ASSESSING THE PREPAREDNESS OF THE JAPANESE HEALTH CARE SYSTEM INFRASTRUCTURE FOR AN ALZHEIMER'S TREATMENT

Data Appendix

This appendix provides an overview of the model, sources for model parameters, and details on the capacity projections for the projection of healthcare infrastructure for Alzheimer's treatment in Japan.

The simulation model has two parts. First, a Markov model simulates transitions between the following disease states: normal cognition (no mild cognitive impairment [MCI] and no Alzheimer's dementia) to MCI to Alzheimer's dementia. People move through the disease states based on annual transition probabilities from the literature (Table A-1).

Second, within the MCI state, a systems dynamic model simulates three health care system capacity constraints within the diagnosis and treatment phases. The systems dynamic model uses stocks and flows to allow people to move through the phases and to delay people in phases when there is not enough capacity. For example, in the diagnosis phase, the initial constraint is the first dementia specialist visit. Based on the specialists' capacity for visits, people move to biomarker testing step; if the number of people exceeds the specialists' capacity, then those people remain at the specialist visit step until the following year (i.e., they queue for the next year). The model uses a one-year time step for the entire diagnosis and treatment phases, i.e., if a person is delayed at any step due to inadequate capacity, they remain at that step until the following year. After exiting each capacity step, a subset of people may exit the model at each "decision point" (see the diamonds in the conceptual framework in Figure 1 in the main report) if the next step is not indicated. For example, at the first dementia specialist visit, specialists would determine whether biomarker testing is indicated for a given patient. See Table A-1 for the assumptions for the share of patients that proceed at each decision point.

Table A-1. Model parameters, values, and sources

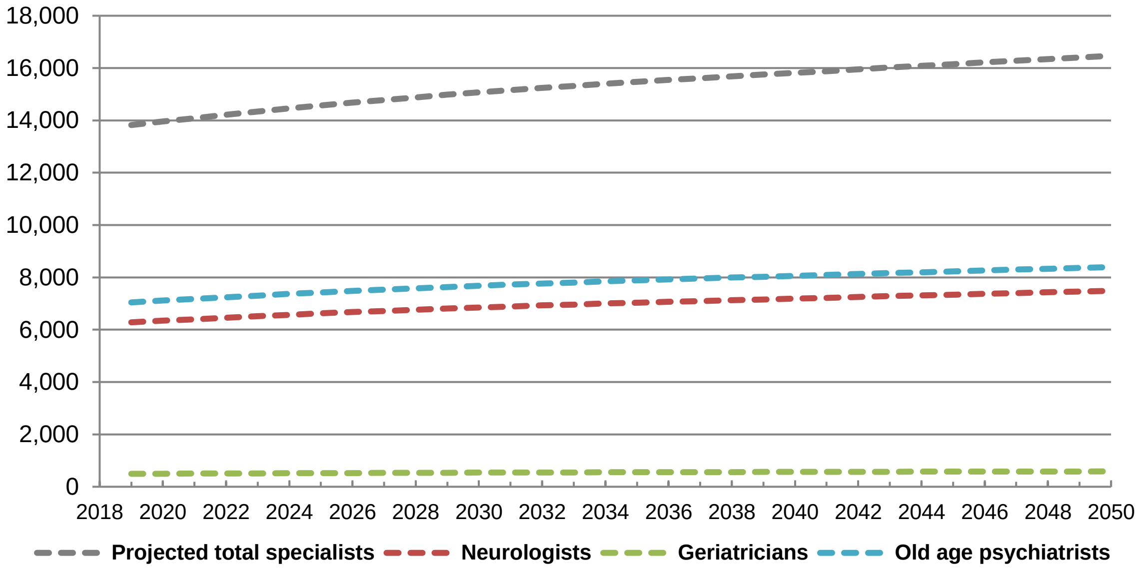
Parameter	Description	Value	Source
Population in 2017 (millions)			
Age 50+ without mild cognitive impairment (MCI) and Alzheimer's dementia	Population estimate of people 50 years and older, minus those with MCI and Alzheimer's dementia	46.892	Ministry of Health, Labour and Welfare, Japan (2017) Petersen et al. (2018), Alzheimer Association Japan (2019)
MCI	Estimated number of people with MCI based on a meta-analysis of MCI prevalence	7.058	Petersen et al. (2018)
Alzheimer's dementia	Estimated number of Alzheimer's dementia patients based on dementia prevalence and AD etiology estimates	3.027	Alzheimer's Association, Japan (2019), Montgomery et al. (2018)
Dead	Estimated mortality among the age 50+ population	1.300	Ministry of Health, Labour and Welfare, Japan (2017)
Annual mortality rates			
Age 50+ without cognitive impairment and Alzheimer's dementia	Derived from all-cause mortality rate among those without cognitive impairment, adjusted to the average age each year from 2017–2050	1.4 – 2.7%	Ministry of Health, Labour and Welfare, Japan (2017), Vassilaki et al. (2015), Rossetti et al. (2010), Spackman et al. (2012)
MCI	Derived from all-cause mortality rate, adjusted to the average age each year from 2017–2050, and adjusted for increased mortality in MCI cohorts	5.2%	Ministry of Health, Labour and Welfare, Japan (2017), Vassilaki et al. (2015)
Alzheimer's dementia	Derived from weighted average of mortality rate for patients in mild, moderate, and severe stages of Alzheimer's disease, adjusted to the average age each year from 2017–2050	14.9%	Ministry of Health, Labour and Welfare, Japan (2017), Rossetti et al. (2010), Spackman et al. (2012)
Annual disease state transition probabilities			
Probability of transitioning to MCI	Interpolated from Yesavage et al. (2002) based on the average age of the 50+ cohort for each year between 2017–2050	2.3-3.2%	Yesavage et al. (2002), Ministry of Health, Labour and Welfare, Japan (2017)
Probability of transitioning from MCI due to AD to Alzheimer's dementia *without* treatment	Derived from a meta-analysis	6.5%	Mitchell and Shiri-Feshki (2009)

