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IMPLICATIONS OF ALZHEIMER'S TREATMENT FOR ORGANIZATION AND PAYMENT OF MEDICAL PRACTICES IN THE EU-5 COUNTRIES

TECHNICAL REPORT

SOEREN MATTKE, ANDREAS ULLRICH AND MO WANG

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About the Authors

Soeren Mattke is a Research Professor of Economics at the University of Southern California, Dornsife College of Letters, Arts and Sciences, and the Director of the Center for Improving Chronic Illness Care.

Mo Wang is a Graduate Research Assistant in the Economics Department of the College.

Andreas Ullrich is a Visiting Scientist at the Charité University Hospital and Center for Global Health in Berlin, Germany, and a former Adviser to the Assistant Director General for Noncommunicable Disease and Mental Health at the WHO.

For questions about the report, please contact Dr. Mattke at mattke@usc.edu



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OVERVIEW AND OBJECTIVES OF THE STUDY

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-

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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 disease-modifying treatments when they arrive. Time, however, is limited as recent trial results suggest that we may see the first disease-modifying treatments as early as 2021.

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 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.

Combined with the fact that payment for labor-intensive diagnostic workups and counseling tends to be less well reimbursed than procedures, this lack of therapeutic consequences means that physicians have limited motivation to evaluate and formally diagnose dementia patients today. 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 dementia specialists in the U.S. (Liu, Hlavka, Hillestad, & Mattke, 2017), Canada (Hlavka, Mattke, & Liu, 2019) Japan (Mattke et al., 2019) and six European countries (Hlavka et al., 2019) will create substantial bottlenecks for treatment delivery.

This project builds on this earlier work and analyzes how practice organization and payment models could be changed to accommodate the substantial increase in demand for dementia specialty care that a disease-modifying treatment for Alzheimer's disease will bring about. The study covers the five largest EU economies (Germany, France, Italy, Spain and the U.K.)¹.

TECHNICAL APPROACH

The study uses a combination of desk research and expert interviews to describe the current patient journeys in the included countries, to capture obstacles to access that result from these journeys and to identify potential changes to payment models and care delivery that might improve access. Desk

1. On March 2017, the U.K. Government announced the beginning of its withdrawal (Brexit) process from the EU scheduled for February 2020. Research into health system readiness for a disease-modifying treatment for Alzheimer's disease was conducted during 2019.

research covered the websites of national (e.g., Bundesärztekammer) and multilateral (e.g., OECD Health Data) organizations that publish health system capacity data, advocacy organizations (e.g., Alzheimer Europe, Alzheimer’s Disease International), payers and specialty societies as well as research published in peer-reviewed journals and technical reports. A total of 30 expert interviews were held with policy experts, clinical and health services researchers, clinicians and payer representatives in the EU-5 countries, using a semi-structured interview protocol.

We developed a stylized patient journey (**Figure 1**) to capture the current pathway which dementia patients take through identification based on screening for mild cognitive impairment (MCI) or subjective 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 each of the five countries the status quo regarding coverage, capacity and capabilities:



Coverage

- Are the services under each step currently covered by health insurance?
- 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

FRANCE

HEALTH SYSTEM OVERVIEW

France has near-universal healthcare coverage through a statutory social health insurance (SHI) system (*assurance maladie*) that is financed by an earmarked tax on income and taxes on alcohol, tobacco and pharmaceutical companies, which covers about 77% of healthcare cost (Chevreul, Brigham, Durand-Zaleski, & Hernández-Quevedo, 2015). About 90% of the population has additional insurance coverage through voluntary health insurance (*mutuelle*) that covers large parts of cost-sharing requirements and some services outside of the statutory benefits package. Lower-income groups are eligible for a publicly financed supplemental insurance (*complémentaire santé solidaire*). Long-term care for elderly and disabled is provided partially by the National Solidarity Fund (*Caisse nationale de solidarité pour l'autonomie* (CNSA) and *Fonds de solidarité vieillesse* (FSV)) and there is income-dependent public coverage of long-term care services (Doty, Nadash, & Racco, 2015).

Patients with Alzheimer's disease and other forms of dementia are entitled to a scheme called ALD (*Affection Longue Durée* — Long Term Disease). This specific social protection scheme has been introduced for several chronic diseases, including Alzheimer's disease (ALD15). A list of medical services and tests for these ALDs is covered without patient cost-sharing.

Central government agencies set the annual budget for the SHI, define the range of covered benefits and maintain the regulatory framework for provision of healthcare. Regional agencies (*Agences régionales de santé* — ARS) are in charge of capacity planning and negotiations about service volume with local providers taking the needs of the population into account.

Healthcare is provided in private practices for primary care and specialist outpatient services and in hospitals for inpatient, day hospital and specialty outpatient care. Almost all physicians in private practice work under contract with the statutory insurance scheme that pays them fee-for-service based on negotiated fee schedules. Hospitals operate under prospective payment systems (DRG system) for both inpatient and specialized outpatient care (day hospital) and have salaried staff.

DEMENTIA PLANNING

After three plans dedicated to Alzheimer's and related diseases (1st Plan 2001–2005, 2nd plan 2004–2008, 3rd plan 2008–2012), France had established the first comprehensive plan for neurodegenerative diseases, covering 2014 to 2019. This plan is broader and incorporates Alzheimer's, Parkinson's, multiple sclerosis and other neurodegenerative diseases. The neurodegenerative diseases plan (Plan Maladies Neurodégénératives 2014–2019) was issued by the Ministries of Health, Ageing and

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Family and of Research (French government, 2018). The plan emphasizes the need for care pathways for these disorders generally, and specifically for Alzheimer's disease, even in the absence of a disease-modifying treatment.

MCI SCREENING

There is no covered benefit or organized screening program for MCI in France at the present. The national dementia guideline maintains a positive list of recommended services that does not contain screening of asymptomatic patients (Haute Autorité de Santé, 2018a). While visits to Primary Care Physicians (PCPs) are not capacity constrained with limited wait times for appointments, practitioners are reportedly reluctant to seek out cognitive impairment proactively because of lack of training in memory care and a perception of limited therapeutic consequences. On the other hand, the attitude towards testing for MCI or even prior to symptoms in the general population is quite positive with 90% interviewed agreeing to be tested (Sawaya & Bouillot, 2013).

Introduction of a screening program would be decided by the Health Ministry in consultation with the HAS, which would require high-grade evidence for clinical benefit and cost-effectiveness, which is the case for breast and cervical cancer screening with the national cancer institute (INCa) providing overall guidance. Actual uptake of a screening program and resulting benefits in terms of health outcome would depend on national Alzheimer's disease screening guidelines to be developed, changing PCPs' attitude towards greater accommodation of patients' desire for earlier detection as well as better screening tools.

CASE FINDING

The current national guidelines for dementia management (Haute Autorité de Santé, 2018a, 2018b) give very detailed advice in how to detect early signs of MCI. The national plan for neurodegenerative disorders 2014–2019 highlight access to care, including diagnosis and care as a priority (Ministere des Affaires sociales, 2014). The plan for the prevention of loss of autonomy, which brings together a national policy for all neurodegenerative disorders (Agences Régionales de Santé, 2017), highlights the importance of early diagnosis as a key element to keep autonomy as long as possible. A joint statement of several medical associations, including the neurological society (Fédération des Centres Mémoires — FCM) and the federation of general practitioners (College de Médecine Générale), claims the inclusion into the national plan for neurodegenerative disorders is a strategy of early detection (Krolak-Salmon et al., 2018).

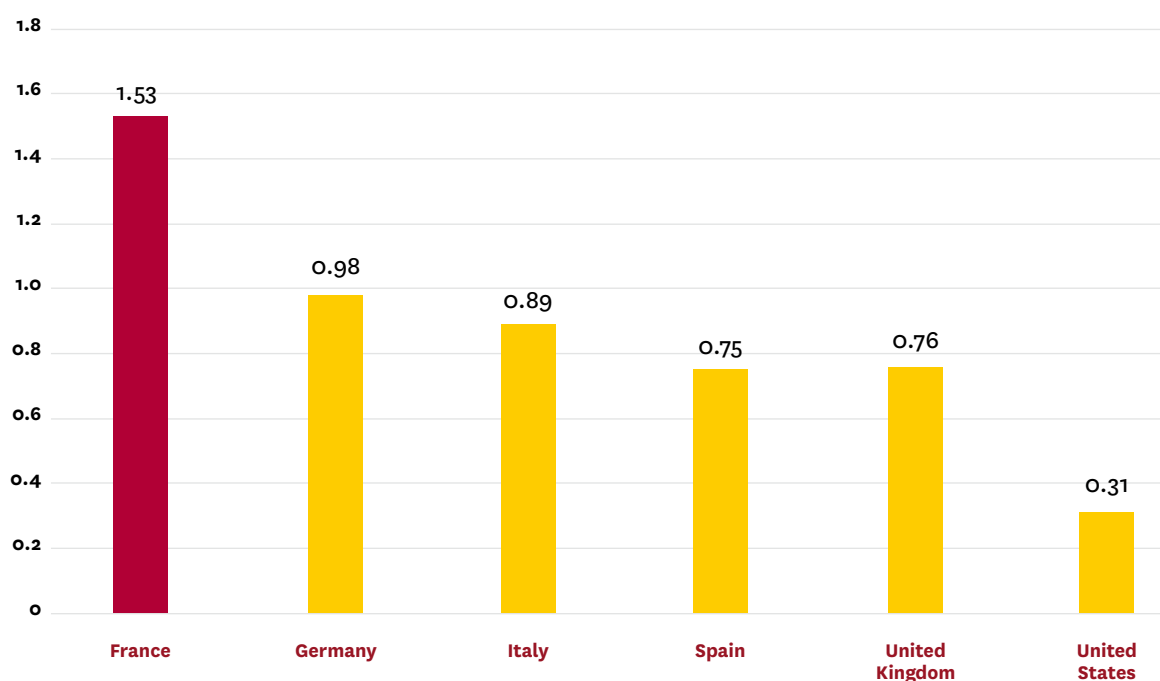
The evaluation of patients with subjective memory complaints would start in primary care and is covered under SHI at a rate of 69 Euro (*consultation de repérage du Trouble Neurocognitif*) for the initial evaluation and brief cognitive assessment, which is viewed as adequate for the required effort. While the comparatively high density of primary care physicians in France implies sufficient capacity to assess memory complaints (**Figure 2**), many physicians remain reluctant to handle such concerns because of a fatalistic attitude and limited confidence in

their abilities to conduct a proper work-up (Harmand et al., 2018).

