the capacity to deliver infusions are based on the relative capacity of the Japanese 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 Japan 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**

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### **BASE CASE SCENARIO**

Figure 5 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 15 months initially, mostly because of capacity limitation for specialist visits. As more people will have been seen by specialists, capacity for biomarker testing and infusion capacity will become the constraints. Waiting times for infusion delivery, albeit for only about two months, will persist until 2030. By 2031, we project that the backlog of cases will have been cleared so that patients can access treatment without wait.

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**FIGURE 5: PROJECTED WAIT TIMES FOR ALZHEIMER'S DISEASE DIAGNOSIS, TESTING, AND TREATMENT**

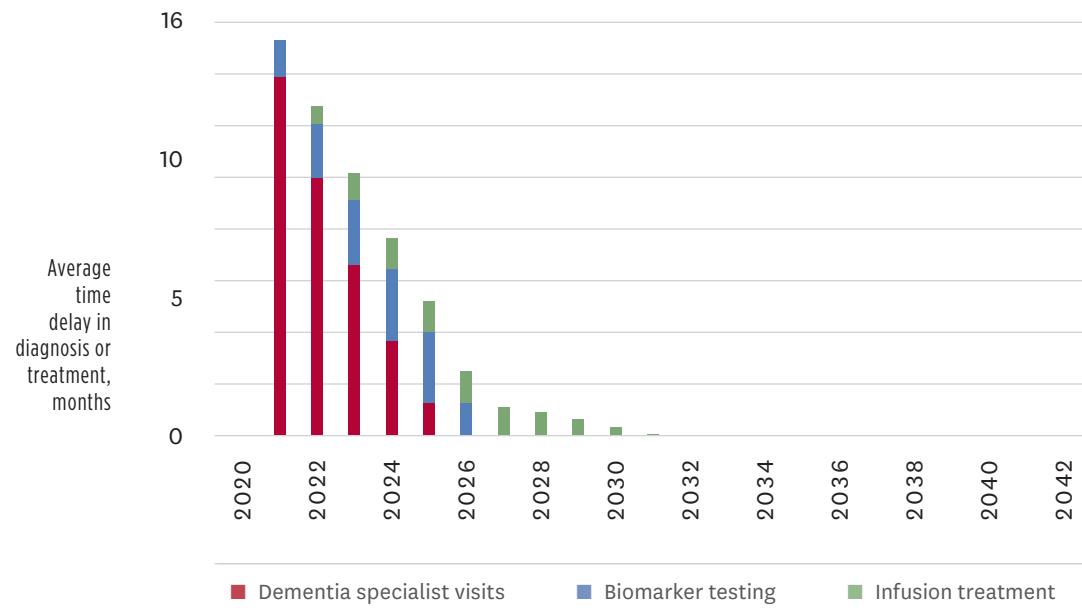
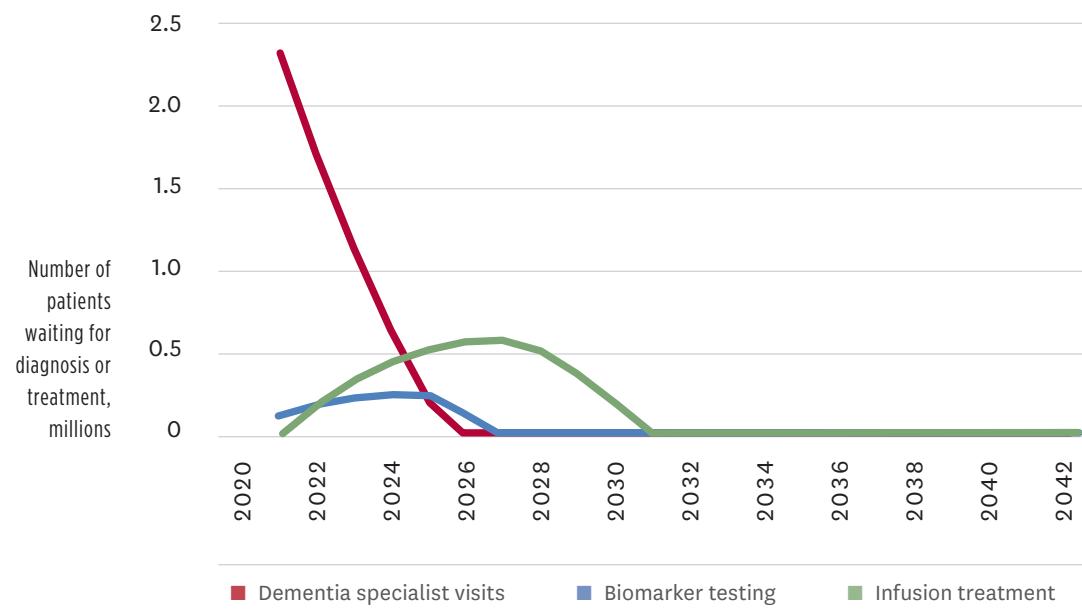