Parameter	Description	Value	Source
Probability of transitioning from MCI due to AD to Alzheimer's dementia *with* treatment	Calculated as a product of a transitioning from MCI due to AD to Alzheimer's dementia and an assumed relative risk reduction of 30%	4.55%	—
Patient uptake and epidemiological parameters			
Share of the population who receive cognitive screening each year	Assumption based on expert input	60%	Liu et al. (2017)
Share of the MCI population who receive further evaluation by a dementia specialist each year	Assumption based on expert input	50%	Liu et al. (2017)
Share of MCI patients eligible for biomarker test	Assumption based on expert input	90%	Liu et al. (2017)
Share of MCI patients who have clinically relevant amyloid burden	Average of two estimates by Ong et al. (2015) and Doraiswamy et al. (2014)	45%	Ong et al. (2015); Doraiswamy et al. (2014)
Share of MCI patients with amyloid who have no contradictions for treatment	Assumption based on expert input	80%	Liu et al. (2017)
Capacity parameters			
Dementia specialists	Estimated total number of neurologists, geriatricians, and geriatric psychiatrists able to diagnose MCI due to AD	13,956 in 2020 See Figure A-1 for the projected number of specialists	Ministry of Health, Labour and Welfare, Japan (2016), Projections based on Ministry of Health, Labour and Welfare (2018) Expert input for share of specialists who practice dementia care
Average visits by a dementia specialist per year	Estimated annual number of ambulatory visits by a full-time clinical neurologist	2,860	Dall et al. (2013)
Dementia specialists fraction of excess capacity	Assumption based on expert input	5%	Liu et al. (2017)
PET scanners	Number of scanners; estimated growth in PET scanners based on projecting historical trends forward	586 in 2017 See Figure A-2 for the projected number of PET scanners	OECD (2018a)