As a result, dementia, in particular in its early stages, remains underdiagnosed (Defontaines et al., 2016). Selected practices, however, have started assessing cognitive complaints systematically based on the MMSE test, using dedicated technicians. The resulting score informs their decision whether to refer (or not refer) patients for further evaluation. In France, patients are mostly diagnosed at the mild-moderate stage with an estimated delay of two to three years. (Dartigues & Helmer, 2009)

Figure 2: Density of primary care providers in France.

GPs per 1,000 population [2016]



Data from OECD Health Statistics (2019).

With adequate capacity and coverage, the main obstacle to increased detection of early-stage cognitive decline is better education and training for PCPs, both in terms of awareness and technical skills.

COGNITIVE TESTING

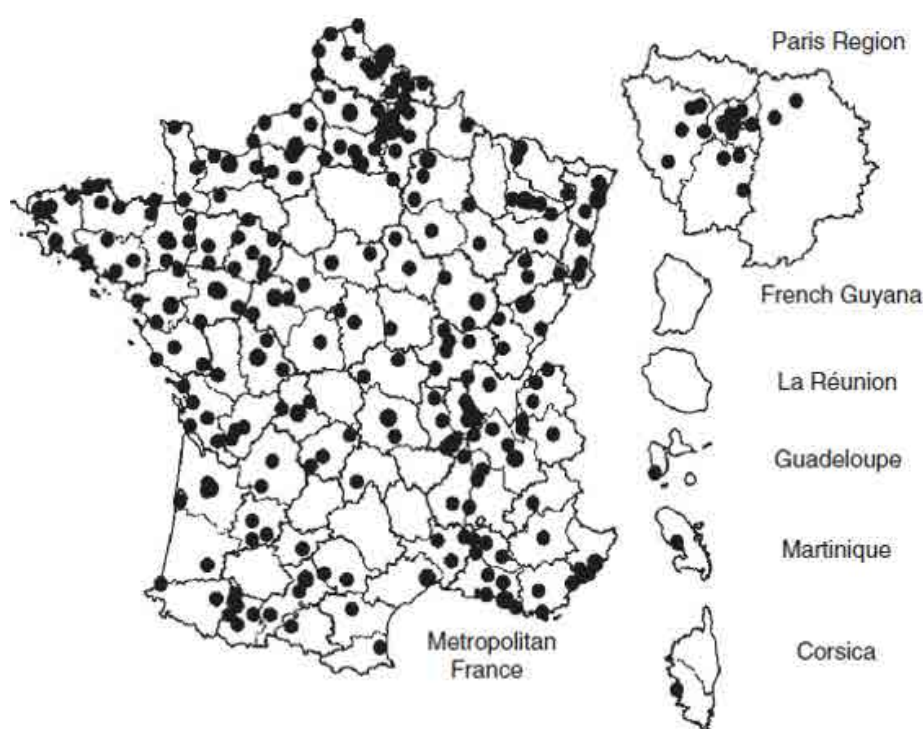
Evaluation of a verified cognitive complaint by a specialist is a covered benefit under the SHI. About half of the patients are seen in specialized outpatient clinics and half by neurologists or geriatricians in private practice. The network of outpatient clinics (Figure 3) consists of about 400 memory centers (*consultations mémoire* - CM) that

THE NETWORK OF OUTPATIENT CLINICS CONSISTS OF ABOUT 400 MEMORY CENTERS THAT FOCUS ON ROUTINE CARE PROVISION AND 28 MEMORY AND RESEARCH CENTERS THAT HANDLE COMPLEX CASES AND CONDUCT RESEARCH.

focus on routine care provision and 28 memory and research centers (*Centres mémoire de ressources et de recherche*—CMRR) attached to university hospitals that handle complex cases and conduct research. They were initially introduced as part of France's first National Alzheimer and Dementia Plan 2001–2005 (Alzheimer's Disease International, 2008; l'Emploi & Solidarité, 2001) and are usually attached to hospitals with an estimated capacity of one center per 150,000 population. Their multidisciplinary staff are salaried employees of the hospital and outpatient visits are covered as partial hospitalization. Independent neurologists or geriatricians typically work as solo practitioners under contract with the SHI. According to expert input, the current fee level of about 40 Euro for a consultation and 80-100 Euro for cognitive testing is regarded as adequate.

INDEPENDENT
NEUROLOGISTS
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TYPICALLY WORK AS SOLO
PRACTITIONERS UNDER
CONTRACT WITH THE SHI.

Figure 3: Network of outpatient memory clinics in France.

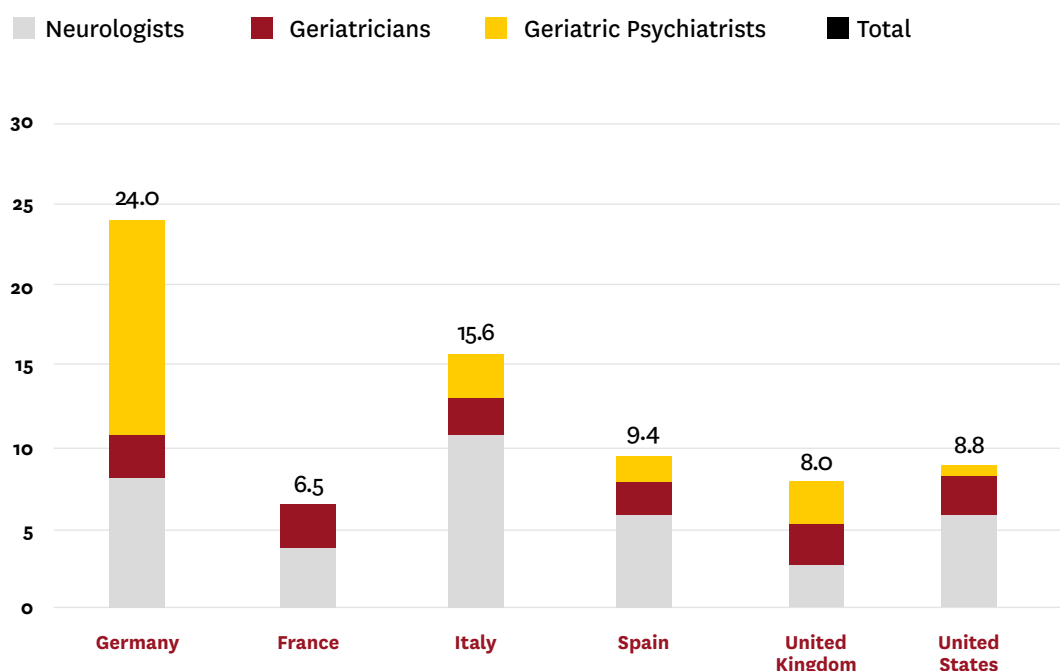


Sourced from Le Duff et al. (2012). Data from 2010.

The capacity of specialists is adequate to handle current demand for services with wait times of about two months, but our experts voiced concerns about scalability, in particular in the short run. An important rate-limiting factor is that psychiatrists in France are not involved in dementia care, which results in a comparatively limited pool of specialists (**Figure 4**). Physicians in private practice are theoretically free to expand volume, but are typically working at capacity already and might find it difficult to change their practice model from solo practice to larger groups. Memory centers would find it easier to increase capacity as their multidisciplinary model allows for task shifting with less reliance on scarce specialist time. They also tend to have consistent standards of care for cognitive testing whereas the extent and quality of testing by private practitioners vary.

Figure 4: Number of dementia specialists in France compared to other countries.

Estimated available specialists per 100,000 population



Data from OECD Health Statistics (2019).

Actually increasing capacity of the memory centers would require upfront planning as their budget and thus staffing levels are determined by the regional planning authorities, who in turn receive funding from the central government. Our experts pointed out that obtaining such a funding increase would be a complex decision, because of the high

INCREASING CAPACITY OF THE MEMORY CENTERS WOULD REQUIRE UPFRONT PLANNING AS THEIR BUDGET AND THUS STAFFING LEVELS ARE DETERMINED BY THE REGIONAL PLANNING AUTHORITIES, WHO IN TURN RECEIVE FUNDING FROM THE CENTRAL GOVERNMENT.

tax burden and public debt combined with the competing needs of an aging population limit flexibility. At the same time, the government has committed to improving care for neurodegenerative disorders (Ministère de l'Éducation Nationale & Ministère des Affaires Sociales, 2014). The decision will likely depend on the efficacy and safety profile of a disease-modifying treatment relative to its price and in particular its ability to achieve cost offsets from reducing dementia incidence.

Expanding capacity in independent neurology practices is likely to require new practice models, such as forming larger groups with the scale to hire support staff and specialization on dementia care. Blueprints for such models exist for outpatient oncology care and multiple sclerosis care. In addition, greater standardization of cognitive testing procedures and quality assurance would be needed.

BIOMARKER TESTING

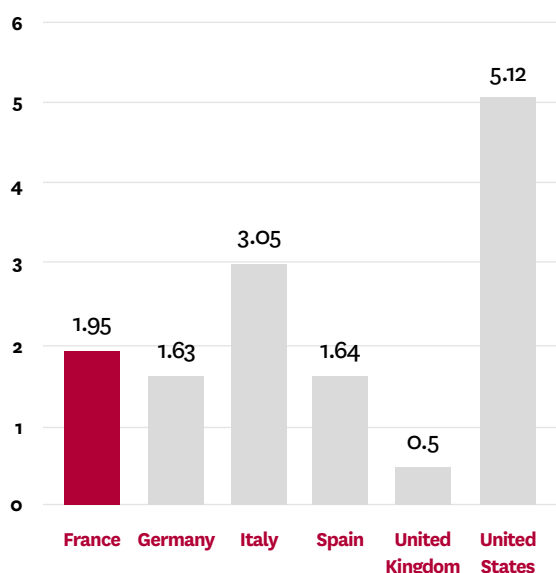
While both positron emission tomography (PET) scans and cerebrospinal fluid (CSF) tests for biomarkers of Alzheimer's disease are approved in France, only CSF testing is currently covered for routine care. Coverage for PET scans can be requested for the differential diagnosis of complex cases, such as atypical presentation or early-onset dementia. Even with coverage, the SHI currently pays providers below cost for PET scans with reimbursement of 1000 Euros for the first 1000 exams conducted on each device per year and 550 Euros for subsequent tests, against an estimated cost of around 1200 Euros (Talbot, 2010). Lumbar puncture and testing of CSF are adequately covered (Haute Autorité de Santé, 2005). The PET tracer is not reimbursed and needs to be covered out of the hospital budget.

