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IMPLICATIONS OF AN ALZHEIMER'S TREATMENT FOR ORGANIZATION AND PAYMENT OF MEDICAL PRACTICES IN BRAZIL

Technical Report

Soeren Mattke, Otelo Corrêa dos Santos Filho and Mo Wang

ABOUT THIS REPORT

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

A draft version of this report was reviewed and discussed by a multidisciplinary expert panel, who also provided input on the assumptions used for the simulation. The participants were Elaine Fernandes Mateus, João Paulo Reis Neto, Dr. Leonardo Cruz de Souza, Dr. Rodrigo Rizek Schultz and Roney Pereira Pinto. Their willingness to be acknowledged does not imply agreement with the report's assumptions and conclusions

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OVERVIEW AND OBJECTIVES OF THE STUDY

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Alzheimer's disease is a progressive neurodegenerative disorder that leads to loss of cognitive functions and ultimately to dementia and care dependency¹. The exact pathophysiology remains unknown, but disease is characterized by two hallmark pathologies: β -amyloid plaque deposition and neurofibrillary tangles of hyperphosphorylated tau in the brain, which are believed to lead to loss of nerve cells and thereby cognitive decline². It has been established that the pathophysiologic changes precede cognitive decline by years, even decades, and this realization has led to defining the disease based on those changes rather than the resulting symptoms, the so-called A/T/N (amyloid, tau, neurodegeneration) Research Framework³.

The improved understanding of the disease biology has informed the development of treatments that mainly attempt to decrease the burden of amyloid and tau in the brain, and after decades of failed clinical trials, aducanumab, the first such treatment in decades was approved in the U.S. in June 2021 and might be approved in other countries in the near future. This and other treatments in clinical trials are used in early stages of the disease, mild cognitive impairment (MCI) or mild dementia to prevent the progression to more advanced dementia stages.

This preventive paradigm, however, creates a challenge for healthcare systems, as a large number of patients with mild or no symptoms have to go through a complex diagnostic process, which involves neurocognitive evaluation, advanced imaging and biomarker testing. Because of the large pool of prevalent cases, most of whom have never been formally diagnosed, demand for services is likely to outstrip capacity, and as the COVID-19 pandemic has taught us, even the most sophisticated healthcare systems can be overwhelmed by sudden surges in the demand for services. The arrival of a disease-modifying treatment for Alzheimer's disease may result in a similar scenario, in which current health system capacity is insufficient to cope with the expected influx of patients, who will seek diagnosis and treatment. Unlike the COVID-19 pandemic, there is still time for healthcare systems to prepare to ensure the needed capacity is in place to provide access to new treatments when they arrive. Time, however, is limited.

The challenge is that medical care for dementia is mainly focused on diagnosis and counseling at the moment. Patients may undergo neurocognitive testing to document and quantify the degree of impairment and rarely imaging and biomarker testing to identify the etiology. With historic the lack of disease-modifying treatment options, physicians are typically confined to managing symptoms and counseling patients and their families on the expected course of their disease and the consequences for their lives.

At the same time, the complexities of determining treatment eligibility and monitoring treatment response and side effects mean that Alzheimer's care will likely have to remain in the hands of specialists. Thus, the advent of a disease-modifying treatment for Alzheimer's disease will meet an unprepared healthcare delivery system. As we had shown in recent reports, the limited capacity of memory services will create substantial bottlenecks for treatment delivery even in the G7 countries⁴⁻⁶.

This project builds on this earlier work and estimates supply and demand of diagnostic services to identify patients, who are potentially eligible for a disease-modifying treatment, in Brazil and analyzes how practice organization and payment models could be changed to accommodate the substantial increase in demand that the treatment will bring about.

TECHNICAL APPROACH

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The study used a combination of desk research and expert interviews to describe the current patient journey in Brazil, to capture obstacles to access that result from this journey and to identify potential changes to payment models and care delivery that might improve access. Desk research covered the websites of national and multilateral organizations that publish health system capacity data, advocacy organizations, payers and specialty societies as well as research published in peer-reviewed journals and technical reports. A total of 12 expert interviews were held with policy experts, clinical and health services researchers, clinicians and payer representatives in Brazil using a semi-structured interview protocol. A multidisciplinary group of five experts reviewed and discussed a draft version of the report and provided input to the final version. The data retrieved in this search were used in our existing capacity simulation model to predict wait times and queues under different scenarios.

We developed a stylized patient journey (*figure 1*) to capture the current pathway which dementia patients take through identification based on screening or memory complaints, evaluation with neurocognitive testing, imaging, and biomarkers and then finally diagnosis and treatment delivery.

Figure 1: Stylized patient journey



For each step of the patient journey, we analyze for Brazil the status quo regarding coverage, capacity, and capabilities:

COVERAGE

- Are the services under each step currently covered?
- Are payment levels adequate to ensure actual delivery of the service?

CAPACITY

- Is current capacity to deliver services sufficient to meet expected demand?
- Would the capacity actually be devoted to the respective care step, given prevailing incentives and organization of care?

CAPABILITIES

- Do providers have appropriate training, tools and technology to perform the required services?

We comment on possible changes to coverage, capacity and capabilities that might be required to reduce the obstacles to access to a disease-modifying treatment for Alzheimer's disease as well as memory care in general.

RESULTS

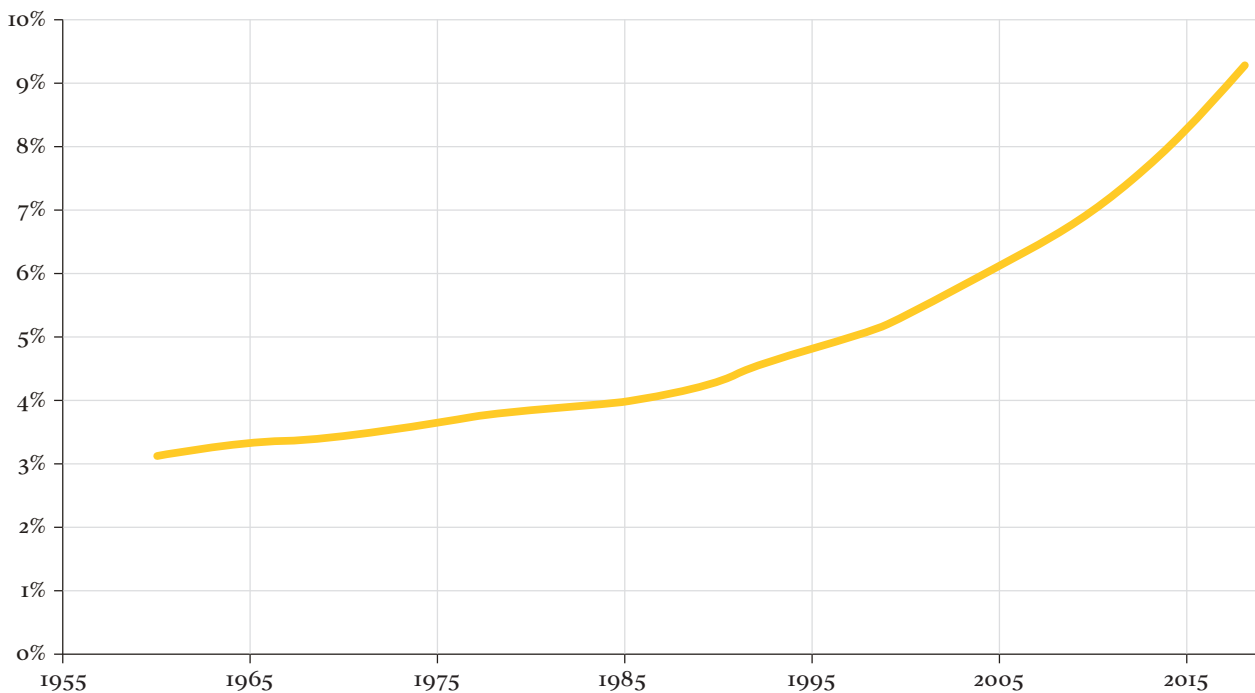
RESULTS

HEALTH SYSTEM OVERVIEW

Overview of organization and governance

Brazil is a federal state that covers close to half of the South American continent with substantial diversity in geography and economic development. Its population of around 210 million makes Brazil the sixth most populous country on earth. It is the ninth largest world economy and a member of the G20 group. With a proportion of individuals aged 65 and older of nine percent in 2019⁷, Brazil remains a relatively young country compared to G7 countries, like Germany (21.4%) and Japan (28.2%) or even China (12.6%). However, the twin effect of increased longevity and falling fertility rates means that Brazil – like other fast-growing economies – is ageing rapidly with substantial implications for the burden of ageing-related diseases, like dementia (*figure 2*).

Figure 2: Trend in share of population aged 65 and older in Brazil



Source: The World Bank⁷

The foundation of today’s healthcare system in Brazil can be found in the transition to democracy after 20 years of military rule. In 1988, a constitutional right to medical care was established that led to the foundation of the National Public Healthcare System (SUS – Sistema Único de Saúde) as institution to organize and finance universal and free access to care for all legal residents of Brazil⁸. Its guiding principles are called Universalization, meaning that all aspects of care ought to be available, Equity, meaning that equal care is accessible to everyone, and Integrality, meaning “the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community”⁹. As a consequence, medical services under the SUS are provided at no cost to patients and most prescription drugs are either free or heavily subsidized¹⁰.

The SUS is based on a devolved model under which the federal Ministry of Health defines a policy framework for funding, planning, standard setting, oversight and evaluation¹⁰. It also provides the health IT infrastructure for the country. The Ministry is only involved in care provision for selected strategic areas, such as complex oncology care, and for financing the High-Cost Drug Program which is explained in detail later in the report.