Figure 6 illustrates the effects of the capacity constraints on the number of patients in the respective queues. Initially, nearly two and a half million Japanese patients are estimated to wait for their specialist appointment, but that wait list is projected to clear by 2026. Up to 600,000 patients would have to wait for biomarker testing or treatment delivery in the first few years.

**FIGURE 6: 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 alternate scenarios are shown in Table 3.

**TABLE 3. CAPACITY ASSUMPTIONS ACROSS SCENARIOS**

SCENARIO	SPECIALISTS	BIOMARKER TESTING	INFUSIONS
Base case	80% of neurologists, 40% of geriatricians, and all geriatric psychiatrists with 5% excess capacity for visits	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: Shift to 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: Shift to CSF testing and investment in infusion delivery facilities (or non-intravenous administration)	Same as base case	80% PET with historical capacity projected forward, 20% CSF with no capacity constraint	No capacity constraint
Alternative 3: No capacity constraints	No capacity constraint	No capacity constraint	No capacity constraint

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Alternative scenario 1 reflects expanded use of CSF biomarker testing such that less than 80 percent of biomarker testing is conducted using PET and more than 20 percent using CSF. This may be possible if resources are dedicated to performing lumbar punctures and to conducting assays. It may be possible that capacity for CSF testing could rapidly be expanded if planning, policies, regulations, and reimbursements encourage investments. This may require training, developing standard protocols, and establishing laboratory networks with adequate reimbursement. If more than 20 percent of biomarker testing were based on CSF testing, wait times for testing would be completely eliminated.

In alternative scenario 2, the elimination of the infusion delivery constraint could reflect adequate capacity growth of infusion services, or a therapy that does not require intravenous delivery (i.e., could be administered subcutaneously). Eliminating the infusion constraint may be possible if increasing infusion center capacity becomes a priority, and/or if home infusions are utilized more widely.

Alternative scenario 3 illustrates the case in which all three capacity constraints and the associated wait times are eliminated, which would require either substantial increases in specialist capacity or improved triaging of patients at the primary care level. Given the long training times for dementia specialists, net increases in capacity seem unlikely, but increased task shifting to other specialists, primary care providers and other healthcare professionals could lessen the burden. The introduction of a blood-based test (A. Nakamura et al., 2018) (Palmqvist et al., 2019) for Alzheimer's disease biomarkers would allow identifying patients with MCI due to other causes earlier in the process and thus reducing specialist referrals. 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	2022	2030	2040	2050
Base case	15.3	0.3	0	0
Alternative 1: <i>Investment in CSF</i>	13.9	0.3	0.1	0
Alternative 2: <i>Investment in CSF and infusion delivery (or non-intravenous administration)</i>	13.9	0	0	0
Alternative 3: <i>No capacity constraints</i>	0	0	0	0

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

Figure 7 shows the cumulative incident dementia due to Alzheimer's disease cases between 2022 and 2050 in the base case and alternative scenarios. These changes would help to avoid between one and seven percent of additional cases of dementia due to Alzheimer's disease. If all constraints were removed, up to 644,000 cases of dementia due to Alzheimer's disease could be averted in Japan between 2022-2050, assuming that the treatment reduces the risk of progression from MCI due to Alzheimer's disease to manifest dementia by 30 percent. Of note, simply increasing the share of patients, who undergo confirmatory biomarker testing based on CSF testing, from ten percent to 20 percent would eliminate queues for biomarker testing.