Memory centers have sufficient capacity to conduct lumbar punctures at current demand levels and their access to hospital facilities and staff allows them to scale up if needed. Neurologists in private practice do not conduct lumbar punctures and would be unlikely to offer this procedure because of a lack of training and adequate facilities, such as procedure rooms and recovery beds.

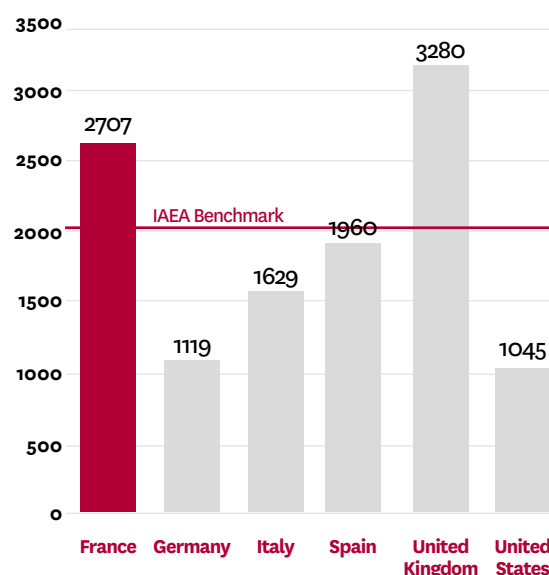
France has comparatively low PET density and high utilization rates (Figure 5), which suggests that room to increase capacity is limited. Further, the number of PET scanners is centrally regulated, and 120 of the 149 approved devices are already installed (OECD, 2019).

Figure 5: Density and utilization of PET scanners in France.

PET scanners per 1M population



Annual PET scans per device



Data from OECD Health Statistics (2019), The German Society for Nuclear Medicine (DGN) (2019), and NHS England (2019). The International Atomic Energy Association (IAEA) recommends 2000 annual scans per device as minimum threshold for efficient utilization.

In addition, cyclotron coverage is centered on urban areas with parts of rural France and the island of Corsica without geographic proximity to a facility that could produce the amyloid tracer (Figure 6).

The first step towards routinizing biomarker testing would be coverage for routine cases, which in turn would require the availability of a disease-modifying treatment or evidence for net clinical benefit from an accurate diagnosis in the absence of a treatment. As testing would likely occur in memory centers, their budgets and DRG payments would have to be adjusted. Capacity expansion is likely to rely heavily on CSF testing, since the memory centers already have suitable staff and facilities, whereas installing additional PET devices would take multiple years for budget allocation, planning, building permits and installation.

The final interpretation of cognitive and biomarker test results and treatment decision would mostly take place in memory centers but could be handled by neurologists in private practice. In both settings, the consultation would be covered. As with cognitive testing, capacity and funding would have to be increased substantially to accommodate the expected demand.

Coverage of a disease-modifying treatment would be determined based on a clinical evaluation by the Health Authorities (Haute Autorité de Santé, 2016). For drugs with substantial budget impact (over ~€20million spending per year) and for those which the manufacturer claims major/important/moderate clinical added value (ASMR I/II/III), the Health Economic Committee (*Commission évaluation économique et de santé publique - CEESP*) conducts an economic assessment in addition to the assessment of clinical benefit, relative to standard of care is part of the evaluation (Haute Autorité de Santé, 2016). Of note, containment of prescription drug spending has recently become a policy focus in

focus in France and has resulted in the delisting of all symptomatic treatments for Alzheimer’s disease by the SHI based on a finding of insufficient clinical value. If covered, memory centers would be reimbursed for the cost of the treatment plus cost of delivery either through an adjusted DRG payment or a dedicated add-on payment. No robust data exist on capacity for intravenous delivery but experts expected memory centers to be able to accommodate the expected volume, whereas treatment delivery in private practice would be less likely.

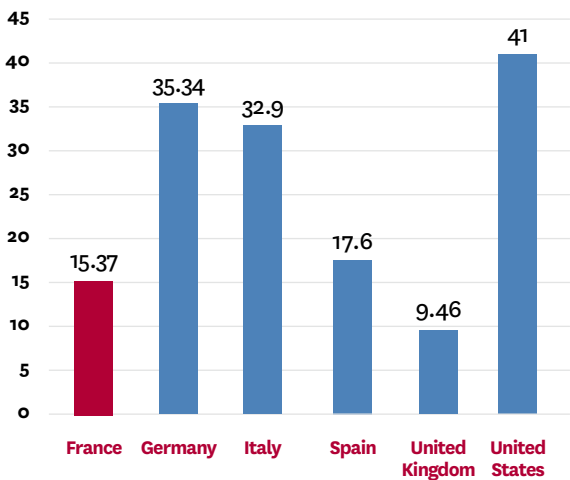
CONTAINMENT OF PRESCRIPTION DRUG SPENDING HAS RECENTLY BECOME A POLICY FOCUS IN FRANCE AND HAS RESULTED IN THE DELISTING OF ALL SYMPTOMATIC TREATMENTS FOR ALZHEIMER’S DISEASE.

MONITORING

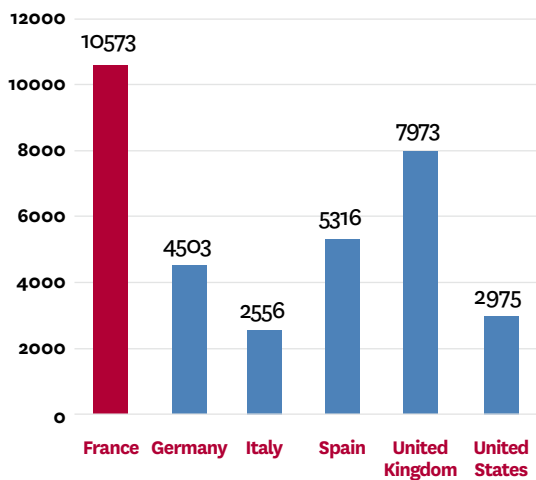
Imaging and consultations to monitor the effectiveness and safety of treatment would be covered based on the drug’s label and guidelines. As PCPs are not likely to be qualified to handle monitoring, the need for additional specialist visits could strain the available capacity further. In addition, comparatively low density and high utilization rates of MRI scanners in France suggest limited flexibility to adapt to future needs and expanding capacity would take years because of the centralized planning process (Figure 7).

Figure 7: Density and utilization of MRI scanners in France.

MRI scanners per 1M population



Annual MRI scans per device



Data from OECD Health Statistics (2019).

PREPARING THE
MEMORY CENTERS
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AND IMAGING
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SUMMARY

France has a well-resourced healthcare system with near-universal coverage for medical and social care and limited cost-sharing. There is a clear pathway to coverage of a disease-modifying treatment for Alzheimer's disease, given appropriate value for money, which would also trigger coverage of the services required to determine treatment eligibility and monitoring of effectiveness and safety. A national planning process that started with the first dementia plan in 2001 led to the establishment of over 400 memory centers as the core institutions for regionalized and localized dementia care. These centers are well-equipped to handle a future Alzheimer's treatment for three reasons. First, they are staffed by multidisciplinary care teams, which promotes task shifting from scarce specialists to less well-trained professionals. Second, they are attached to hospitals, which grants them access to the facilities and staff

needed for services like lumbar punctures and intravenous treatment. Third, they are mostly led by neurologists, a specialty that tends to be more comfortable with the medicalized aspects that a treatment is likely to require.

Preparing the memory centers for the delivery of a treatment will require substantial investments, as they currently operate at capacity, and France has comparatively low numbers of dementia specialists and imaging equipment. There is awareness of this challenge in the dementia community and strong political support in the form of national plans and declarations of professional societies to make a treatment accessible. But the centralized nature of the resource allocation and planning process can lead to delays in decision making and implementation, implying the need to start a dialog early on.



RESULTS

GERMANY

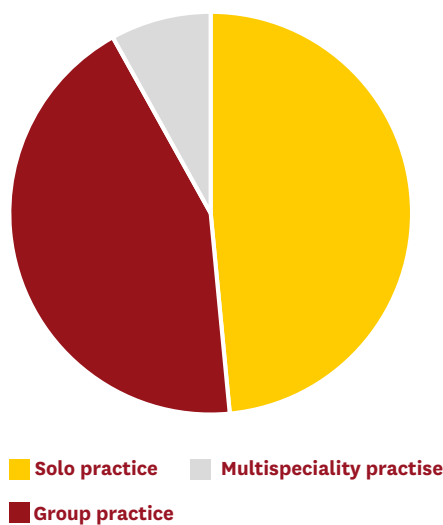
HEALTH SYSTEM OVERVIEW

Germany has near-universal coverage through a social insurance system that is financed by a payroll tax and administered by around 100 highly regulated not-for-profit insurers, the Krankenkassen (Sickness Funds) (Radtke, 2019). Stability of the tax rate is an important policy objective and several budget control mechanisms are in place to restrict the growth of healthcare spending to wage growth. Earners of higher incomes may opt out and purchase private health insurance with risk-rated premiums. Privately insured patients largely use the same delivery system as their socially insured counterparts, but often get preferential treatment, because private carriers pay higher rates (Reinhard & Miriam, 2014).

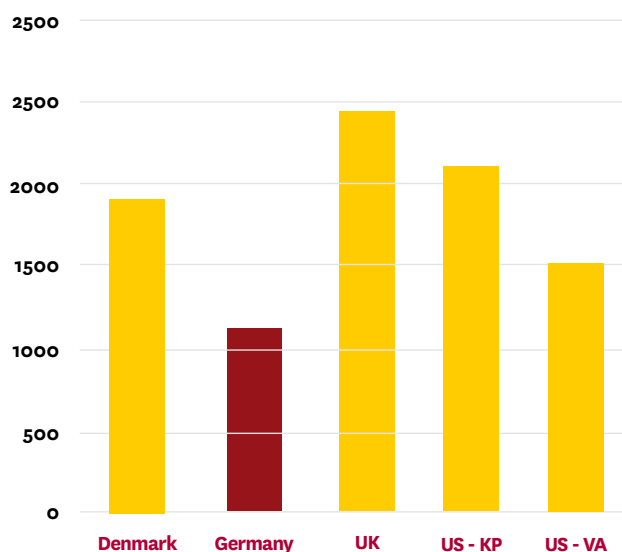
Healthcare services are split into two sectors that are separately organized and financed. Outpatient care is provided by independent physicians in private practice under contract with the Sickness Funds. Practices tend to be small and single specialty (Figure 8).

Figure 8: Composition of medical practices in Germany.

Share of physicians by practice model



Average panel size in primary care



Data from Ärztemonitor. Ergebnisse zur zweiten Befragung in Frühjahr (2014).