The states are in charge of organization of care in their territory under this federal framework¹¹. An important responsibility is capacity planning and workforce development to meet current and projected needs of their residents. States oversee and evaluate care delivery but – like the federal ministry – only provide medical care, if services are not delivered at the municipal level, such as in oncology and cardiac procedures¹¹. States are, however, responsible for public health tasks, such as health surveillance and epidemiologic trends.

The 5,570 municipalities are responsible for the provision of primary care as well as ensuring access to specialty, hospital, and emergency services, including capacity planning and capital investment. An important characteristic is the participatory decision making. At the government level, bipartite and tripartite commissions allow for shared decisions between the three jurisdictional levels of the Federation: The Union, the States and the Municipalities, and civil society is involved in the formulation of strategy, evaluation and accountability through Councils and Health Conferences⁸. Capital investment decisions and funding are the responsibility of the jurisdiction that operates a facility.

A separate private system financed by insurance companies exists alongside the SUS that covers around a quarter of the population or around 47 million people. It is referred to as the supplemental system, even though it rather fits the definition of a duplicative system in the OECD taxonomy¹², as members of these insurance plans remain eligible for SUS services. Private insurance coverage is commonly provided as workplace benefit. In addition, a small, wealthy subset of the population purchases care directly from private facilities.

Financing healthcare

According to OECD data, Brazil spends a relatively high proportion of its GDP (9.4%) on healthcare, which is close to high-income countries like the U.K. (10.0%) and Spain (9.0%), and higher than other middle-income countries, like China (5.0%) and Turkey (4.4%). However, the share of government spending is only 43 percent compared to 78 percent in the U.K., 71 percent in Spain, 77 percent in Turkey and 58 percent in China.

The SUS is jointly financed by the Ministry of Health, States and Municipalities. According to a constitutional amendment, states must contribute a minimum of 12 percent and municipalities 15 percent of their revenues to healthcare. While the federal government is the main funder of the SUS, contributing half of the funding and redistributing funds from richer to poorer states, the size of the federal contribution depends on economic conditions and the political climate⁸ and its share has declined, placing greater burden on municipalities. The first federal source of revenue constitutes of a variety of taxes on sales, corporate profits, property, etc. As those taxes are not earmarked for the SUS, funding needs to compete with other demands on the budget, in particular debt servicing. A deep recession starting in 2014 led to loss of revenue, rising public debt and the introduction of austerity policies¹⁰ that capped federal contributions to the SUS at the inflation-adjusted 2017 spending⁸. The second source of federal funds are payroll contributions from employers and employees to the INSS (National Institute of Social Security), where SUS funding competes with other obligations, like pensions, unemployment benefits and disability payments⁸. As a consequence of a combination of growing needs and constrained resources, the SUS is considered substantially underfunded¹⁰.

The private sector consists of traditional health insurers and private health companies, which unite financing and care delivery. Premiums are typically paid by private and public employers, and some employers are self-insured. Insurance premiums are tax-deductible for employers, as are personal expenditures on healthcare services. Together with a tax exemption for not-for-profit providers, it is estimated that subsidies for the private sector amount to about 30% of federal expenditure on healthcare⁸. The National Supplemental Health Agency (ANS) regulates the private sector and, for example, enforces mandates to cover preexisting conditions and to not impose limits on coverage and defines the minimum mandatory coverage of drugs and procedures⁸. It also sets standards for wait times for elective specialty care (*table 1*).

Table 1: Maximum permitted wait times for elective services in private sector

Service	Maximum permitted wait (working days)
Basic consultation - pediatrics, medical clinic, general surgery, gynecology and obstetrics	7
Consultation with other specialists	14
Diagnostic lab services	3
Other diagnostic services, such as imaging	10
Day hospital care	10
Elective inpatient care	21
High complexity procedures	21

Source:²¹

If an insurer cannot meet those standards, the patient can file a complaint with ANS, which will investigate and may impose a penalty. However, ANS will take available capacity relative to population needs into account, when evaluating complaints. In contrast to services provided by the SUS, which are free to holders of an insurance card, co-payments are common and variable under private insurance with no legal limit to maximum annual contributions¹⁰.

Due to the long wait times for consultations with specialists and diagnostic tests, it is relatively common, especially in poor populations, to pay for medical care out of pocket, especially in popular clinics where the consultation and tests are paid in cash. According to the 2019 IBGE Health National Research (Pesquisa Nacional de Saúde – IBGE 2019), the largest share of people (46.8%) named the Family Health Unit as their primary source of care. Private offices or clinics (out of pocket) were named by 22.9 percent of the people, and the Public Emergency Care Units (UPAs), emergency room or emergency of a public hospital by for 14.1 percent, which contributes to the high share of out-of-pocket expenditures mentioned above²².

Healthcare delivery and payment

The public care delivery system is heavily reliant on primary care, which is mostly provided in municipally owned facilities with salaried staff. Different care models exist from traditional primary care offices to primary health teams that were introduced under the Family Health Program, which are staffed by a physician and clinical and non-clinical support personnel⁸. These teams have a panel of 2,000 to 4,000 patients²³ and offer a broad range of services, including health promotion and chronic disease management, and are now serving close to two-thirds of the population⁸. Primary care physicians serve as gatekeepers and a referral is necessary for specialist consultations and elective admissions and procedures in the public system, whereas privately insured Brazilians may see a specialist of their choice in their plan's network without referral. Delivery of primary care under the private health insurance system is a recent development, as most privately insured Brazilians still see SUS primary care clinicians, if they want to obtain primary care services.

While the SUS operates selected federal, state and municipal units, specialty care is largely provided by the not-for-profit and for-profit hospitals and other facilities, with the exception of highly complex care, such as oncology, transplantation and dialysis. Municipalities can establish partnerships with other municipalities to achieve the scale necessary for these complex services. The SUS contracts for most specialized services at regulated rates in private establishments, mainly university and philanthropic entities, and those facilities must allocate a defined service volume to SUS patients under those contracts. Conversely, even specialists employed in public facilities may see privately insured patients²⁴.

The wait time for procedures, exams and consultations in the private sector is defined by ANS determination, as mentioned above. However, wait times for elective specialist consultations and procedures for people covered by the SUS may be substantial²⁵. A recent study analyzed wait times for specialist appointments in the State of Espírito Santo and found an increase from an average of 419 days in 2014 to 1077 days in 2016²⁶. Similarly, a 2010 analysis of the Federal Audit Tribunal²⁷ found substantial delays in access to cancer treatment that contributed to 60 percent of patients being diagnosed at advanced stages. The median waiting times for chemotherapy and radiation were 76.3 days and 113.4 days, respectively and only 35.6 percent and 15.9 percent, respectively, of patients underwent treatment within 30 days of diagnosis. A 2011 study in Rio Grande do Sul suggested an unmet need of nearly 500,000 consultations or procedures for the state's population of 10.6 million people²⁸. A 2019 survey by the Health Commission of the Legislative Assembly of Mato Grosso stated that the average time for a patient to be seen in the public system for specialist consultations and procedures was 493 days²⁹. We were not able to identify systematically collected data for memory care related services in SUS but were told by the experts interviewed for the study that wait times can go up to two years with substantial variability by region and socioeconomic status.

Social care delivery and payment

In-home social care is mostly provided by family caregivers in Brazil, predominately spouses and daughters who are physically and emotionally close to the patient¹³. In a recent study, most caregivers were women (64.1%), white (56.3%), with low schooling (15.6% were illiterate and 40.6% had incomplete elementary school), and Catholic (71.9%). Most patients were over 80 years old (54.7%), lived alone (68.7%), and 37.5% lived with their daughter, 31.3% with a partner, 25% with their son or other relative and 6.2% alone. (Roger Flores Cecon, Luiza Vieira et al. 2021) Caregiving exacts a heavy burden, as support from public protection services is limited and programs for developing skills are lacking. Caregivers suffer from loss of personal time and space, burnout and other mental and physical health issues, loss or reduction of employment, and withdrawal from their social and affective needs.

Primary health teams provide some support for social care through their home visit program, which we describe in detail later¹⁴. Wealthier residents also have private-pay options such as paid caregivers and private day care centers, and a few charitable organizations offer community-based or institutional social care. The SUS covers or provides some public long-term care services, such as nursing homes and day care centers, under a means-tested benefit that takes personal and family income and assets into account¹⁵. However, as of 2009 only 30% of the municipalities - mostly in the southeastern region of the country had public long-term care institutions¹⁶. Over half (57%) of the 1451 long-term care facilities that were operating in 2019 data were located in the southeastern region¹⁷.

With a demographic shift to an ageing population, declining fertility rates and increased workforce participation for women, the traditional reliance on family caregiver has become less sustainable, leading to calls for increased professional caregiving¹⁸ and better social protection¹⁹. Others have called for increased efforts to train and support family caregivers²⁰.

DEMENTIA PLANNING

While the 2015 Pan-American Health Organization (PAHO) Regional Plan of Action on Dementia urges member countries to develop dementia plans³⁰, so far only Argentina, Chile, Costa Rica and Mexico have done so³¹. In the absence of a formal plan, memory care in Brazil is planned and governed as part of general health system coordination. In addition, specific legal protections are awarded to the elderly in the 1988 Constitution, which established Councils for the Defense of the Rights of the Elderly at Municipal, State and Federal levels, and the 2006 National Health Policy for the Elderly (Ordinance 2528/GM of the Ministry of Health). On October 1, 2003, Law No. 10,741, of the Elderly Statute, was signed, which states that family, governments, and society must support this social group. Similarly, state laws and measures aim to protect older adults, provide subsidies that guarantee their community participation, defend their dignity, care for their well-being, and ensure their right to life. However, the State's provision of services is largely limited to medical care and assigns the commitment to social care to the family.