Parameter	Description	Value	Source
CSF testing fraction of total biomarker testing by CSF and PET	Assumption based on expert input from Japan	Base case scenario: 10% Alternative scenarios 1 and 2: 25%	Expert input
Current PET scanners fraction of excess capacity	Assumption based on expert input	50%	Liu et al. (2017)
New PET scanners fraction of excess capacity	Assumption based on expert input	80%	Liu et al. (2017)
Infusions	Estimated based on the historical number of infusions of therapeutic or prophylactic substances, excluding chemotherapy and biologic response modifiers, in the U.S., and scaled to Japan based on population size and relative health care system capacity; growth rates from the U.S. analysis	See Figure A-3 for the projected infusion capacity in Japan, which is based on U.S. scaled to the Japanese population and relative health care system capacity (Table A-2)	NAMCS and NHAMCS 2011 and 2013 data from Centers for Disease Control and Prevention (last updated 2017); OECD (2018a and 2018b); Liu et al. (2017)
Current infusion centers fraction of excess capacity	Assumption based on expert input	10%	Liu et al. (2017)
New infusion centers fraction of excess capacity	Assumption based on expert input	80%	Liu et al. (2017)

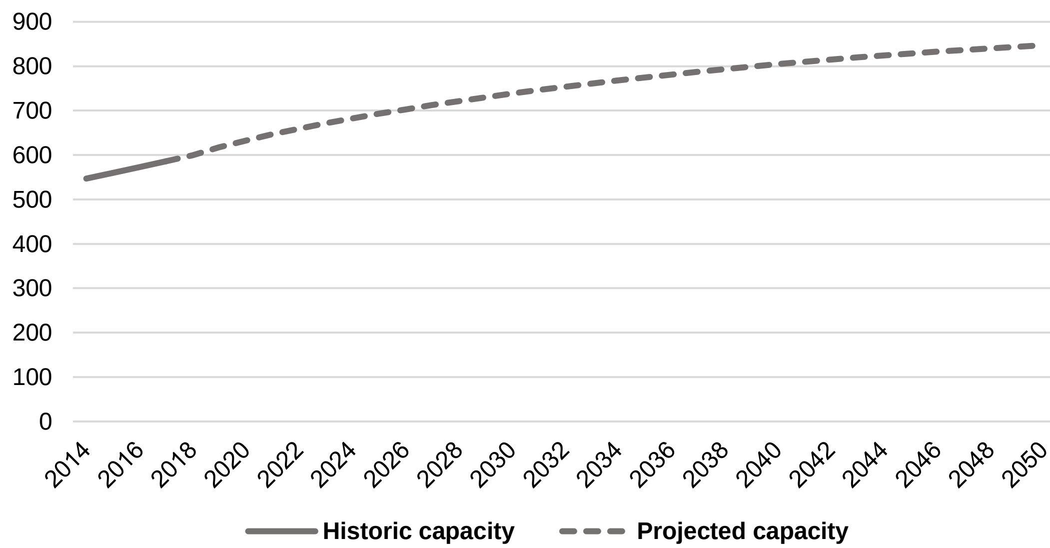
NOTE: MCI = mild cognitive impairment, AD = Alzheimer's disease, CSF = cerebrospinal fluid. Based on expert input, we assume that geriatric psychiatrists represent 40% of all psychiatrists

Figure A-1. Projected number of specialists in Japan



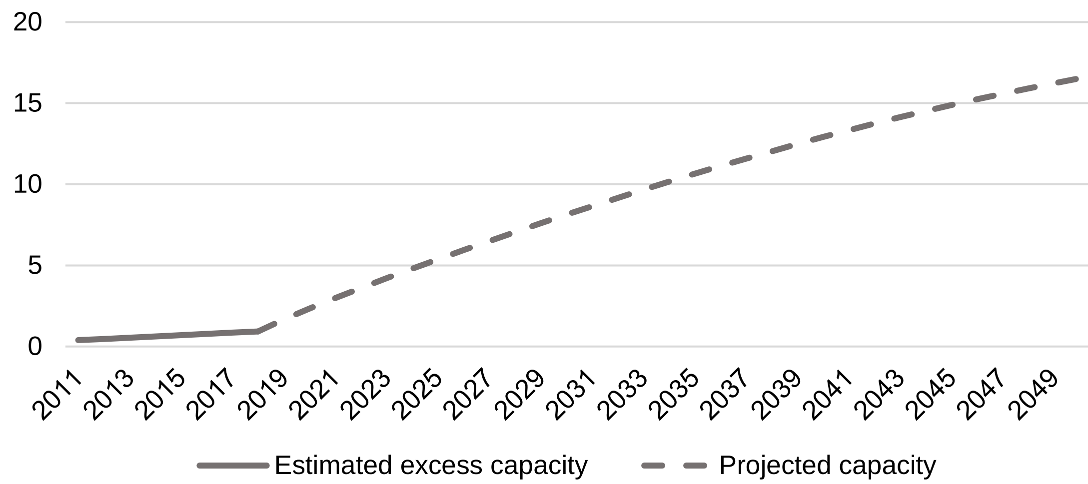
NOTES: The data shown reflect projections based on the Ministry of Health, Labour and Welfare's forecast for physician growth between 2018 and 2040 (Ministry of Health, Labour and Welfare (2018)), and our projection that carries forward the 2017-2040 growth rate of 1.26% as the annual growth rate between 2040 and 2050, adjusted to specialist count data from the Ministry of Health, Labour and Welfare, Japan (2016).