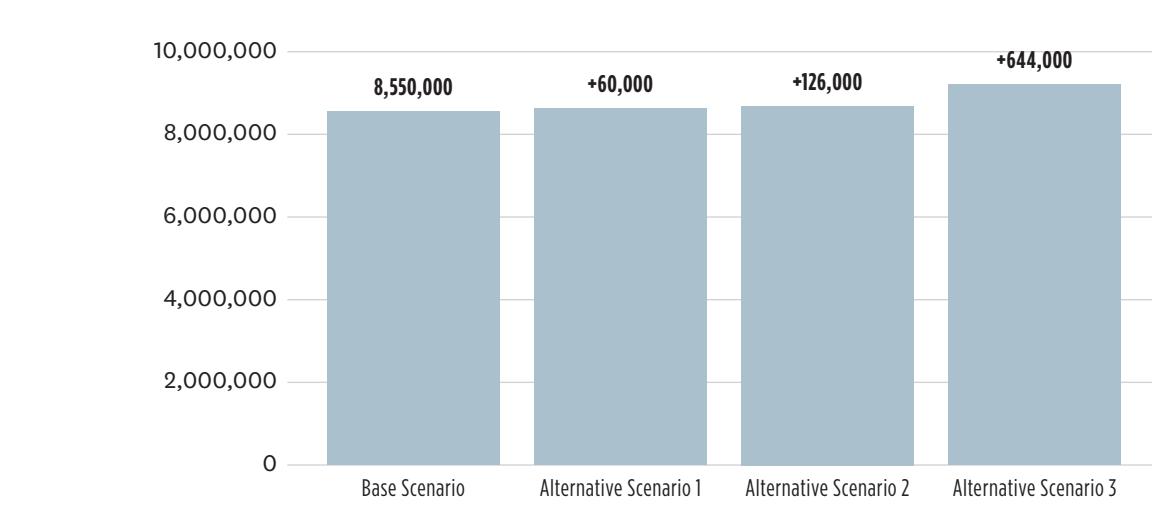
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FIGURE 7: CUMULATIVE INCIDENT CASES OF DEMENTIA DUE TO ALZHEIMER'S DISEASE CASES AVERTED, 2023-2050



## 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. For example, there is limited access to primary care physicians in some provinces, which could make MCI detection more challenging. 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. Although not all neurologists, geriatricians, and geriatric psychiatrists (and other psychiatrists focusing on neuropsychiatry) may choose to provide evaluation and diagnostic services to people with MCI, we made a simplifying assumption that these specialists could conduct 5 percent more visits overall than visits in the status quo. In addition, these specialists typically see different types of patients. Neurologists tend to see younger patients, geriatricians see older patients who are more likely to have comorbidities, and geriatric psychiatrists see older patients who have mood and or behavioral issues. As our model does not stratify patients by age, i.e., we consider the entire cohort of people ages 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 be more likely to be frail or have comorbidities that could preclude them from the treatment, but 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.

Any 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 in Japan is difficult to predict, but it is likely that providers would add infusion capacity, if an intravenous treatment were approved and covered by health insurance.

## Discussion

A disease-modifying therapy for Alzheimer's disease may become available for the first time in the coming years. 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 up to 644,000 Japanese could progress from MCI due to Alzheimer's disease to dementia due to Alzheimer's disease 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, with the annual average waiting times peaking at 15 months in the year prior to launch, and wait times, albeit limited, could persist for a decade. Peak wait times in Japan are projected to be similar to those in the U.K. (14 months) and Germany (11 months) and shorter than in the U.S. (19 months) and Canada (28 months). Queues in Japan will clear more slowly than in Europe because of the reliance on capacity-constrained PET testing for biomarkers.