The federal Ministry of Health has issued guidelines³² for diagnosis and pharmacologic and non-pharmacologic management of Alzheimer's disease that are binding for SUS facilities and included donepezil, memantine, rivastigmine and galantamine in the list of essential medicines for patients with diagnosed Alzheimer's disease, which means that they are available free of charge³³. Several professional associations have also developed clinical guidelines for memory care, the Brazilian Academy of Neurology has published guidelines for diagnostic evaluation³⁴ and management of cognitive decline (Vale, Corrêa Neto et al. 2011) and psychological and behavioral symptoms of dementia³⁵. The Brazilian Society of Geriatrics and Gerontology published in 2011 the "Clinical guidelines for the diagnosis and treatment of Alzheimer's disease"³⁶.

For the private system, ANS has issued general guidelines for elder care, the "well-cared elderly program" (Idoso bem cuidado), with recommendations for private insurers in 2017²¹. The guidelines recommend a shift to preventive and integrated care to avoid costly exacerbations of chronic diseases and a shift towards performance-based payments. Several pilot projects have been launched under this program.

In a recent survey of Argentina, Brazil, China, India and Saudi Arabia, Brazil scored the lowest on a dementia preparedness index because of low ratings for strategy and commitment, care standards and the built environment³⁷.

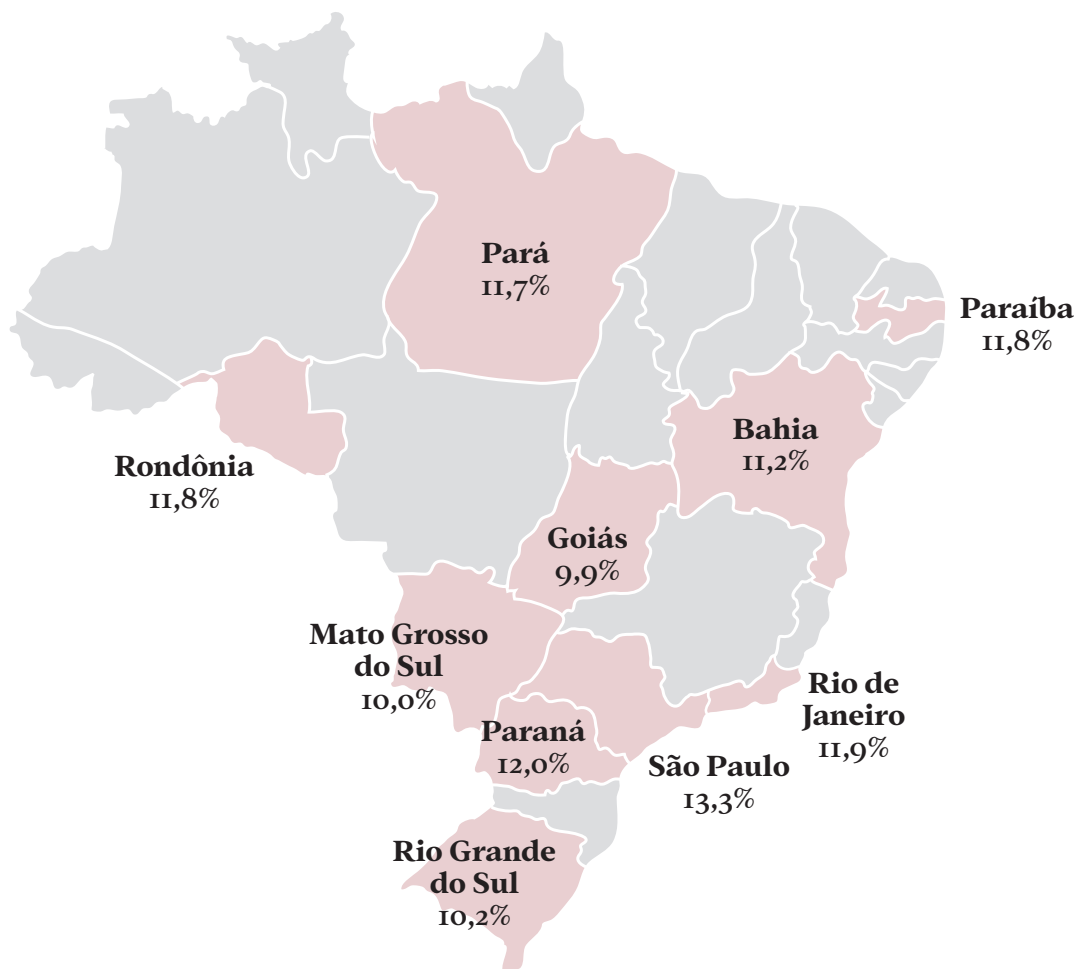
Febraz, the Federation of Brazilian Alzheimer's Association, represents the interests of patients with dementia and their families in the policy dialog with municipal, state, and federal managers and advocates for compliance with the above-mentioned laws.

DEMENTIA IMPACT

Based on a longitudinal study by Godinho et al the prevalence of MCI in Brazil is 6.1 percent in the population of 60 years and older³⁸. Chaimowicz and Burdorf carried out a systematic review of Brazilian studies of dementia prevalence and derived a combined estimate between 7.1 and 8.3 percent among subjects aged 65 years and older³⁹. Importantly, dementia prevalence was over twice as high in illiterate compared to literate subjects, which may explain a relatively high rate in younger cohorts⁴⁰ as well as the disproportionate burden in socioeconomically disadvantaged groups⁴¹.

Nitrini estimated an incidence of dementia of 13.8 cases per 1,000 person-years⁴². Thus, around 1.25 million Brazilians would live with MCI and around 1.5 million with dementia based on those sources. With population ageing, the number of Brazilians with dementia is projected to triple by 2050⁴³. The estimated dementia burden is consistent with an estimate released by the Global Burden of Disease program of 1,691,024 (1,440,967 to 1,983,529) cases⁴⁴. The Global Burden of Disease 2016 data⁴⁵ show substantial differences in dementia prevalence by state (*figure 3*), from around 10 percent in Goiás and Rio Grande Do Sul to 13.3 percent in Sao Paulo, which also had the largest increase in prevalence of 2.3 percentage points since 2000.

Figure 3: Dementia prevalence in selected Brazilian provinces (2016)



These estimates for dementia prevalence suggest that published estimates for MCI prevalence of around six percent⁴⁶ are almost certainly too low as the trajectory of the disease implies that MCI prevalence should be higher than dementia prevalence. Applying prevalence estimates from a recent meta-analysis of global studies⁴⁷ would suggest around 5 million cases of MCI for 2022 or a prevalence of 8.57 percent among subjects aged 50 years and older (*table 2*).

Table 2: Projected burden of MCI in Brazil, 2022

Age Group	MCI Cases	Population	MCI Prevalence
50-54	385,856	12,861,867	3.0%
55-59	502,782	11,692,613	4.3%
60-64	667,129	9,957,156	6.7%
65-69	663,876	7,903,288	8.4%
70-74	593,485	5,876,091	10.1%
75-79	585,942	3,959,070	14.8%
80-84	633,454	2,513,706	25.2%
85+	858,955	2,284,454	37.6%
Sum	4,891,480	57,048,245	8.57%

This increased disease burden means that dementia is now the sixth most common cause of mortality in both women and men over the age of 70, and the second and fourth, respectively, most common cause of disability⁴⁸. While age-standardized mortality rates are stable, age-adjusted prevalence of dementia has increased by 5.2 percent from 1990 to 2016⁴⁴. Ferriti et al. used a standardized instrument to collect data on the economic impact of dementia¹³. They estimated total direct and indirect costs of \$1,406 per case-month (in 2016 USD), of which over 80 percent was due to the effect on family caregivers. Applied to the overall number of cases, the economic impact of dementia would be around \$25 billion per year in Brazil.

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SCREENING FOR COGNITIVE DECLINE

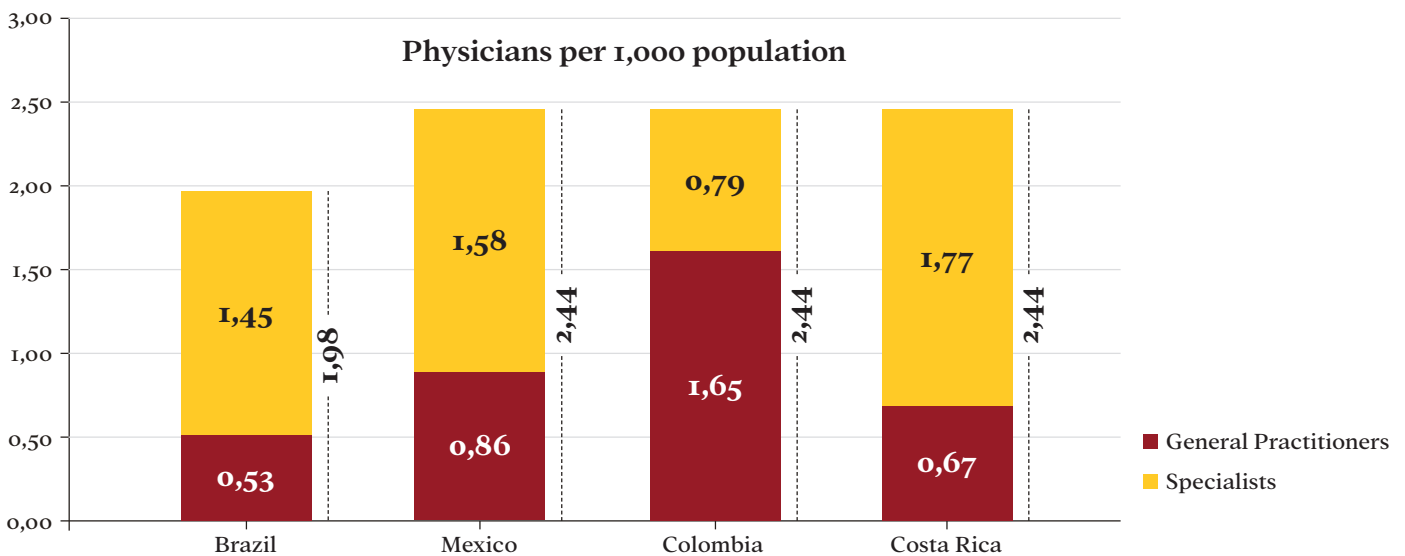
Opportunistic screening in the form of a cognitive assessment when elderly patients come in for a primary care visit is recommended in a guideline issued by the federal Ministry of Health, but systematic screening is currently not recommended or covered³².