The sickness funds enter into umbrella contracts with regional physician associations (Kassenärztliche Vereinigung – KV) for provision of all outpatient services. Every physician seeking to treat socially insured patients must be a member of this association. The sickness funds contribute a risk-adjusted capitation payment for each member to a pool administered by the association. The physician associations allocate each member practice a risk-adjusted quarterly payment per patient for covered services based on the casemix of the practice and its range of services. Practices then bill against that allocation with fees for each service that are based on a relative value scale called Einheitlicher Bewertungsmaßstab (EBM). Services that exceed the allocation are still paid albeit at a discounted rate, and some services are paid outside of the allocation via separate agreements.

Thus, practices functionally operate under a global budget as far as services covered

social insurance are concerned, which account for the bulk of their revenues. Practices can augment income with higher margin services for privately insured patients, services outside of sickness fund coverage and, for highly specialized practices, participation in clinical trials. This business model creates incentives to run high-volume practices, as their budget allocation is based on their quarterly census, but limit the use of physician time devoted to each encounter.

Hospitals – largely public or not-for-profit – with salaried staff provide inpatient care. They are paid by the Sickness Funds based on DRGs for medical admissions and per diem rates for psychiatric admissions with add-on fees for selected high-cost services and medical products. Service volume at each hospital is typically capped contractually. Hospitals are not to provide outpatient care with the exception of services related to inpatient admission and highly specialized services that are not offered by private practices. Those services are also paid under a prospective payment system with fairly low rates and usually cross-subsidized with payments for inpatient care and research funding. Especially in academic medical centers, the range of services is influenced by non-commercial objectives, like research priorities.

PRACTICES
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AS FAR AS SERVICES
COVERED UNDER
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DEMENTIA PLANNING

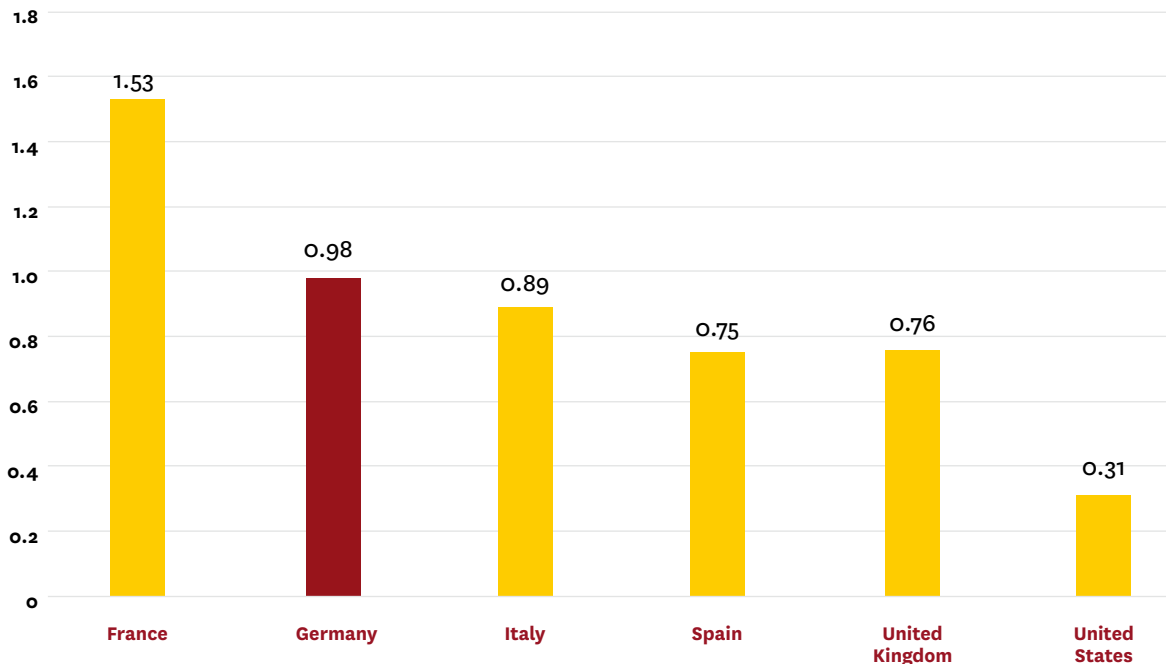
Germany does not have a national dementia plan in place, but several states have formulated their own, mostly with a focus on awareness and support for patients and caregivers. A multi-stakeholder alliance (Allianz für Menschen mit Demenz), coordinated by the Ministries of Family Affairs and of Health, launched a project in 2018 to develop such a strategy.

MCI SCREENING

Screening of asymptomatic patients is currently not recommended in the S3 Dementia Guideline (Frölich, 2010) and not covered in Germany for lack of evidence on net benefit (Mathes, 2017). It is offered as an optional service under the so-called IGeL catalog, a range of optional services that patients need to pay for out-of-pocket. It could, however, be conducted as part of a covered geriatric assessment that is covered for all patients above age 80 and for chronically ill or frail patients above age 70. Access to primary care is mostly seen as adequate, with geographic barriers primarily in the rural parts of the former East Germany, as overall density of primary care physicians is comparatively high (**Figure 9**). We learned from the interviews that primary care physicians tend to be reluctant to look proactively for signs of cognitive decline, as they are reluctant to convey bad news with limited therapeutic options and fear negative effects on patients and their families. Further, tools that are specific for the detection of early-stage cognitive decline are lacking.

Figure 9: Density of primary care physicians in Germany.

GPs per 1,000 population [2016]



Data from OECD Health Statistics (2019).

Introduction of a screening benefit would require a decision of the G-BA (Gemeinsamer Bundesausschuss - Federal Joint Committee), a body with representation of sickness funds and providers that issues directives for coverage under Germany's social insurance scheme. This body tends to rely heavily on evidence from randomized controlled trials for its recommendations and would require conclusive evidence of net clinical benefit to recommend a screening program. Even with coverage, education of primary care providers and better tools for MCI detection and tracking would be necessary to achieve uptake.

CASE FINDING

Services as part of work-up of a patient presenting with a memory complaint are covered based on physician judgment. There is a dedicated billing code for cognitive screening tests, like the MMSE, but coverage levels for these tests and evaluation of memory complaints are considered low relative to the required time. Specialist visits and imaging require a referral from the patient's primary care providers for sickness fund patients, but this requirement is not consistently enforced. Patients have a free choice of providers, who contract with the sickness funds. The perception of low payments levels combined with the limited familiarity of general practitioners with the differential diagnosis implies that patients are typically referred to specialists with limited additional work-up.

The incentives created by the current payment system to refer rather than evaluate complex cases have shaped the business model of primary care practices and are difficult to counteract. Against that background, the introduction of a blood-based test for the Alzheimer's pathology (Palmqvist et al., 2019) might be a key contribution to improving the initial evaluation of patients with memory complaints, as the test would permit triaging patients with limited effort required of the provider. In addition, improving the knowledge base of primary care providers to assess patients with memory complaints with tools and resources would be important.

THE INCENTIVES CREATED BY THE CURRENT PAYMENT SYSTEM TO REFER RATHER THAN EVALUATE COMPLEX CASES HAVE SHAPED THE BUSINESS MODEL OF PRIMARY CARE PRACTICES AND ARE DIFFICULT TO COUNTERACT.

COGNITIVE TESTING

Neurocognitive testing as part of the evaluation of a patient with a memory complaint is a covered benefit, but sickness funds commonly restrict coverage of testing to providers with documented training and/or certification in these methods. For physicians in

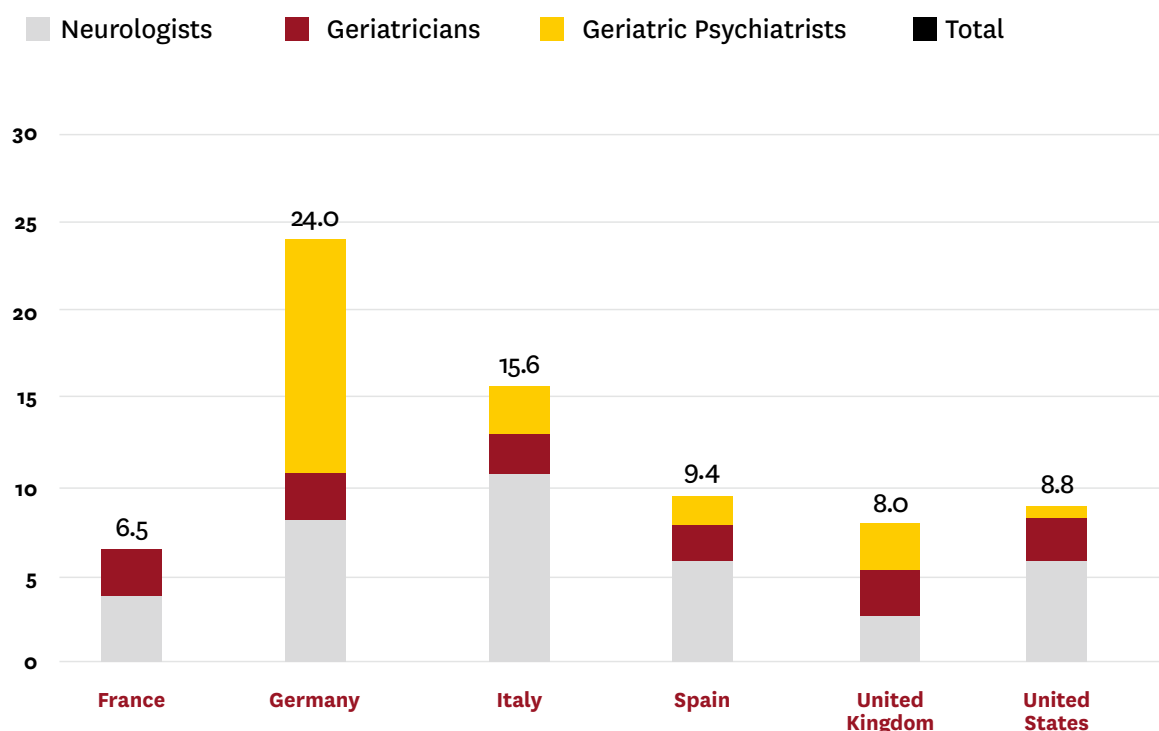
NEUROCOGNITIVE TESTING AS PART OF THE EVALUATION OF A PATIENT WITH A MEMORY COMPLAINT IS A COVERED BENEFIT, BUT SICKNESS FUNDS COMMONLY RESTRICT COVERAGE OF TESTING TO PROVIDERS WITH DOCUMENTED TRAINING AND/OR CERTIFICATION IN THESE METHOD.

private practice, payment levels are regarded as attractive, because billing (EBM 30930) is based on actual time use in five-minute increments, albeit with an upper limit of about three hours. However, the overall caps to a practice's budget may reduce the value of the billing code. Testing is also being conducted in hospital-based memory clinics that are paid through a prospective payment system.