As the fastest ageing of the G7 countries, Japan has embarked on several policy initiatives that can become the basis for efforts to reduce wait times for access to a disease-modifying therapy for Alzheimer's diseases. Most notably, as part of its call for action on research and development, the Government's New Orange Plan calls for better models for care and prevention of dementia.

### EARLY DETECTION

Japan has a unique program that screens elderly drivers for cognitive decline. While the focus is currently on identifying those with manifest dementia, who are no longer fit to drive, it could become an avenue through which patients with MCI due to Alzheimer's disease could be identified at an early stage (see Box 1).

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#### **Box 1: Cognitive screening as part of driver's license renewal**

*After the recent revision of the Road Traffic Act, since March 2017 it has been mandatory for drivers 75 years of age or older to take a 30-minute cognitive function screening test at the time of license renewal every three years. The test includes three parts: temporal orientation, cued recall and the ability to draw a clock. Based on these assessments, cognitive function is assessed to be impaired, mildly impaired or normal. Individuals who are judged to have impaired cognitive function or who commit certain traffic violations (running a red light or forgetting to signal for a turn) have to take a provisional aptitude test administered by a specialist or submit a medical certificate issued by their physician. If diagnosed with dementia, the driver's license is suspended or rescinded at the judgment of the prefectural public safety commission.*

*Prior to the law, efforts to support safe driving by older adults including compulsory education about the effects of aging at the time of license renewal for adults over 70 and encouragement of voluntary return (e.g. via incentives) were already in place, with over 345,000 license forfeits in 2016 reported by the National Police Agency. Since 2009, compulsory cognitive testing for adults above 75 upon renewal had been required but used only as a basis for delivering individualized advice rather than having a formal screening function. Those who were evaluated and found to be cognitively impaired did not need to see a doctor unless they violated traffic regulations.*

*In the year following the implementation of mandatory cognitive screening, 253,900 people aged 75 or older voluntarily returned their licenses, which was a 56 percent increase over the previous year. About 2.1 million elderly drivers seeking to renew their licenses were tested and 57,000 drivers screened positive for cognitive decline, according to the National Police Agency (NPA). Of these, the NPA reported that 16,000 presented for follow-up medical checks (an 8.5-fold increase from the previous year), following which licenses were revoked or suspended for 1,892 people who were formally diagnosed with dementia.*

## 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 Japan. 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. An alternative is to qualify 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. Japan has an ambitious effort under way to expand the range of healthcare professions who are trained in dementia care (see Box 2). While currently focused on the needs of patients with manifest dementia, those programs could form the basis for training physicians in diagnostic evaluation of MCI.

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### **Box 2: Kakaritsuke Physicians, Dementia Support Doctors and Primary Care Physicians**

*Several efforts are in place to strengthen community-based geriatric and dementia care in Japan. A critical part is the concept of the Kakaritsuke Physician, which reimagines the role of the primary care physician as extending beyond the boundaries of healthcare to take a leadership role in coordinating home and community-based care for the elderly (Suzuki, 2016). Kakaritsuke Physicians undergo a period of training for 3 years, including teamwork, multidisciplinary coordination, and implementation of home medical care. More than 10,000 physicians have been or are currently being trained in this system. As part of their role, dementia care training is critical for Kakaritsuke Physicians. The training covers the diagnosis and treatment of dementia as well as the organization of continuous medical care and support for patients and families among other partners such as home visiting nurse stations, comprehensive community support centers, and care managers.*

*While the Kakaritsuke Physician supports community-based care for the elderly in general, Dementia Support Doctors (DSD) focus specifically on the support of dementia patients by promoting cooperation between primary care, dementia specialists and specialized medical institutions. Their roles include (i) supporting primary care doctors and care professionals engaged in dementia care; (ii) establishing interdisciplinary liaison systems led by a Community Comprehensive Care Center; and (iii) providing education about dementia-specific training to primary care doctors and education for residents. This scheme was initiated in 2005, and by 2016 had exceeded its targets of training 5,000 doctors. Almost half of the DSDs trained*