The Alzheimer Society is in discussion with Congress about bill for the creation of the National Dementia Plan, covering prevention, early diagnosis and treatment activities and the guidance given to long-term institutions and those who care for patients at home⁴⁹. For the public sector, a population screening program for cognitive decline could be created and implemented by the Ministry of Health through a directive or through a bill enacted by parliament and implemented by the Ministry of Health. Private sector insurance companies have discretion on which screening programs to offer or can be compelled by ANS to offer them, but they frequently follow the public sector’s guidance.

CASE FINDING

Further assessment of a subjective memory complaints or patients with suspected memory decline during an office visit are covered in the public and private systems. Patients will typically present in primary care settings, which are usually accessible. However, Brazil has a low number of primary care physicians relative to population compared to other Latin American countries, even though its absolute physician density is not much lower. (figure 4) As a consequence, wait times for elective consultations are common, and privately insured patients may reportedly skip the queue. The above-described health team approach helps to ameliorate the low number of physicians, as tasks are shifted to less-trained clinical and nonclinical personnel. However, the high degree of task shifting today means that there are limits to adding additional responsibilities to family health teams.

Figure 4: Density of Physicians in Latin American countries



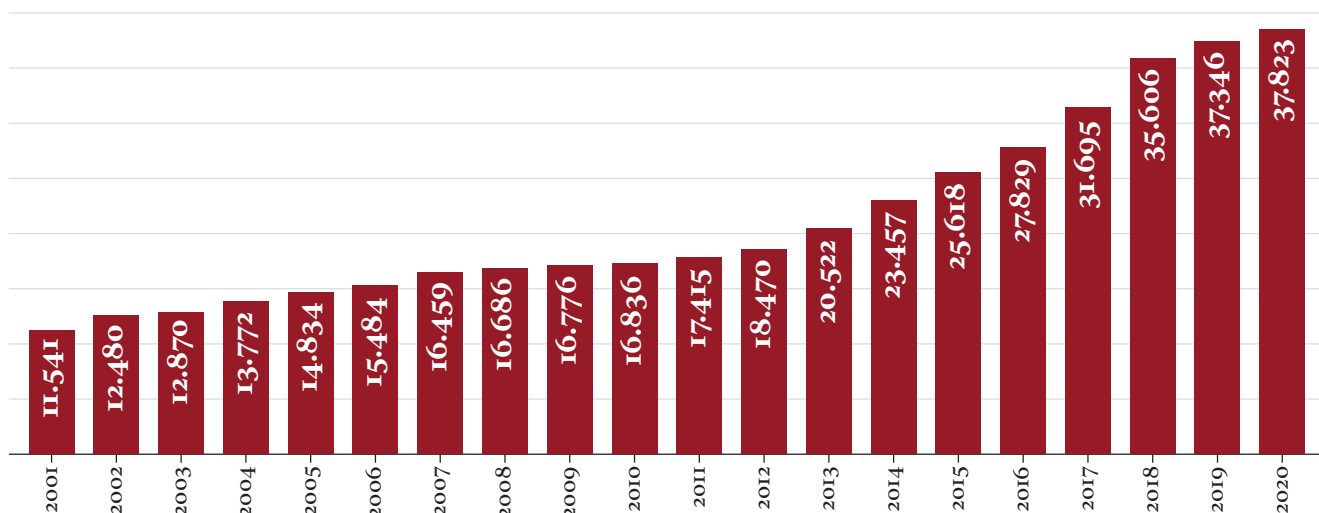
Source: OECD Health Data 2020, data for 2019 or most recent

The reasons for the comparatively low share of primary care physicians are manifold. Brazil started increasing both the number of medical schools and slots in those schools dramatically in this century. The number of schools grew from 81 in 2000 to 357 in 2020 that together offered 37,823 undergraduate vacancies, over twice of the number in 2010 (figure 5). However, the increase was predominately in private schools, which now account for over half of enrollment⁵⁰. The combination of higher tuition and better earnings prospects in specialty medicine, in particular procedural specialties, contributes to limited interest in careers in primary care. According to a 2020 survey, only 3.7 percent of medical students expressed such an interest⁵¹. Thus, an increase in overall physician density did not increase the density of primary care physicians, although the 2013 More Doctors Law is trying to correct the imbalance⁵². In 2019, it was replaced by the “Doctors for Brazil” program,

and today it has 15,120 doctors distributed throughout the country. The Program has an educational character of improvement, through activities teaching-service. When entering the Mais Médicos para Brasil project, the physician is enrolled in a training program called Specialization in Primary Care that is offered by Federal Education Institutions of the University Network Open Health System (UNASUS) with a curriculum that is developed and monitored by experienced Brazilian physicians. Trainee physicians are proctored during the program.

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Figure 5: Evolution of the available undergraduate medical school training slots



Because of limited training of primary care clinicians, according to expert input and an expert panel workshop⁵³, symptoms are often discounted as sign of normal ageing with no follow-up. A 2011 study by Jancinto et al. reviewed the historic medical records of patients, who were formally diagnosed with cognitive impairment by specialists, and found memory concerns were documented in only 16% of patients⁵⁴. Another study estimated a median delay of 1.5 years between onset of dementia symptoms and diagnosis, mostly because decline was considered normal or failure to diagnose⁵⁵. Stigma and the limited sensitivity of brief cognitive tests in persons with limited education compound the problem of delayed and missed diagnoses⁵³. Even if memory complaints are assessed, the extent of work-up in primary care and referral decisions reportedly vary greatly, as there are no recommended clinical pathways at this point. While all elective specialist appointments under the SUS require a referral, the process will vary in the private sector depending on the terms of a policy.

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COGNITIVE TESTING

Patients with suspected cognitive decline may be referred to formal neurocognitive testing, which is a covered service both in the public and in the private system. There is no prescribed or recommended process for initial work-up prior to specialist referral nor to which type of specialist a patient would be referred. We were told that some patients may even be referred to a cardiologist or endocrinologist first to investigate cardiovascular or metabolic causes of cognitive impairment before seeing a dementia specialist, such as a neurologist, geriatric psychiatrist, or geriatrician. While national guidelines may define standard referral pathways for SUS patients, privately insured patients may (and often do) see specialists of their choice.

A network of memory clinics, which are practice or hospital-based units that focus exclusively on evaluation and management of cognitive decline, has yet to emerge in Brazil. Such clinics, which can be led by primary care clinicians or specialists, have become very popular in other countries, as they allow for a higher degree of process standardization and task shifting, increasing efficiency of the practice⁵⁶. Several public universities have established so-called memory centers, which combine clinical care – usually for difficult cases –, research and training⁵⁷.

Patients in the SUS need a referral to a specific specialist, whereas privately insured patients may see any specialist in their network without referral. Wait times are common in the public system, reportedly up to two years with substantial regional variation. Our experts also remarked that specialists' evaluation of suspected cognitive decline varies substantially by specialty and even within specialties, with geriatricians having the highest degree of standardization.

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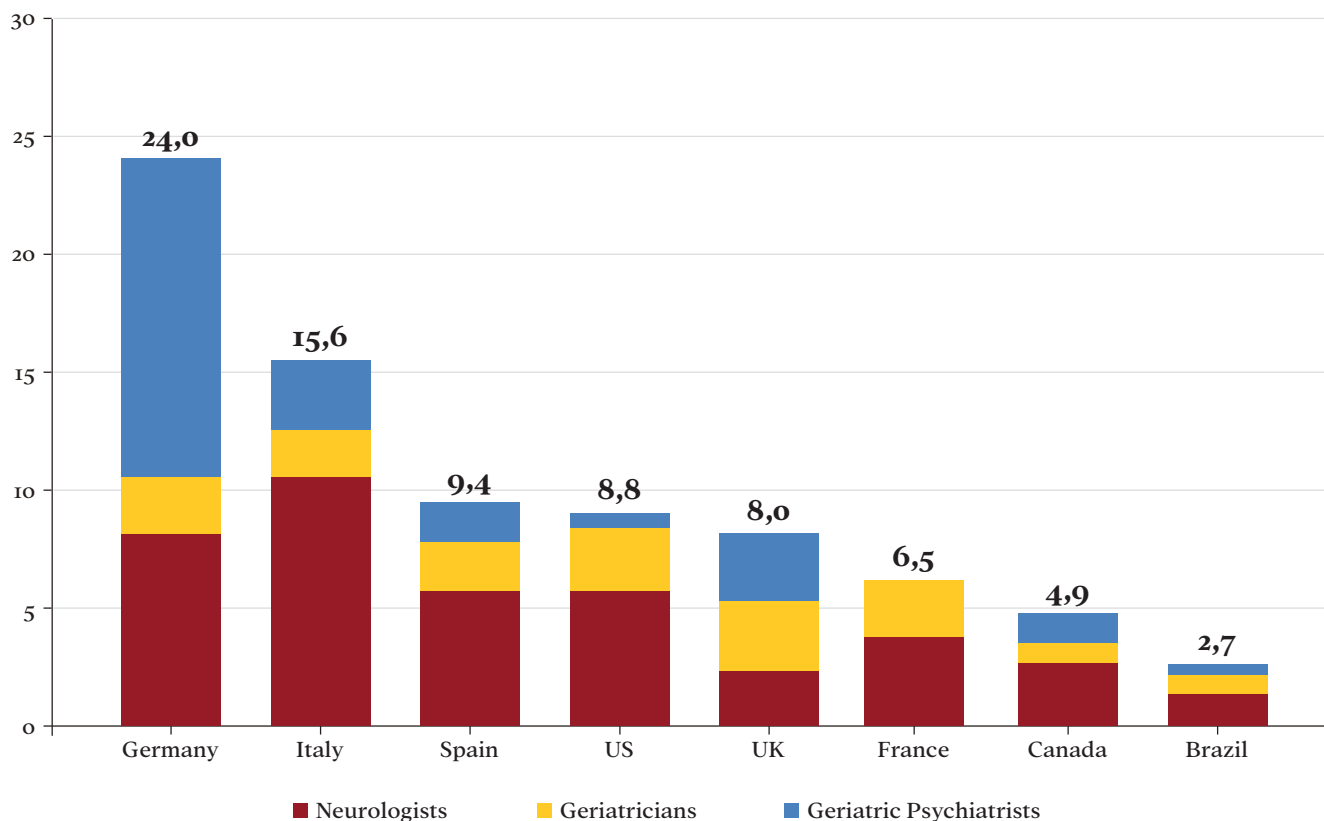
In 2020, 11,977 psychiatrists, 5,779 neurologists and 2,143 geriatricians were licensed to practice in Brazil and our experts estimated that 10, 50, and 80 percent, respectively, were prepared to evaluate and treat dementia patients, resulting in 5,802 dementia specialists, a number that is projected to grow to 15,430 by 2050 using a linear projection of historic growth trends (table 3).