The combination of practice-based and hospital-based specialists has resulted in a functioning ecosystem for cognitive testing with adequate capacity today, as wait times for appointments were typically reported to be less than two months. The fact that general psychiatrists, as one of the larger medical specialties, are commonly involved in dementia care helps alleviate capacity constraints compared to countries that mostly rely on neurologists and geriatricians (Figure 10).

Figure 10: Number of dementia specialists in Germany compared to other countries.

Estimated available specialists per 100,000 population



Data from OECD Health Statistics (2019).

Several specialists mentioned that they had trained technicians, who would administer the tests, to increase throughput and give themselves time to focus on the interpretation of test results and differential diagnosis. It should be cautioned, however, that the reliance of hospital-based clinics suggests limited scalability to accommodate patient demand, if a disease-modifying treatment became available. Private practices may run up against their budget cap and clinics have salaried staff, and thus neither have the incentive to increase volume substantially. Renegotiation of practice budgets and higher staffing levels, possibly with task shifting to less well-trained clinical staff, like nurses, in clinics may become necessary, as might be the introduction of tele-consultation for rural areas.

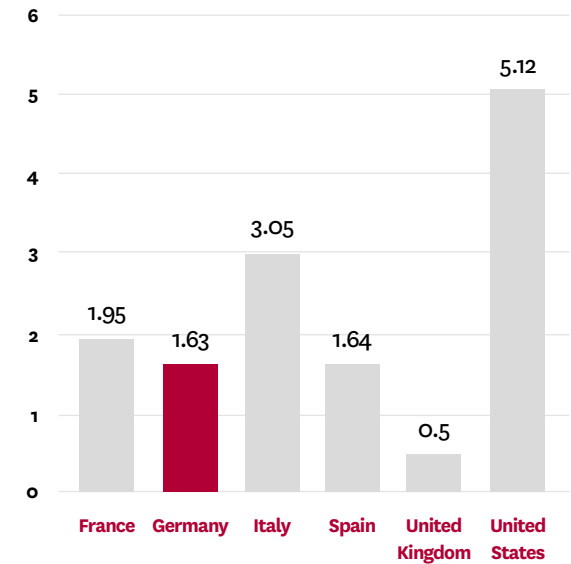
BIOMARKER TESTING

Both PET scans and examination of CSF for the hallmarks of Alzheimer's disease are approved in Germany, but sickness funds only cover CSF testing for routine cases. Coverage of PET scans may be requested, but is usually declined except for unusual cases, such as early-onset disease. In contrast, private insurers mostly cover both CSF testing and PET scans, depending on the individual's policy.

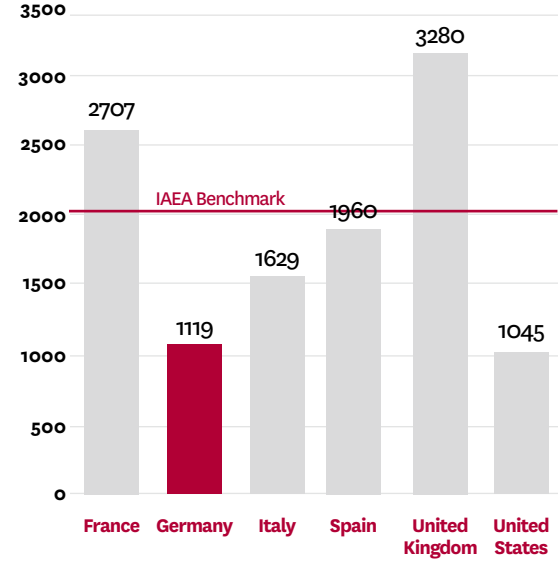
PET capacity is reportedly sufficient for current demand and may be sufficient to absorb additional demand, as utilization rates are comparatively low. But the relatively low number of devices in Germany and the fact that device capacity is mostly devoted to oncology cases might pose an obstacle for capacity expansion (**Figure 11**). Capacity is unlikely to be expanded in the absence of reimbursement.

Figure 11: Density and utilization of PET scanners in Germany.

**PET scanners
per 1M population**



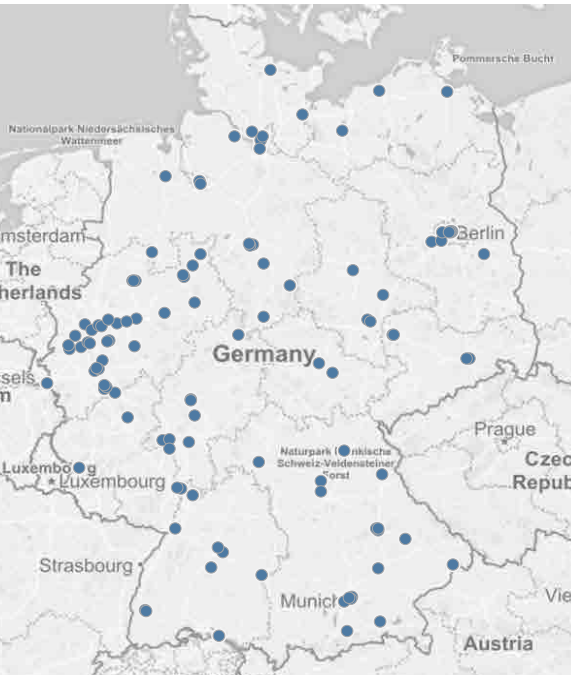
**Annual PET scans
per device**



Data from OECD Health Statistics (2019), The German Society for Nuclear Medicine (DGN) (2019), and NHS England (2019). The International Atomic Energy Association (IAEA) recommends 2000 annual scans per device as minimum threshold for efficient utilization.

Geographical coverage of PET scanners follows the distribution of the population (Figure 12), which suggests geographical obstacles to access in less populated areas.

Figure 12: Geographical distribution of PET scanners in Germany.



Data from The German Society for Nuclear Medicine (DGN) (2019).

However, the availability and coverage of a CSF test for routine clinical use, combined with acceptance of the need for diagnostic lumbar punctures by patients provide a logical pathway to expand capacity for biomarker testing. Payers are likely to prefer greater utilization of CSF testing, as unit costs are lower. Expansion of capacity for diagnostic lumbar puncture would likely have to occur in non-psychiatry specialty settings because neither general practitioners nor (most) psychiatrists are trained and equipped to conduct this procedure. Alternatively, psychiatrists could be trained or re-trained, as they are legally allowed to perform lumbar punctures if they have the necessary skills. Expansion of capacity for PET scans will hinge on a coverage decision. The G-BA currently rules the evidence for routine clinical use as insufficient, but has issued a Request for Information in November 2018 to request stakeholder input on a future coverage decision (Gemeinsamer Bundesausschuss, 2018).

TREATMENT DECISION

Specialist consultations to arrive at a treatment recommendation based on the results of cognitive and biomarker testing are covered. For physicians in private practice, the consultation is paid as an office visit, but payment levels are perceived as low relative to the required effort. Non-psychiatry memory clinics receive a quarterly prospective payment for each patient of about 90 Euro that is to cover all services rendered, including blood tests and imaging. They typically cross-subsidize these outpatient services with funding for clinical trials and inpatient services. Payment levels are attractive for psychiatry-based memory clinics as they can charge for a partial admission or day-stay. Because of this particularity, capacity for dementia-related services has grown in memory clinics run by psychiatric hospitals, whereas other specialists are reluctant to expand for lack of a business case, in spite of comparatively high specialist density as mentioned above. Memory clinics and specialists in private practice focus on diagnosis and counseling today and many, in particular psychiatrists, may find it difficult to shift to the more medicalized environment of offering a disease-modifying treatment.

CAPACITY FOR
DEMENTIA-RELATED
SERVICES HAS GROWN
IN MEMORY CLINICS
RUN BY PSYCHIATRIC
HOSPITALS, WHEREAS
OTHER SPECIALISTS ARE
RELUCTANT TO EXPAND FOR
LACK OF A BUSINESS CASE.

Consequently, alignment of payment with resource use would be the most important step to increase specialty capacity, especially in private practices. This is an important consideration because hospital-based clinics are not supposed to provide routine outpatient care, and sickness funds might restrict their ability to grow. Similarly, the ability of non-psychiatry clinics to cross-subsidize outpatient memory care might be limited. A potential pathway could be so-called *Rahmenverträge* (Umbrella Agreements), which are in place, for example, for outpatient oncology care and disease management programs for several chronic conditions. These agreements define eligibility criteria for patients and standards for practices, such as clinical pathways, range of services, as well as potential add-on payments.

Capacity could also be expanded through a greater number of treatment-oriented memory clinics, modeled after practices that provide treatment for multiple sclerosis and immunologic conditions. These practices use multidisciplinary teams to offer the full range of diagnostic and therapeutic services for complex conditions, but are unlikely to emerge well ahead of the approval of a disease-modifying treatment.

TREATMENT DELIVERY

Decisions about coverage and price of market-approved prescription drugs follow a federal process. The G-BA conducts health technology assessments to assess the value of a new treatment relative to standard of care with a heavy emphasis on data from randomized clinical trials and issues a recommendation based on a multi-criteria evaluation. This recommendation serves as the basis for price negotiations between the manufacturer and the sickness funds. Drugs dispensed

in pharmacies and administered in outpatient clinics or practices are procured through licensed pharmacies, which invoice sickness funds based on the negotiated price plus a dispensing fee¹.

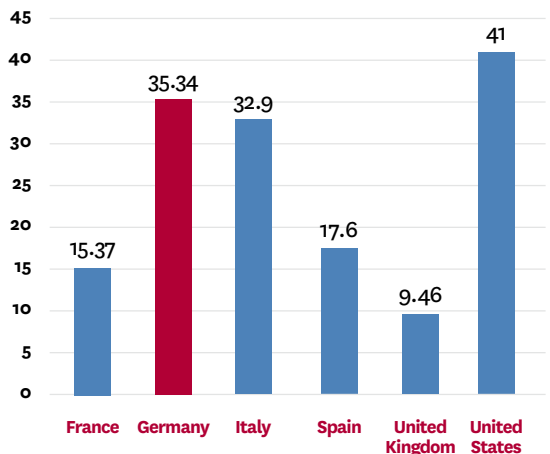
Administration of parenteral treatments would likely be initiated in a practice or clinic but could transition to the patient’s home. No data exist on capacity for infusion delivery but our experts expected that specialists, memory clinics and home infusion services could easily expand capacity if a disease-modifying treatment were approved.