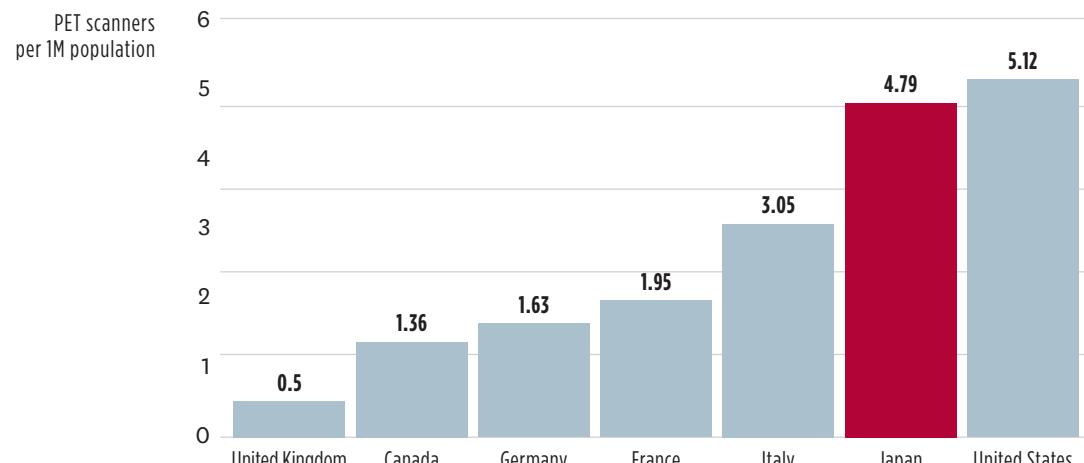
*between 2005-2011 were specialized in fields generally related to dementia, such as psychiatry, neurology, geriatric medicine and neurosurgery, while the remaining were specialized in other fields of internal medicine, orthopedics, and urology.*

*The DSDs also support an educational initiative to enhance knowledge of dementia care in primary care, the Skill Up Program of Dementia Medicine for Primary Care Doctors, which was launched in 2006. Under the government's New Orange Plan strategy on dementia care, Japan aims to train 10,000 DSD and 75,000 primary care doctors in dementia care by 2020.*

### DIAGNOSTIC CAPACITY

The capacity to confirm the Alzheimer's pathology with biomarkers is not a pressing concern in Japan, in contrast to other countries, largely because of long specialist waits. Compared to other G7 countries, Japan has a high density of PET scanners, second only to the U.S. (Figure 8) and availability of a CSF test.

FIGURE 8: DENSITY OF PET SCANNERS IN G7 COUNTRIES



If specialist capacity were addressed, increased use of CSF testing in combination with the high PET capacity could avoid wait times for biomarker testing, according to our experts. CSF testing would also remediate geographic obstacles to access in rural areas, in which operating PET scanners would not be economically viable. While many physicians are trained in performing lumbar punctures during their post-graduate training, there are some challenges to increase CSF testing, such as patient reluctance and limited indications today.

Installing additional PET scanners is challenging because of the cost and strict building requirements to contain radiation levels, which require national and prefecture-level approvals. Our experts suggested

that the process would take years and that facilities would only initiate it, if they were certain that the additional tests were adequately reimbursed. Thus, the more viable and economic path to increased testing capacity with current technologies would lead through more use of CSF testing. Our estimates suggest that use CSF tests for about 20 percent of patients would eliminate wait times for confirmatory tests, even at today's PET capacity.

Alternatively, 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, Hlavka, & 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 a fully automated blood test for amyloid- $\beta$  with published performance (Palmqvist et al., 2019) in patients with suspected MCI prior to a specialist referral could eliminate over half of subsequent specialist visits, and thus reduce initial wait times (Mattke, Cho, Bittner, Hlavka, & Hanson, 2020).