Table 3: Estimated number of dementia specialists in Brazil

	Neurologists	Geriatricians	Geriatric Psychiatrists	All
2020	2,890	1,714	1,198	5,802
2030	4,433	2,747	1,715	8,895
2040	6,050	3,832	2,279	12,162
2050	7,668	4,918	2,844	15,430

These numbers mean that, in spite of its high ratio of specialists to generalists, Brazil has a comparatively low number of dementia specialist relative to its population (*figure 6*) because specialist training focused on operative and interventional specialties for a long time.

Figure 6: Number of dementia specialists per 100,000 capita in Brazil compared to other countries



BIOMARKER TESTING

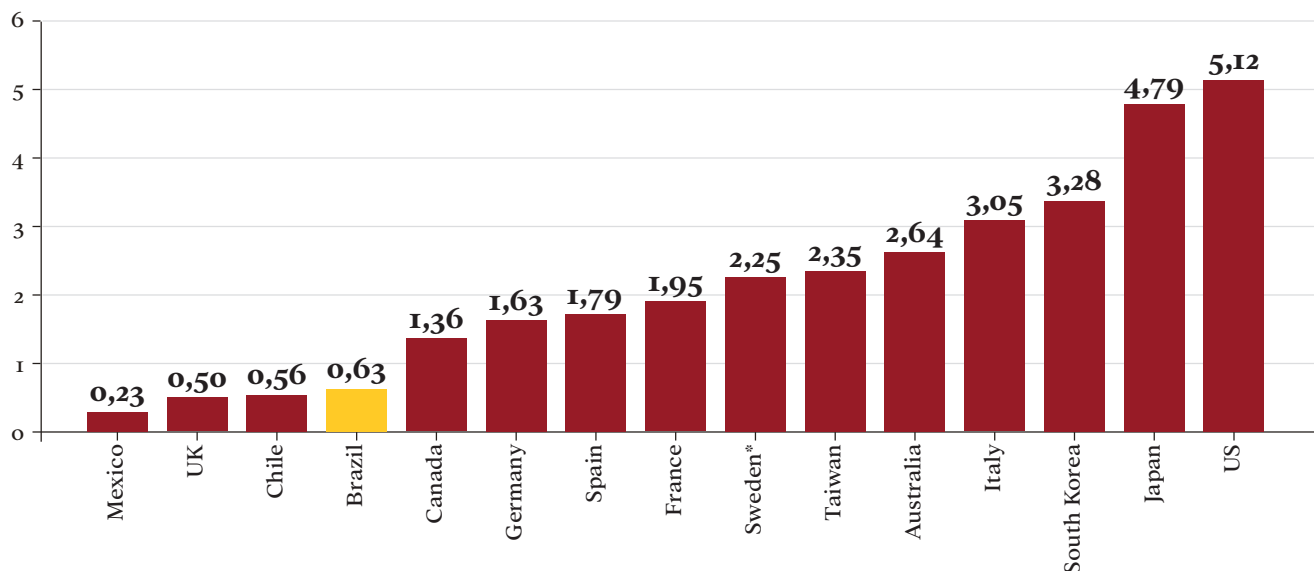
As mentioned above, a formal diagnosis of Alzheimer’s disease requires confirmation of the underlying pathophysiology with biomarker testing, which can currently be conducted with a PET scan or CSF testing³.

A CSF test for amyloid is approved but not covered for routine clinical use under SUS or private insurance. The beta-amyloid ligands for PET scanning are not approved for clinical use in Brazil and therefore only available as part of clinical studies. In addition, SUS currently covers PET scans only for selected cancer types for cost reasons, and, according to our experts, budget constraints make it unlikely that large scale use would be approved to investigate eligibility for a disease-modifying treatment, as most imaging facilities are privately owned, and municipalities have to pay for scans at negotiated rates.

Physicians may request authorization for biomarker testing in unusual cases, such as early onset dementia or rapid progression, or as part of clinical studies, or patients may pay out-of-pocket. However, according to our experts, requests for coverage are commonly declined because of concerns about cost, especially for patients in the public system.

As *figure 7* shows, Brazil has a similar number of PET scanners per 1 million population as the U.K. and Chile and almost three times as many as Mexico. We were unable to identify utilization data, as private insurers do not report number of diagnostic exams. However, utilization data reported by SUS range from four to 2,218 scans per device and year, suggesting substantial free capacity.

Figure 7: Density of PET Scanners



As expected, PET scanners (*figure 8*) and cyclotrons (*figure 9*) to produce the amyloid tracers are mostly located in the more populous and wealthy south of the country and usually only in the largest cities, leaving many regions and even states without geographic access.

Figure 8: Location of PET scanners in Brazil

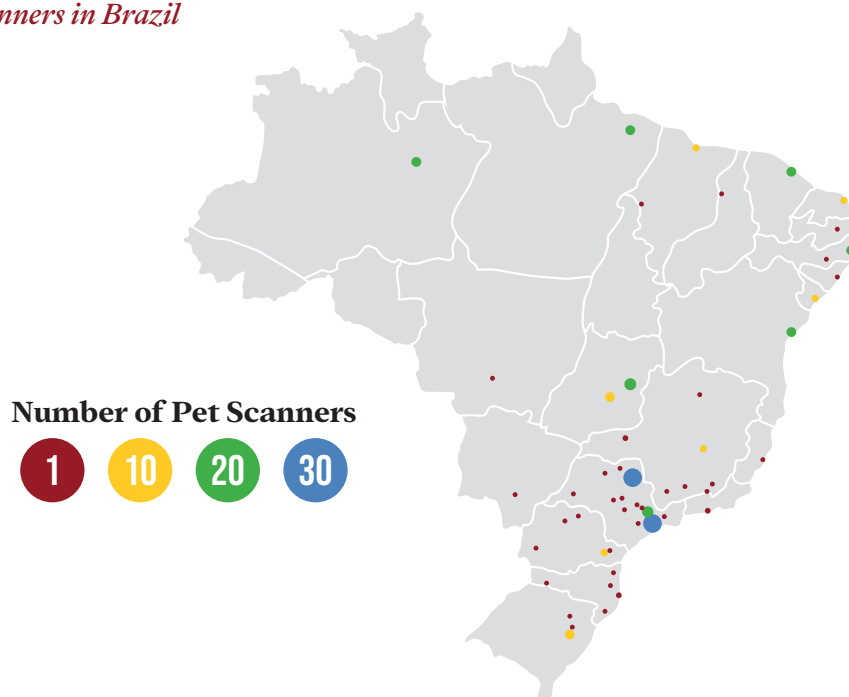
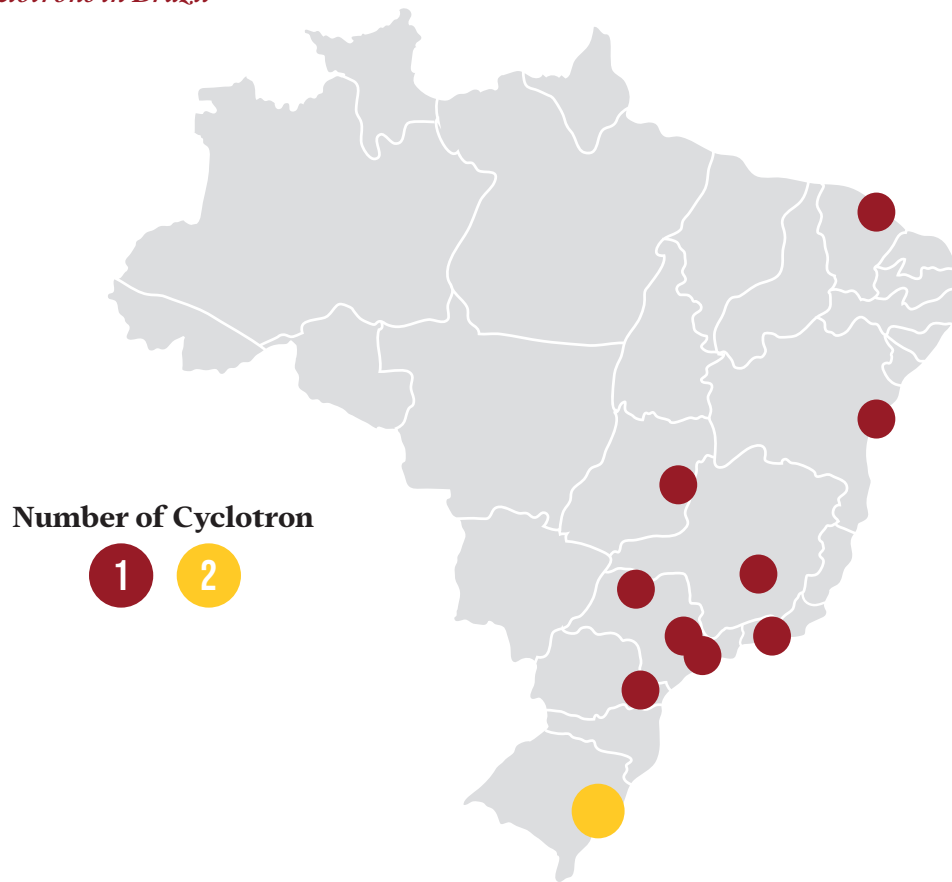