Figure A-2. Projected number of PET scanners in Japan



NOTES: The solid line reflects historical data on the number of PET scanners in Japan (OECD, 2018a) for 2014 and 2017 (2015 and 2016 are interpolated). The dotted line is our projection assuming the historical trend continues with an initial 5 percent annual growth rate and decreasing to a 0.7 percent growth rate in 2050.

Figure A-3. Projected excess capacity for infusions in Japan (millions)



NOTES: The solid line reflects historical data on the number of infusions in Japan based on our health care system capacity index relative to the number of infusions administered in the U.S. (see Table A-2), and our assumption of 10 percent excess capacity for additional infusions. The dotted line is our projection assuming the historical trend continues with a 10 percent annual growth rate initially and decreasing to a 1.3 percent growth rate in 2050, and that new infusion services could dedicate 80 percent of their capacity to an Alzheimer's disease-modifying therapy.

Table A-2. Health care system capacity index

	Hospital beds	Active nurses	MRI scanners	PET scanners	Health care system capacity index
Japan	470%	136%	84%	103%	198,3%

NOTES: Each component of the index is a relative value on per-capita basis between Japan and the United States based on OECD data (OECD, 2018a and 2018b). We average the four component values to calculate the health care system capacity index for Japan, relative to the United States at 100 percent.

References

Alzheimer's Association, Japan, "Alzheimer's and Dementia in Japan", 2019. As of July 1, 2019: https://www.alz.org/jp/dementia-alzheimers-japan.asp

Centers for Disease Control and Prevention, "Ambulatory Health Care Data: Questionnaires, Datasets, and Related Documentation," August 31, 2017. As of October 4, 2017: https://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm

Dall, T. M., M. V. Storm, R. Chakrabarti, O. Drogan, C. M. Keran, P. D. Donofrio, V. W. Henderson, H. J. Kaminski, J. C. Stevens, and T. R. Vidic, "Supply and demand analysis of the current and future US neurology workforce," *Neurology*, Vol. 81, No. 5, Jul 30, 2013, pp. 470-478. https://www.ncbi.nlm.nih.gov/pubmed/23596071

Doraiswamy, P. M., R. A. Sperling, K. Johnson, E. M. Reiman, T. Z. Wong, M. N. Sabbagh, C. H. Sadowsky, A. S. Fleisher, A. Carpenter, A. D. Joshi, M. Lu, M. Grundman, M. A. Mintun, D. M. Skovronsky, M. J. Pontecorvo, Av A. Study Group, and Av A. Study Group, "Florbetapir F 18 amyloid PET and 36-month cognitive decline: a prospective multicenter study," *Mol Psychiatry*, Vol. 19, No. 9, Sep, 2014, pp. 1044-1051. https://www.ncbi.nlm.nih.gov/pubmed/24614494

Liu, Jodi L., Jakub P. Hlávka, Richard Hillestad, and Soeren Mattke, *Assessing the Preparedness of the U.S. Health Care System Infrastructure for an Alzheimer's Treatment*, Santa Monica, CA: RAND Corporation, 2017. https://www.rand.org/pubs/research_reports/RR2272.html

Ministry of Health, Labour and Welfare, Japan, *Handbook of Health and Welfare Statistics 2017*, 2017. As of July 1, 2019: https://www.mhlw.go.jp/english/database/db-hh/1-2.html