### GEOGRAPHIC IMBALANCES

An important consideration in analyzing the health system infrastructure to delivery an Alzheimer's disease treatment in Japan is that the national view may disguise regional imbalances between supply and demand of memory services. Differential migration of younger populations towards urban areas (particularly Tokyo) has led to a disproportionate share of the elderly in rural-remote Japan, where almost 30 percent of the population are over 65 years old compared to less than 25 percent in predominantly urban areas.

At the same time, rural areas tend to have fewer healthcare resources per capita. While the total number of physicians per 100,000 population has increased in Japan since 2000, the increase was mostly seen in urban areas, whereas rural areas had a decrease in physicians numbers relative to demand. This discrepancy is projected to increase as a larger share of physicians in rural areas is nearing retirement age (Matsumoto et al., 2018), partly because of selective migration to urban areas (Hara, Otsubo, Kunisawa, & Imanaka, 2017). Similarly, PET scanners and other advanced imaging technology are predominately installed in urban areas (Matsumoto, Koike, Kashima, & Awai, 2015) and there are fewer hospital beds per capita in rural than in urban areas (Zhang & Oyama, 2016).

While installing additional fixed infrastructure in rural areas may not be economically viable, technology innovations, such as mobile PET scanners and tele-consultation models, may present options to improve access to memory care, if the prerequisite approvals can be obtained. For instance, specialized medical services at the locally designated Medical Center for Dementia may be provided at the prefecture level but remain relatively inaccessible to the rural population, resulting in considerable observed differences in resources and actual utilization across existing Medical Centers (Awata, 2014).

## Conclusion

In spite of recent setbacks, there is optimism that a disease-modifying therapy for Alzheimer's disease will be available soon. Many countries do not have sufficient infrastructure to deliver such a therapy to a large population of people with MCI due to Alzheimer's disease, and Japan is no exception. Without efforts to

expand capacity, we estimate that projected wait times for access to treatment could peak at 15 months, which is comparable to the United Kingdom. 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. In addition, Japan faces the challenge of disproportionate ageing in rural areas that have limited infrastructure for specialty care.

At the same time, the fact that Japan is the most aged of the G7 countries has spawned numerous initiatives to advance dementia care. The New Orange Plan is a comprehensive national dementia strategy and the government has just recently announced an initiative to promote preventive measures to reduce the rate of progression from MCI to manifest dementia. Several care models have been implemented that could provide the basis for an enhanced infrastructure to deliver and Alzheimer's treatment and Japan has become a leader in developing dementia support technologies (See Box 3).

### **Box 3: Adaptation of technological innovations supporting dementia care**

*A critical pillar of the Abe administration's 2015 New Orange Plan to address dementia is research and development, including developing and support the use of technology that supports integrated community care.*

*Notable applications of technology in Japan include:*

- » Novel low-cost mobile-health solutions to help track dementia patients, such as long-lasting wearable stickers with QR codes bearing personal identification or GPS-enabled devices that can be embedded into clothing or shoes
- » Monitoring devices and home-based sensors that detect changes in behavior, such as teapots that alert family members if not in regular use
- » Information and communications solutions, including the acceleration of electronic records-sharing platforms for providers to enable integrated care, and innovations for patients that support independent living such as picture phones or supportive clocks
- » Robotics in the form of assistive technology such as home assistants or as part of dementia care such as PARO therapy seals, small furry robots designed to provide stimulation and interactivity to patients

*While these technologies at present focus on supporting the care and management of manifest dementia, they could be adapted to the support of patients with MCI, if a disease-modifying therapy kept larger number of patients at an MCI stage.*

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The changes necessary to expand capacity 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. Without these changes, we estimate that up to 644,000 Japanese will progress from MCI to manifest dementia due to Alzheimer's disease while waiting for treatment between 2022 and 2050. With a disease-modifying therapy for Alzheimer's disease potentially being available within a few years, preciously little time remains left 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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## About This Report

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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 Japan. 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](http://cesr.usc.edu/research/publications)

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