Figure 9: Location of cyclotrons in Brazil



Because of high cost and limited accessibility of PET scanners, our experts expect biomarker testing to be overwhelmingly done with CSF assays because of cost reasons and because installing additional PET scanners would take time. They also stated that there were no operational obstacles to scaling up CSF testing, as a range of specialists and even some primary care physicians are trained in performing lumbar punctures and patients tend to be accepting of the procedure. In patients with difficult lumbar anatomy, the procedure is being performed through a cervical access, leaving only an estimated 25 percent patients with contraindications, such as anticoagulation treatment, or strong aversion to lumbar puncture with PET scans as the only option. A concern, however, is the paucity of laboratories that are able to conduct CSF testing for the Alzheimer's pathology.

Another path to creating sufficient testing capacity in Brazil is the introduction of blood-based biomarker for the Alzheimer's pathology. Recent studies have shown that fully automated blood tests for beta-amyloid⁵⁸ and tau⁵⁹ have achieved levels of sensitivity and specificity that allows using them as triage tool in the evaluation process of patients with cognitive decline. A recent study projected that the use of a blood test in patients with suspected MCI based on the MMSE can reduce the need for confirmatory testing by about 60 percent and help to reduce need for specialist visits, as fewer patients without an eventual indication for a disease-modifying treatment would be referred⁶⁰.

Another path to creating sufficient testing capacity in Brazil is the introduction of blood-based biomarker for the Alzheimer's pathology.

TREATMENT DECISION

An office visit with a dementia specialist to discuss results from the neurocognitive evaluation and biomarker testing in order to decide on eligibility for disease-modifying treatment would be covered as routine care. As mentioned earlier, specialist capacity is widely regarded as insufficient with reported wait times even today and with limited room to expand volume, in particular in rural areas.

TREATMENT DELIVERY

The Brazilian Health Surveillance Agency (Agencia Nacional de Vigilância Sanitária – ANVISA) is the food and drug regulatory agency in Brazil⁶¹. ANVISA is responsible for the regulatory approval of therapies in Brazil. After regulatory (ANVISA) and price approval (Câmara de Regulação do Mercado de Medicamentos – CMED), the products can be commercialized but for reimbursement there are additional Health Technology Appraisal (HTA) steps for both the public and the private systems.

Within the SUS, the HTA process is performed, at the federal level, by the National Commission for Technology Incorporation (CONITEC), that was established in 2011 as health technology assessment agency to provide evidence-based recommendations for coverage of new pharmaceuticals, procedures and devices under the SUS²⁴.

In the private system, some treatments are mandatory by Law, but others are reviewed by the National Agency of Supplementary Healthcare (ANS), which is responsible for the HTA process that defines the minimum mandatory coverage list for all the private Health Maintenance Organizations (HMOs). It is also relevant to say that ANS' regulation determines that there is no mandatory coverage for oral non-oncological outpatient drugs, i.e., coverage is only available under the SUS and out-of-pocket, for the wealthier patients. In the private system, insurers can expand coverage, despite the minimum mandatory coverage list determined by ANS. In those cases, reimbursement tends to be faster and broader in the private system in comparison to the SUS.

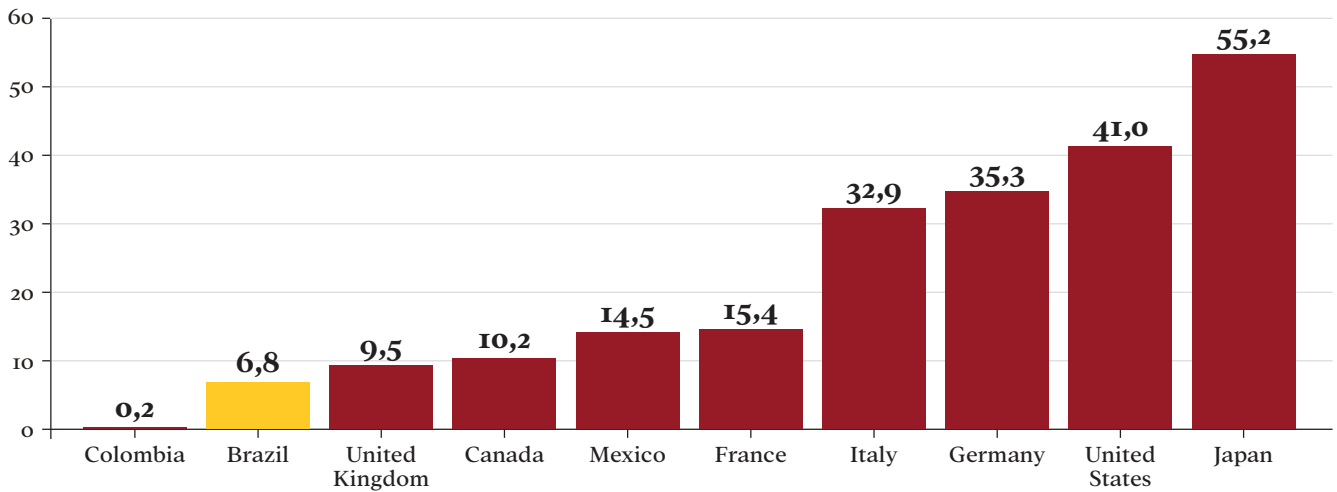
Importantly, drugs administered in facilities, such as intravenous therapies for rheumatoid arthritis, are covered as a procedure, and both SUS and private insurance provide coverage after a positive recommendation after the HTA process. State Health Departments are responsible for planning of infusion capacity.

There are currently 172 drugs listed that require prior authorization, including all symptomatic treatments for dementia (donepezil, galantamine, rivastigmine and memantine). The treating physician must file a request detailing the diagnosis and need for the treatment together with the prescription, which will be evaluated for compliance with the official Clinical Protocols and Therapeutic Guidelines (Protocolos Clínicos e Diretrizes Terapêuticas -PCDT) by independent experts.

MONITORING

Office visits and imaging for monitoring of treatment effect and safety are likely to be covered in line with the drug's label and guidelines. Capacity for MRI scanning is likely to constitute a bottleneck, as Brazil has substantial wait times for elective diagnostic imaging in the public sector already today. As of 2012, Brazil had 1,347 MRI scanners installed, which implies a device density close to that of Canada and the U.K. (figure 10) As with PET scans, utilization data are only available for the public sector, and utilization data suggest around 1,000 scans per year and device, which would be quite low compared to other countries that report 2,000 to 5,000 scans per year and device. According to our experts, the wait times in the public sector are a result of imaging facilities prioritizing higher-paying patients with private insurance. Similarly, capacity for follow-up visits with specialists may be limited as outlined above.

Figure 10: Number of MRI scanners per 1 million population in Brazil compared to other countries



CAPACITY PROJECTIONS

OVERVIEW AND OBJECTIVES OF THE STUDY

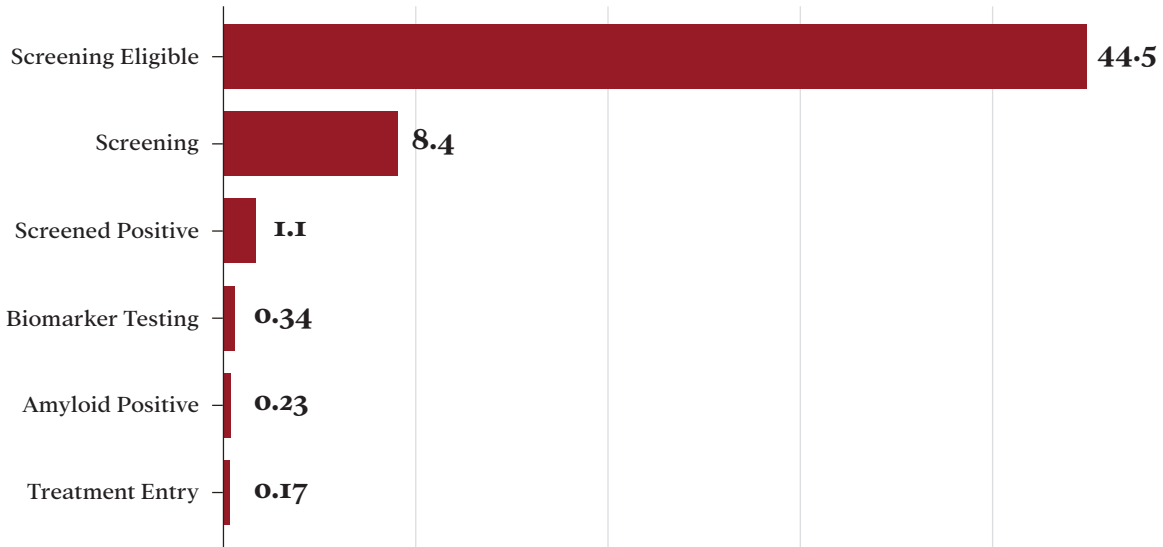
We use the collected data to predict wait times for access to a disease-modifying treatment with a simulation model using the following assumptions and parameters:

-
- When a treatment becomes available, 20% of Brazilians 50 years and older, who have never had a cognitive evaluation, will see their health team for an a cognitive test each year.
 - *Each subsequent year, 10% of those who previously tested negative return for another evaluation.*
 - The health team will identify those with manifest dementia and those with obvious explanation for cognitive decline (depression, prior stroke, etc.) and conduct a blood test for the Alzheimer's pathology, which we assume to be commercially available with the first treatment is broadly accessible.
 - 80% of those with suspected MCI due to AD will get referred to a specialist for confirmatory neurocognitive testing.
 - Specialists will identify false positives and order confirmatory biomarker testing for true positives.
 - *27% will be false positive based on published data for specificity of MMSE.*
 - *75% of biomarker tests will be based on CSF examination.*
 - 55% will be amyloid-positive based on IDEAS study⁶².
 - 75% will have a confirmed treatment indication after full diagnostic evaluation, as specialists might determine a different etiology to be mainly responsible for cognitive decline or a different life-limiting disease to make a clinical benefit unlikely.
-

BASE CASE PROJECTION

Figure 11 shows the projected demand for diagnostic services in the first year assuming cognitive evaluations start in 2022.