MONITORING

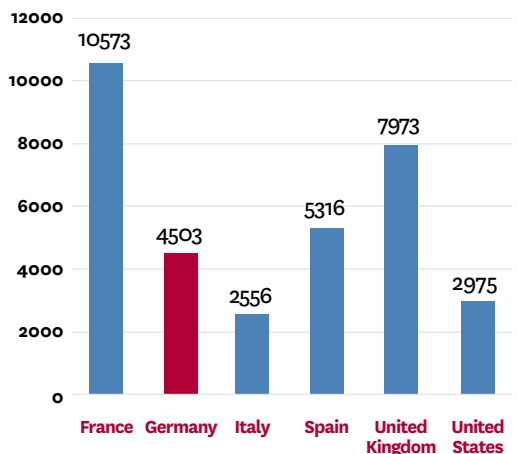
Office visits and imaging to monitor treatment effectiveness and safety will be covered according to the drug’s label and guidelines. As Germany has a comparatively high number of MRI scanners per population, but low utilization rates, MRI capacity is likely sufficient (Figure 13) but experts voiced concerns about the capacity of neuroradiologists, given the high number of expected scans during follow-up.

Figure 13: Density and utilization of MRI scanners in Germany.

MRI scanners per 1M population



Annual MRI scans per device



Data from OECD Health Statistics (2019).

Similarly, the need for follow-up visits will compound any capacity constraints for specialist care and there is no established infrastructure to support the large number of patients, who would remain in a prolonged MCI state. Primary care providers might lack the experience and tools to take on a great role in monitoring treatment effects and detecting and handling adverse effects like Amyloid Related Imaging Abnormalities (ARIA). As stated above, higher payment rates for memory-related services and expansion of treatment-oriented memory centers could better leverage existing specialty capacity.

SUMMARY

Germany has a well-resourced healthcare system with a comprehensive range of benefits and near-universal coverage. Innovations in diagnosis and treatment are sufficient

1. Legally, the requirement only applies to coverage under the Affordable Care Act, but in practice most health plans apply it for all policies.

INNOVATIONS IN
DIAGNOSIS AND
TREATMENT ARE ADOPTED
AND DISSEMINATED
REASONABLY FAST, AS
DECISION MAKING ABOUT
WHICH SERVICES AND
PRODUCTS TO COVER
AND AT WHAT PRICE
IS DEVOLVED TO THE
SICKNESS FUND AND
PROVIDER ASSOCIATIONS.

with adopted and disseminated reasonably fast, as decision making about which services and products to cover and at what price is devolved to the sickness fund and provider associations. A disease-modifying treatment for Alzheimer's disease as well as services around its administration are likely to be covered, assuming adequate value for money.

While capacity looks adequate to absorb the required increase in service volume, obstacles could arise from the centrally set policy that contribution rates to the sickness funds ought not to grow faster than wages as the underlying tax base. This policy is enforced through a combination of price controls and volume limits that functionally resembles global budgets for providers. Thus, the business case for providers to actually increase service volume fast enough is blunted.

There are three potential pathways to better align supply of and demand for memory care services. The first would be to reduce expected demand through better technology to distinguish treatment candidates from non-candidates earlier in the patient journey. Better cognitive screening tools and risk-prediction algorithms suitable for primary care settings and a blood-based biomarker could reduce the number of false-positives, who would line up for expensive and time-consuming cognitive and biomarker testing. The second would be to introduce criteria for when to stop treatment for lack of effect, as this would reduce the number of patients. The third would be to reach an understanding among stakeholders and policymakers that a temporary increase in spending for memory care services to address the large number of prevalent cases would be a worthwhile long-term investment. Germany has compulsory long-term care insurance administered by the sickness funds, i.e., savings from reducing social and nursing home care can offset higher medical costs for the same set of actors. The necessary basis to reach such an understanding would be a thorough and rigorous documentation of the long-term impact of a disease-modifying treatment on health and spending. The vehicle, through which to channel such investments, could be the umbrella contracts that are in place for care management of other complex conditions, such as oncology and pulmonary disease.

GERMANY HAS
COMPULSORY LONG-
TERM CARE INSURANCE
ADMINISTERED BY THE
SICKNESS FUNDS, I.E.,
SAVINGS FROM REDUCING
SOCIAL AND NURSING
HOME CARE CAN OFFSET
HIGHER MEDICAL COSTS
FOR THE SAME SET OF
ACTORS.



RESULTS

ITALY

HEALTH SYSTEM OVERVIEW

Italy's National Health Service (SSN) provides universal coverage to all residents, predominately (82%) funded by a mix of national and regional tax revenues (Ferré et al., 2014). A fixed proportion (38.5%, 2012 data) of the national value-added tax (VAT) accounts for 47% of the SSN financing and is used for a national equalization fund that redistributes funds to poorer regions. Regions levy a surcharge on the national personal income tax (*addizionale IRPEF*) and an earmarked corporate tax (IRAP) that cover 35% of total SSN funds. Regions may vary the tax rates to balance their healthcare budgets.

REGIONAL VARIATION IN FUNDING RESULTS IN SUBSTANTIAL DIFFERENCES IN HEALTHCARE SPENDING.

Regional variation in funding results in substantial differences in healthcare spending. According to the Ministry of Health and Finance Data, the regional per capita healthcare expenditure in 2012 ranged from 10.2% below the national average to 17.7% above. In general, northern and central regions were above the national average while regions in the south were below. Because of their lower tax base, less prosperous regions have limited room to increase spending, for

example to absorb the budget impact of novel treatment options, as they would need to increase regional taxes disproportionately with negative effects on their economy.

While primary and inpatient care are free at the point of use for all residents, out-of-pocket payments account for about 18% of the total expenditure and are largely used for diagnostic procedures, non-urgent emergency department visits, and specialist visits as well as pharmaceutical products. Private health insurance plays a minor role in terms of health service financing with only 1% of total health expenditures.

There is no uniform public coverage of social care services, so long-term care is largely the responsibility of the individual and his/her family. The National Fund for Dependency (*Fondo nazionale per la non autosufficienza* — FNA) provides support for persons with severe disabilities and elderly persons in need of long-term care, but is underfunded due to austerity measures. Benefits are means and asset dependent (Hohnerlein, 2018). Long-term care is traditionally not the responsibility of the Ministry of Health and falls into the competency of local municipalities.

Health system governance in Italy is shared between national, regional and local institutions. The Ministry of Health, which serves as the main institution at the national level, is responsible for setting fundamental guidelines, distributing of funds to the regional health authorities and designing the central benefits package (LEA) that is available to all residents.

The 20 regions (of which five have some degree of autonomy) share planning responsibilities with the central government and are exclusively responsible for the delivery of services in the regions by financing, organizing, monitoring, and delivering health care through their local and community health care units. Each region carries out legislative activities through the Regional Council and executive functions through the regional Department of Health. The duties of the regional Department of Health include drafting the three-year Regional Health Plan, coordinating health and social

care and managing local health units. Regions also play leading roles in other health-related disciplines, including food safety, health organization, and scientific research. At the local level, the 143 geographically based local health authorities (ASLs) control the provision of preventive medicine, public health, and primary care through their directly managed hospitals. Secondary and specialist care is delivered directly by the local health authorities or by public and accredited private providers.

Primary care services in Italy are usually operated by solo practitioners and delivered by health districts, which are the operative branches of local health authorities. General Practitioners (GPs) and pediatricians are independent professionals under contract with the SSN via the ASLs. More specifically, GPs and pediatricians who delivering primary care are organizationally included within the local health authorities and are paid via a combination of capitation and fee-for-service with a regulated fee schedule. They serve as gatekeepers for referrals to specialty care and are incentivized to limit referrals and prescriptions.

Once patients receive a referral, they are free to see any public or accredited private provider. Patients also have options to skip the wait time or choose a specific specialist by paying for the specialist visit out-of-pocket. Prescriptions originating from that visit would still be reimbursed by the SSN. Outpatient specialty care is coordinated by ASL and delivered through either local health authorities or public and accredited private providers. Most specialists are hospital employees and practice in outpatient clinics that are attached to their hospital, but they are allowed to treat private-pay patients either in the clinic or in a separate facility. Apart from the co-payment, outpatient specialty care is covered by the SSN with the referral from GPs by a tariff per unit of service.

Inpatient care is provided by a network of accredited public and private hospitals, with as many as 30% of admissions handled by private hospitals in some regions (Lazio, Campania, Molise, Lombardy). Hospitals in Italy are divided into three levels (Basic, Level I and Level II) based on their specialization and capacity to treat emergencies. Hospital care is paid on a DRG basis with add-on payments for certain procedures. Rates for hospital and outpatient care delivered in local health units, public hospitals, and accredited public practice are determined by the ASLs using the national rates as reference.

MOST SPECIALISTS ARE
HOSPITAL EMPLOYEES
AND PRACTICE IN
OUTPATIENT CLINICS THAT
ARE ATTACHED TO THEIR
HOSPITAL, BUT THEY
ARE ALLOWED TO TREAT
PRIVATE-PAY PATIENTS
EITHER IN THE CLINIC OR
IN A SEPARATE FACILITY.

DEMENTIA PLANNING

As dementia is recognized as a substantial public health problem, government agencies have embarked on several planning activities. A joint conference of the central and regional governments issued a national dementia plan in 2014 (Presidency of The Council of Ministers Unified Conference, 2014). The plan provides a framework for dementia care and defines four objectives:

1. To raise public awareness to promote strategies for primary and secondary prevention, create a standing high level platform across health authorities and develop information systems to monitor health system progress.
2. To reorient and further develop the health care system in accordance with the needs of integrated care for dementia patients and to develop a national observatory.
3. To develop and implement standards of care regionally and locally and to promote provider education.
4. To educate the public to reduce stigma and barriers to access for patients and their families.

THE ITALIAN
MEDICINES AGENCY IN
COLLABORATION WITH
AN EXPERT GROUP
HAS LAUNCHED THE
INTERCEPTOR PROJECT,
A PROSPECTIVE STUDY
TO USE BIOMARKERS
AND COGNITIVE TESTS
IN PATIENTS WITH MCI
TO BE ABLE TO PREDICT
WHICH SUBSET IS AT RISK
OF PROGRESSION TO
ALZHEIMER'S DISEASE.