Ministry of Health, Labour and Welfare, Japan, *Overview of surveys on doctors, dentists, and pharmacists, 2016.* As of July 1, 2019: https://www.mhlw.go.jp/toukei/saikin/hw/ishi/16/ and https://www.mhlw.go.jp/toukei/saikin/hw/ishi/16/dl/kekka_1.pdf

Ministry of Health, Labour and Welfare, Japan, *Demand and supply estimation of doctors*, 2018. As of July 1, 2019: https://www.mhlw.go.jp/file/05-Shingikai-10801000-Iseikyoku-Soumuka/0000203368.pdf

Mitchell, A. J., and M. Shiri-Feshki, "Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies," *Acta Psychiatr Scand*, Vol. 119, No. 4, Apr, 2009, pp. 252-265. https://www.ncbi.nlm.nih.gov/pubmed/19236314

Montgomery, W., Ueda, K., Jorgensen, M., Stathis, S., Cheng, Y., & Nakamura, T.. Epidemiology, associated burden, and current clinical practice for the diagnosis and management of Alzheimer's disease in Japan. *Clinicoecon Outcomes Res*, 10, 13-28, 2018. doi:10.2147/ceor.S146788. https://www.ncbi.nlm.nih.gov/pubmed/29343976

Ong, K. T., V. L. Villemagne, A. Bahar-Fuchs, F. Lamb, N. Langdon, A. M. Catafau, . . . , and C. C. Rowe, "A beta imaging with 18F-florbetaben in prodromal Alzheimer's disease: a prospective outcome study," *Journal of Neurology Neurosurgery and Psychiatry*, Vol. 86, No. 4, 2015, pp. 431-436.

Organisation for Economic Co-Operation and Development (OECD), "Health Care Resources," 2018a. As of December 7, 2018: https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_REAC

———, "Health Care Resources: Hospital beds," 2018b. As of December 7, 2018: https://stats.oecd.org/index.aspx?queryid=30183#

Petersen, R. C., O. Lopez, M. J. Armstrong, T. S. D. Getchius, M. Ganguli, D. Gloss, G. S. Gronseth, D. Marson, T. Pringsheim, G. S. Day, M. Sager, J. Stevens, and A. Rae-Grant, "Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology," *Neurology*, Vol. 90, No. 3, Jan 16, 2018, pp. 126-135. https://www.ncbi.nlm.nih.gov/pubmed/29282327

Rossetti, H. C., C. Munro Cullum, L. S. Hynan, and L. H. Lacritz, "The CERAD Neuropsychologic Battery Total Score and the progression of Alzheimer disease," *Alzheimer Dis Assoc Disord*, Vol. 24, No. 2, Apr-Jun, 2010, pp. 138-142. https://www.ncbi.nlm.nih.gov/pubmed/20505431

Spackman, D. E., S. Kadiyala, P. J. Neumann, D. L. Veenstra, and S. D. Sullivan, "Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS," *Curr Alzheimer Res*, Vol. 9, No. 9, Nov, 2012, pp. 1050-1058. https://www.ncbi.nlm.nih.gov/pubmed/22175655

Vassilaki, M., R. H. Cha, J. A. Aakre, T. M. Therneau, Y. E. Geda, M. M. Mielke, D. S. Knopman, R. C. Petersen, and R. O. Roberts, "Mortality in mild cognitive impairment varies by subtype, sex, and lifestyle factors: the Mayo Clinic Study of Aging," *J Alzheimers Dis*, Vol. 45, No. 4, 2015, pp. 1237-1245. https://www.ncbi.nlm.nih.gov/pubmed/25697699

Yesavage, J. A., R. O'Hara, H. Kraemer, A. Noda, J. L. Taylor, S. Ferris, M. C. Gely-Nargeot, A. Rosen, L. Friedman, J. Sheikh, and C. Derouesne, "Modeling the prevalence and incidence of Alzheimer's disease and mild cognitive impairment," *J Psychiatr Res*, Vol. 36, No. 5, Sep-Oct, 2002, pp. 281-286. https://www.ncbi.nlm.nih.gov/pubmed/12127595