Figure 11: Projected patient demand for services in millions



As figure 12 shows, available capacity will not be sufficient to match the projected demand and the biggest obstacle to access is availability of dementia specialist visits. In fact, the combined effect of population growth and population ageing means that the wait list for specialist appointment will continue to grow over time. In contrast, we do not project substantial wait times for confirmatory biomarker testing and treatment delivery but note that this is a consequence of patients not being seen by specialists.

Figure 12: Waitlists for Alzheimer's disease testing and treatment

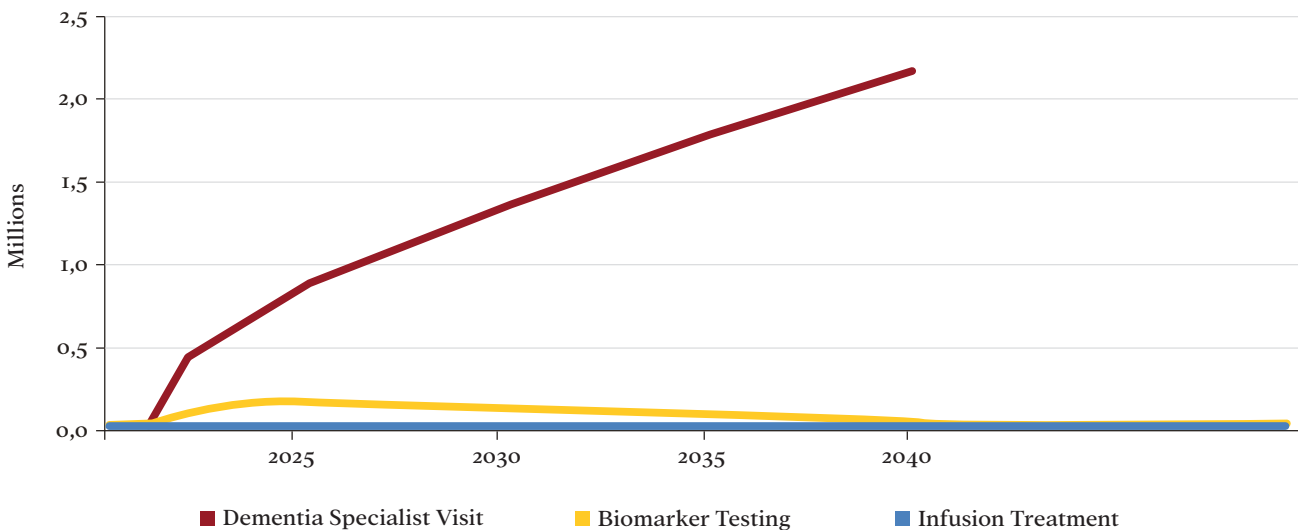
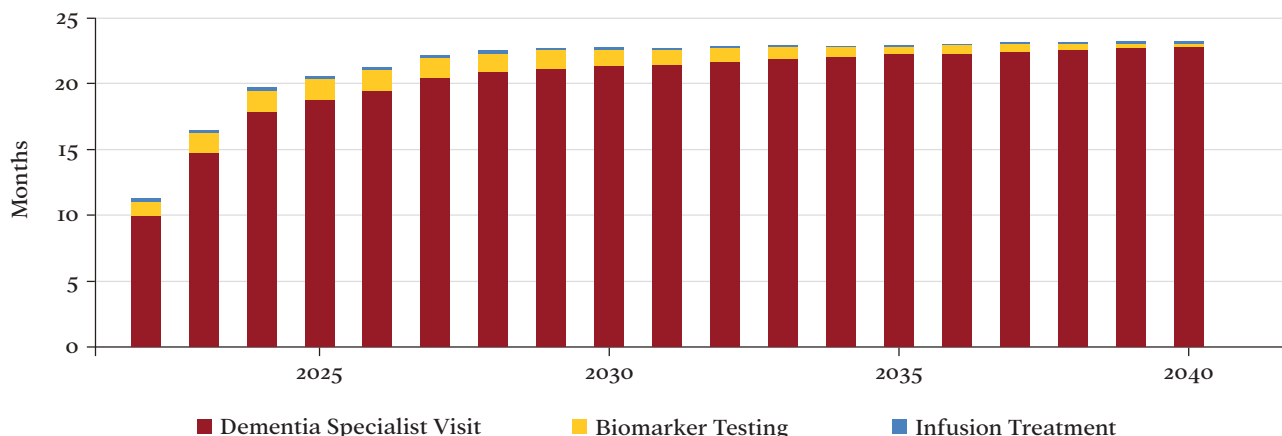


Figure 13 translates the wait lists into wait times for access to treatment. Average wait time increases from about one year in 2022 to around two years in subsequent years and remains at that level over the horizon of the projection. As expected, queues for specialist appointments cause most of the wait time, whereas biomarker testing and infusion treatment are readily accessible after initial diagnostic evaluation.

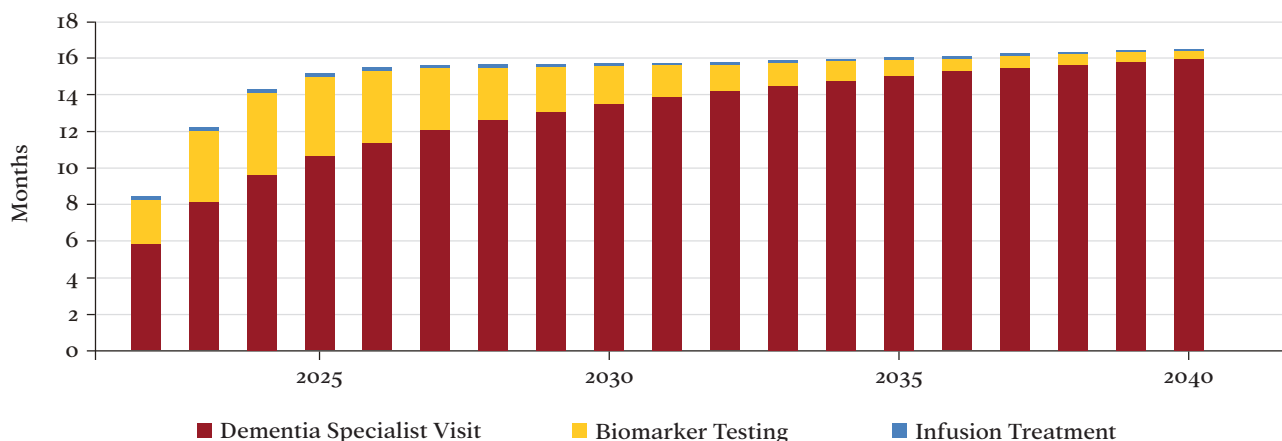
Figure 13: Wait times for Alzheimer’s disease testing and treatment



ALTERNATIVE SCENARIOS

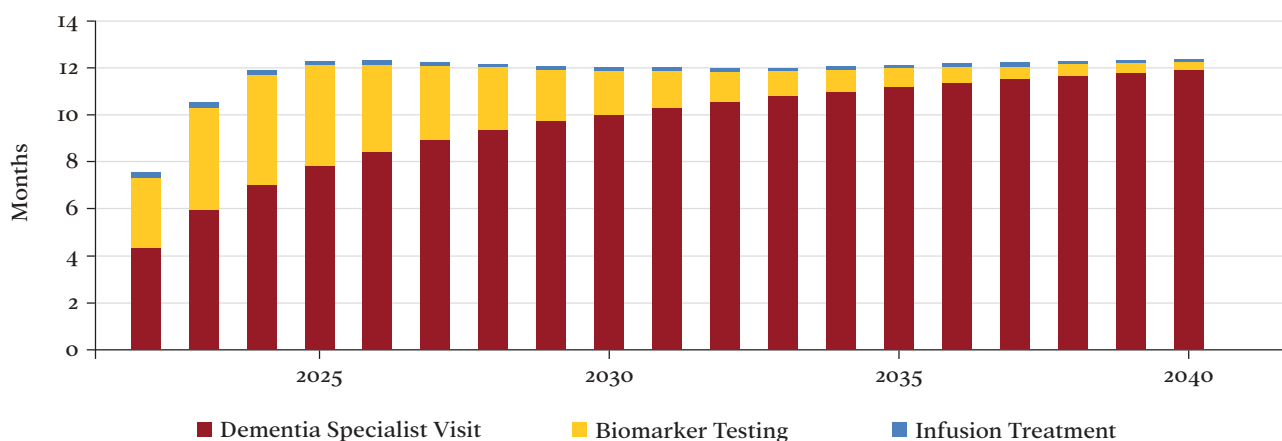
We explore three alternative scenarios to illustrate the effect of changes to the available diagnostic capacity. The first is an increase in the number of dementia specialists by training additional physicians in the diagnosis and evaluation of cognitive decline. In many countries, such as Germany and the U.K., a much larger proportion of psychiatrists are involved in memory care than in Brazil, and we model a scenario, in which 25 percent of Brazilian psychiatrists were dementia specialists vs. the base case scenario that considers only 10%. Figure 14 shows that peak wait times would fall from about 22 to about 16 months under this assumption. As patients are seen by specialists faster, wait times for confirmatory biomarker testing would increase.