A national expert commission has issued recommendations on patients' pathways for dementia based on integrated care (Unificata, 2017). The recommendations, which were endorsed by the joint conference of central government and regions, address early detection, diagnosis and management and define the functions of the institutions involved. The expert group monitors the translation of the national plan into regional planning and implementation. The dementia national observatory brings together updated information about guidelines and patient pathways and a detailed list of memory clinics ("Osservatorio Demenze dell'Istituto Superiore di Santita," 2019). Several regions have translated the recommendations into guidelines (Regione del Veneto, 2019) (Indelicato & Podavitte, 2016).

The Italian Medicines Agency in collaboration with an expert group has launched the Interceptor Project, a prospective study to use biomarkers and cognitive tests in patients with MCI to be able to predict which subset is at risk of progression to

Alzheimer's disease ("Interceptor – The Project," 2019). The explicit objective of the project is to identify and prioritize these patients for access to a disease-modifying treatment.

MCI SCREENING

There is currently no recommendation or program in Italy that promotes or organizes systematic screening for cognitive impairment or dementia. Screening activities are therefore not covered by the national health system and there is no dedicated capacity in the primary care system.

The National Center for Screening Monitoring, an agency in the Ministry of Health, is responsible for recommending screening programs and to monitor their implementation. The introduction of a screening program for cognitive impairment and/or dementia would

require modifications of the national dementia plan and the regional guidelines and patient pathways. At the level of primary healthcare, capacity would need to be substantially increased to absorb the additional workload.

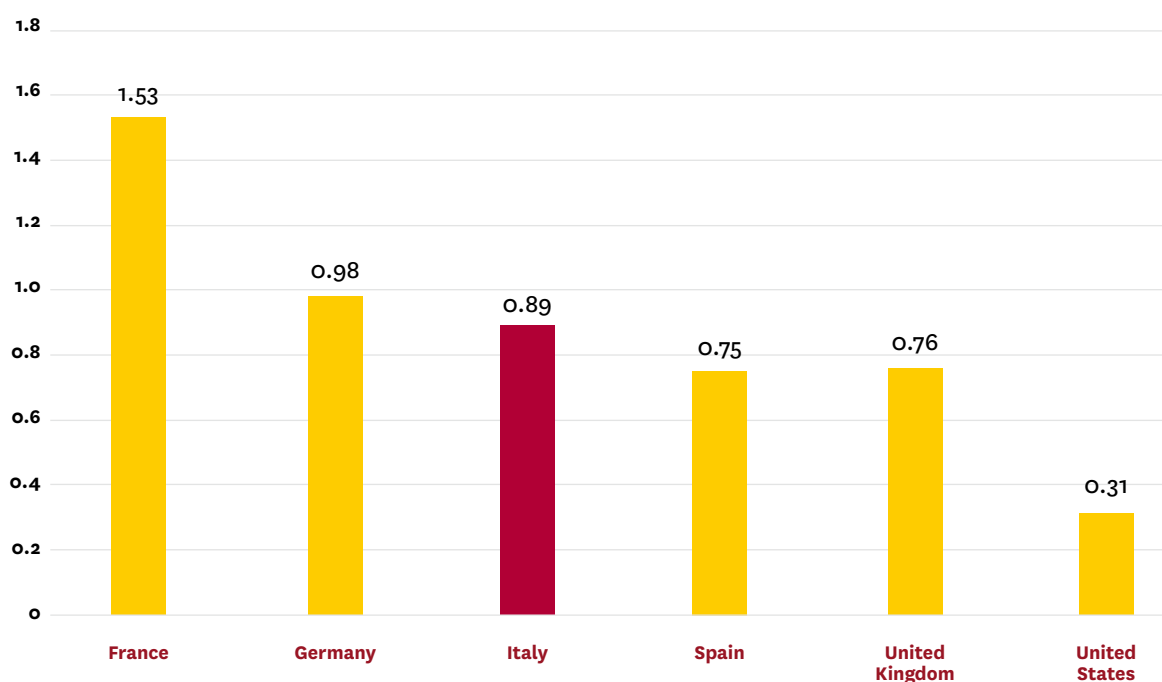
CASE FINDING

Services to evaluate a patient, who presents with a memory complaint in primary care settings, are covered by the national health care package. While access to primary is not constrained with density at the EU-5 average (**Figure 14**), the central role of general practice in the patient journey implies high workload and limited flexibility to add time-consuming tasks, such as initial cognitive testing, into day to day practice. As current payment arrangements put practices under a global budget, they have limited incentive to increase either patient panel size or throughput to accommodate additional demand. Regional dementia guidelines provide directions for primary care physicians on evaluation of memory complaints, but skill levels tend to be limited and underdiagnosis remains common (Veneziani et al., 2016).

THE GROWING REALIZATION THAT CONVENTIONAL PAYMENT AND PRACTICE MODELS FOR PRIMARY CARE ARE NOT CONDUCTIVE TO TREATMENT OF PATIENTS WITH CHRONIC CONDITIONS HAS LED TO EXPERIMENTATION WITH INTEGRATED CARE MODELS IN SOME REGIONS.

Figure 14: Density of primary care providers in Italy.

GPs per 1,000 population [2016]



Source: OECD Health Statistics (2019).

The growing realization that conventional payment and practice models for primary care are not conducive to treatment of patients with chronic conditions has led to experimentation with integrated care models in some regions. These models provide incentives to form primary care group practices and hire support staff and/or form multispecialty groups including specialists (Armeni, Compagni, & Longo, 2014). Other regional authorities are promoting population health approaches that encourage and reward team-based primary care with specialists, nurses, and social workers (Donatini). According to Ministry of Health data, around 70 percent of primary care physicians and 60 percent of pediatricians had joined a team-based practice as of 2012 (Ministero della Salute, 2015). To increase early detection of cognitive decline, these changes in practice models would have to be accompanied by increased public awareness and improved skill levels. While the national dementia plan calls for both, regional implementation is lagging because only the Emilia Romagna region has so far allocated budget to these objectives.

COGNITIVE TESTING

Italy follows a gatekeeping model, i.e., primary care physicians decide whether or not to refer patients with suspected cognitive decline for cognitive testing. Moreover, per capita spending targets for specialty care and prescription drugs reward primary care physicians for cost control. If referred, further evaluation is a covered benefit and the default institutions to receive the patient are the so-called memory centers (*Centro di Disturbo Cognitivo e Demenze* - CDCD). A national network of these clinics with adequate regional coverage (**Figure 15**) was set up following the recommendation of the national dementia plan and ensuing regional recommendations.

Figure 15: Geographic distribution of memory centers in Italy.

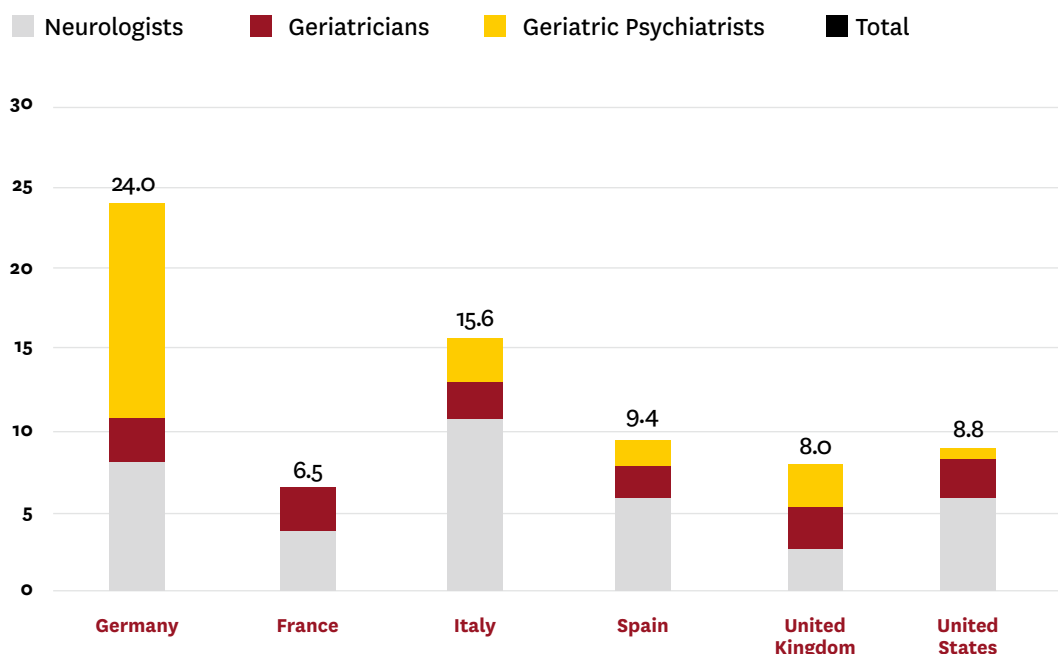


The clinics are staffed by salaried teams of neurologists, geriatricians and psychiatrists and infrequently also by psychologists and other support staff. At current levels of demand and because of the relative high number of dementia specialists per capita (**Figure 16**), the 536 existing memory centers formally have sufficient capacity to assess referred cases within two to three months and nationwide coverage (Osservatorio Demenze dell'Istituto Superiore di Santita, 2019).

Source: Osservatorio Demenze dell'Istituto Superiore di Santita (2019).

Figure 16: Number of dementia specialists per capita in Italy compared to other countries.

Estimated available specialists per 100,000 population



Data from OECD Health Statistics (2019).

However, funding levels and thus staffing of memory clinics vary widely with a north-to-south gradient reflecting differences in regional prosperity and thus healthcare spending (Nembri, 2018). For example, a recent survey of 501 of the 536 memory clinics showed that only half of them administered formal neurocognitive tests to patients with memory complaints, with significantly lower rates in southern Italy and non-university-based centers (Di Pucchio et al., 2018). According to our interviews, limited funding in southern regions also means that several of the listed memory clinics are not functional,

FUNDING LEVELS AND THUS STAFFING OF MEMORY CLINICS VARIES WIDELY WITH A NORTH TO SOUTH GRADIENT REFLECTING DIFFERENCES IN REGIONAL PROSPERITY AND THUS HEALTH CARE SPENDING.

especially outside of the larger cities. These constraints may have contributed to findings that a higher proportion of dementia patients are undiagnosed in Italy than in other European countries (Europe, 2018). The fact that specialists may see patients privately in addition to their duties as employees of the clinics further limits available capacity.

Increasing capacity and capabilities of the memory clinics to the demand created by the advent of a disease-modifying drug would, first and foremost, require additional resources. It may be possible to use existing funds more efficiently, for example by introducing hub and spoke models for clinics and greater use

of ancillary staff and by incentivizing specialists to devote more time to the clinics, but our experts were skeptical that the clinics, especially in poorer regions, could cope with the additional demand without additional funds. Further, standardization of testing

procedures would be required to increase the rate of proper diagnoses.