Figure 14: Wait times for Alzheimer’s disease testing and treatment, assuming 25 percent of psychiatrists qualify as dementia specialists



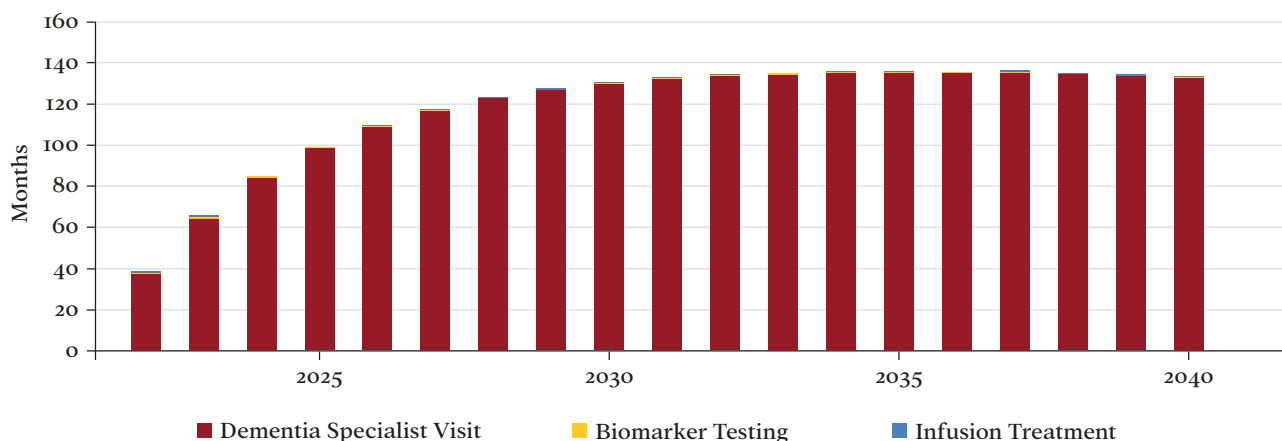
The second scenario assumes improved triage by primary care clinicians in addition to training more psychiatrists in dementia care. For example, the health teams could be trained to detect and treat a larger share of patients with reversible causes of cognitive decline, such as depression and alcohol abuse, and to identify more patients with etiologies other than Alzheimer’s disease, such as past stroke and traumatic brain injury. This would allow to prioritize patients with a potential treatment indication, i.e., reduce specialist referrals of “false positives”. We model the improved diagnostic capabilities as equivalent of increasing the specificity of the blood test by ten percentage points (*figure 15*). Under these assumptions, peak wait times drop to around twelve months.

Figure 15: Wait times for Alzheimer’s disease testing and treatment, assuming 25 percent of psychiatrists qualify as dementia specialists and improved diagnostic capabilities of health teams



Lastly, we explore a scenario in which a blood test for the Alzheimer’s pathology remains unavailable, and patients would be referred to specialists based on the MMSE results alone (*figure 16*). As the specificity of the MMSE for detection of MCI is only 73 percent⁶³ and the test does not differentiate the underlying etiology, a large number of cognitively normal individuals and patients with cognitive decline because of other causes, would be referred and wait times would increase dramatically.

Figure 16: Wait times for Alzheimer’s disease testing and treatment, assuming no blood test for the Alzheimer’s pathology



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. 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 assume that the therapy would be indicated for people with early-stage Alzheimer’s disease (MCI and mild dementia); 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 physicians in some areas, which could make MCI detection more challenging. For example, the number of physicians per capita is 2.5 times higher in the Southeast than in the North region⁶⁴. 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 geriatricians, neurologists and psychiatrists 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 patients with disorders in the brain and nervous system and psychiatrists see 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.

Although we use a proxy measure for infusion capacity, future capacity growth in Brazil is difficult to predict, it is likely that providers would add infusion capacity, if an intravenous treatment were approved and covered by health insurance.

SUMMARY

SUMMARY

Our review shows that Brazil's healthcare system faces the typical challenges of rapidly developing middle-income countries in that it is still encumbered by the need to improve control of infectious diseases and maternal and child health, while being increasingly engulfed by a high burden of non-communicable diseases. Addressing these challenges in such a vast and diverse countries has been complicated by stalled economic growth in recent years. With government debt approaching 80% even prior to the COVID-19 pandemic, 96% in 2020, and interest payment accounting for a quarter of the federal budget, the ability to invest remains limited⁶⁵.

Brazil also has the particular challenge of having oriented medical training towards procedural specialties, which leaves it with comparatively few primary care physicians and non-procedural specialists per capita even though its overall number of physicians is comparable to countries of similar wealth. This imbalance has profound implications for dementia care.

Brazil also has the particular challenge of having oriented medical training towards procedural specialties, which leaves it with comparatively few primary care physicians and non-procedural specialists per capita even though its overall number of physicians is comparable to countries of similar wealth. This imbalance has profound implications for dementia care. Countries with lack of dementia specialists, like Canada, are responding by shifting tasks to primary care settings that tend to be less capacity constrained. The low density of primary care physicians precludes that option for Brazil, as those clinicians are already highly leveraged today in family health teams even after attracting large numbers from abroad under the “More Doctors” initiative²⁴. The problem is exacerbated by the lack of a formal dementia strategy at the federal and the state levels, which leaves Brazil ill-prepared to handle the increasing burden of the disease.

would have to be set at the federal level while operational execution would be up to the states. Using the blueprint of oncology care, the federal government could operate larger, research-oriented facilities, building on the existing memory centers. The states, together with the municipalities, would run community-based institutions. A similar model is being used in France, where regional memory resource and research centers support a network of local memory clinics⁶⁶.

Brazil has several resources that could support the development of such a memory clinic network. There is a robust health IT infrastructure with the unified DataSUS platform emerging. Brazil is one of the countries participating in the strengthening responses to dementia in developing countries (STRiDE) initiative and one of the countries selected for a flagship pilot on early detection and diagnosis of the Davos Alzheimer's Collaborative. An interesting possibility would be to leverage the “family health strategy”, with the training of their teams to practice cognitive assessment in the elderly, including involving community health workers, who provide home care. Today there are about 60,000 family health teams working in Brazil. The family health strategy is the primary care assistance model, which is based on the work of multiprofessional teams in a restricted territory and develops health actions based on knowledge of the local reality and the needs of its population.

Developing such a strategic plan that devises a resource-appropriate approach to memory care would be an important first step. Given the devolved nature of the Brazilian healthcare system, the framework

Developing such a strategic plan that devises a resource-appropriate approach to memory care would be an important first step.

Brazil's population is young compared to high-income countries and other fast-growing economies, but population ageing and an increasing burden of cardiovascular risk factors mean that Brazil, unlike several high-income countries which benefit from tighter risk factor control, will experience a growing disease burden⁶⁷. Our projections suggest that Brazil will not have the infrastructure to handle the expected caseload of patients, who might be eligible for a disease-modifying Alzheimer's treatment, and is unlikely to create this infrastructure fast enough. Nor will SUS resources be sufficient to cover the cost of the diagnostic process and the treatment for millions of patients. This is of substantial concern as large numbers of patients with early-stage Alzheimer's disease might progress to advanced disease stages while waiting for treatment, which would create substantial burden on patients, their families and public finances because of the need for nursing home care. Two avenues exist towards getting the treatment to those who will need it most.

The first is an increased effort in preventing cognitive decline.

The first is an increased effort in preventing cognitive decline. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) has provided clinical trial evidence that targeting modifiable risk factors, such as hypertension, insulin resistance and excessive alcohol use, as well as aggravating factors, such as depression and loneliness, can improve cognitive performance⁶⁸. The WHO has integrated such findings into a guideline for dementia risk reduction⁶⁹. The dual advantage of the public health-oriented interventions for brain health is that they are more scalable than medical interventions and that they simultaneously reduce the risk of other chronic conditions, like diabetes and cardiovascular disease.

The second is improved triage of patients. A recent study has shown that the combination of a brief cognitive test and an automated blood test for the Alzheimer's pathology can reduce the need for follow-up diagnostic evaluation and biomarker testing, thereby reducing cost and freeing up scarce capacity⁶⁰. While we have assumed that such a test will be available in Brazil by the time a disease-modifying treatment is approved and broadly available, wait times are projected to remain long, which necessitates additional triage steps. As not all patients with MCI due to Alzheimer's disease progress to dementia, at least not within the often limited expected lifespan of many affected individuals⁷⁰, identifying patients at low progression risk would allow prioritizing those for evaluation and treatment. A recent study has suggested that a blood test for the tau pathology could be a useful and scalable predictor of progression risk⁷¹. Additional efforts in this area seem warranted especially as better triage might also decrease overall cost. Conversely, our analysis also shows that the availability of a blood test is critical for Brazil.

There is a long road ahead to develop a robust infrastructure for memory care in Brazil, especially for individuals covered through SUS because of chronic funding shortages, and the experience with the COVID-19 pandemic has taught us how hard it is to build infrastructure in the short run. The pillars of Brazil's healthcare system are equitable access and protection of vulnerable populations and a concerted effort of many stakeholders will be needed to ensure that these pillars hold for patients and families affected by dementia. A national dementia plan with an implementation strategy would be an important first step towards this goal.

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