BIOMARKER TESTING

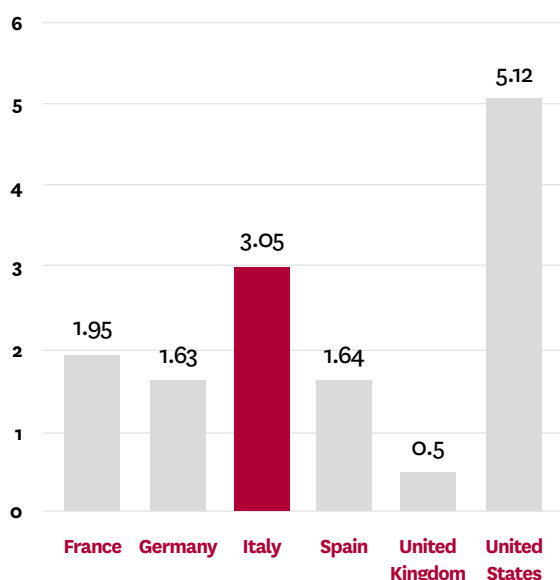
Confirmatory testing for the biological hallmarks of Alzheimer's disease based on CSF testing or PET scans is a covered benefit under Italy's national health system, if ordered by the team at the memory center based on cognitive test results. Biomarker testing would even be covered if a patient saw a dementia specialists outside of the national health system and received a referral for testing. Many memory clinics have staff neurologists or affiliations with hospitals and thus capabilities to conduct lumbar punctures as well as room to ramp up utilization. As biomarker testing is only used rarely today, capacity for lumbar punctures and PET scanning is sufficient for current demand. A concern is, however, that few laboratories in Italy are able to conduct CSF testing for Alzheimer's biomarkers and that standardization of specimen preparation, testing and quality control is limited (Sancesario et al., 2018).

CONFIRMATORY TESTING
FOR THE BIOLOGICAL
HALLMARKS OF
ALZHEIMER'S DISEASE
BASED ON CSF TESTING
OR PET SCANS IS A
COVERED BENEFIT UNDER
ITALY'S NATIONAL
HEALTH SYSTEM, IF
ORDERED BY THE TEAM
AT THE MEMORY CENTER
BASED ON COGNITIVE
TEST RESULTS.

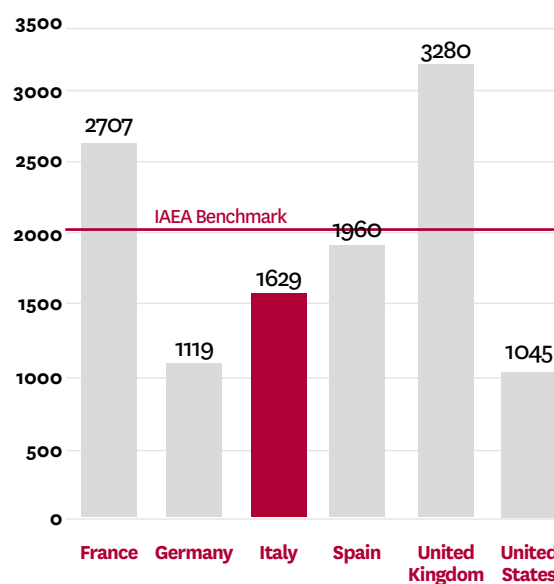
After substantial investment into PET scanner capacity that almost doubled the installed base to 196, from 2007 to 2016, Italy has one of the highest numbers of devices per capita in Europe (Statista, 2019). Combined with a comparatively low utilization rate, excess capacity that could be devoted to scanning for Alzheimer's pathology appears to be available (Figure 17). With the available capacity for lumbar punctures, testing capacity appears to be adequate to accommodate the additional demand triggered by the advent of a disease-modifying treatment, provided sufficient funding were available.

Figure 17: Density and utilization of PET scanners in Italy.

PET scanners per 1M population



Annual PET scans per device



Data from OECD Health Statistics (2019), The German Society for Nuclear Medicine (DGN) (2019), and NHS England (2019). The International Atomic Energy Association (IAEA) recommends 2000 annual scans per device as minimum threshold for efficient utilization.

TREATMENT DECISION

Based on the national recommendations for patient pathways, the memory clinics would be in charge of the decision and follow-up regarding pharmacological and non-pharmacological interventions (Linee di indirizzo Nazionali sui Percorsi Diagnostico Terapeutici Assistenziali per le demenze, 2017). By the time a disease-modifying treatment is approved, it is expected that results from the Interceptor Project will offer guidance on which patients are eligible for treatment and which should be prioritized, given the high risk of disease progression (“Interceptor – The Project,” 2019). The approval of coverage for a treatment is handled by the Italian Medicines Agency (AIFA). Given the expected budget impact, the agency is likely to base coverage decisions on hard endpoints, such as avoidance of nursing home admissions, and a cost–benefit evaluation. Depending on the route of administration, the treatment could be listed in the National Pharmaceutical Formulary as Class A Medicine, i.e., distributed by pharmacies and reimbursed with a modest co-payment that varies across regions, or as Class H, i.e., administered within facilities under specialist supervision without patient co-payment.

TREATMENT DELIVERY AND MONITORING

No data on infusion capacity were available for Italy, but the substantial network of memory centers, which tend to be affiliated with hospitals and staffed by neurologists, suggests that they could offer

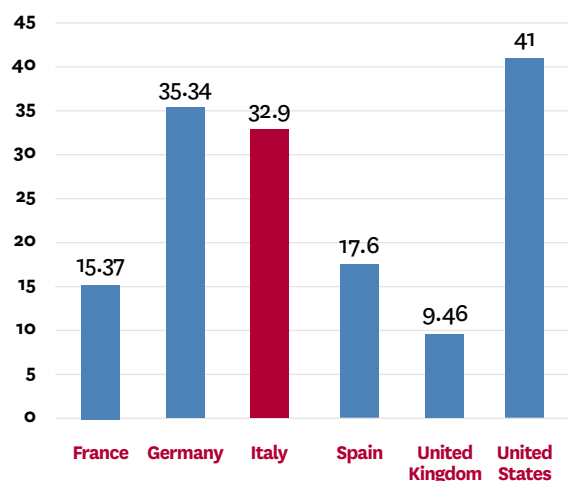
AS ITALY HAS A COMPARATIVELY HIGH NUMBER OF MRI DEVICES PER CAPITA AND LOW UTILIZATION RATES, EXPANSION TO FUTURE NEEDS APPEARS POSSIBLE.

sufficient capacity and capabilities for treatment delivery, even if intravenous infusion were necessary.

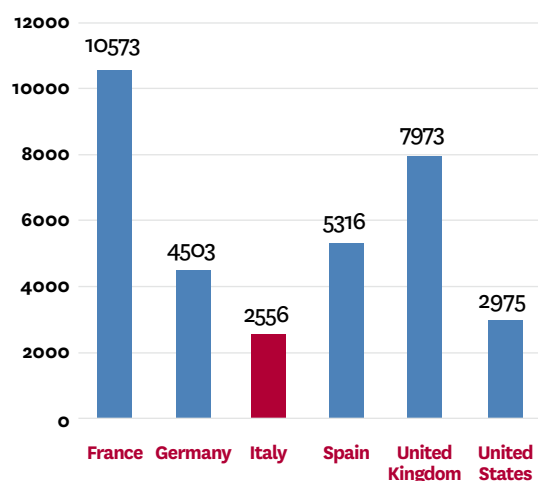
Services to monitor effectiveness and safety of a treatment would be covered by the national health system in alignment with its label and also be coordinated by the memory clinics. As Italy has a comparatively high number of MRI devices per capita and low utilization rates (**Figure 18**), expansion to future needs appears possible.

Figure 18: Density and utilization of MRI scanners in Italy.

MRI scanners per 1M population



Annual MRI scans per device



Data from OECD Health Statistics (2019).

SUMMARY

As with the other EU-5 countries, Italy has universal access to healthcare with limited cost-sharing and a robust delivery system, albeit with regional differences. Italy is unique among the EU-5, however, in that it is the only country with a government-led planning process to prepare for a disease-modifying treatment for Alzheimer's disease, even though this plan was initiated by a previous government and is not yet fully resourced. The cornerstone of the plan is the Interceptor Project, which aims at developing a risk prediction model to identify patients at risk for disease progression using a cost-effective combination of biomarkers and cognitive tests. The project was launched because of a realization that neither capacity nor finances will allow treatment of all patients with MCI, so prioritization will be inevitable.

The project builds on a long-tradition of dementia care planning. In 2000, the Ministry of Health had launched the CRONOS Project (Valerio, Lepore, & Giunco, 2001) as a post-marketing cohort

study after the introduction of the first symptomatic dementia medicines. In addition, to evaluate the effectiveness of those medicines under real-world conditions, the project has catalyzed health system changes, such as the establishment of the first memory clinics, public awareness campaigns to promote early diagnosis of dementia, and educational programs for primary care physicians (Bellelli et al., 2005).

The 2014 national dementia plan provides a framework for patient pathways and service delivery, which has been translated into regional guidelines. A national expert group provides ongoing guidance and a dementia observatory tracks data. While strategic planning in Italy is very thoughtful and infrastructure well developed, many recommendations have not been implemented because of limited funding. Only the Emilia Romagna region has allocated earmarked funds to its regional dementia plan, whereas the planned activities have to compete with other priorities in the remaining regions. Tight public finances, in particular in the less prosperous regions, leave little room to maneuver. A broader policy debate about resourcing the dementia plans seems necessary in light of the potential availability of a disease-modifying treatment, especially as Italy is one of the fastest aging EU countries.

WHILE STRATEGIC
PLANNING IN ITALY IS
VERY THOUGHTFUL
AND INFRASTRUCTURE
WELL DEVELOPED, MANY
RECOMMENDATIONS
HAVE NOT BEEN
IMPLEMENTED BECAUSE
OF LIMITED FUNDING.



RESULTS

SPAIN

HEALTH SYSTEM OVERVIEW

Spain has a National Health System (Sistema Nacional de Salud) with universal coverage of medical care for all Spanish and EU citizens and all other permanent foreign residents in accordance with their work status (Bernal-Delgado et al., 2018). It is tax-funded with 75% of funds coming from central government taxes and 25% of funds raised through regional taxation at the level of the 17 Autonomous Regions (*Comunidades autonomas*). A redistributive mechanism operated by the central government adjusts for some but not all of regional differences in the tax base and hence funding levels. In the aftermath of the 2009 financial crisis, with a decline of GDP by 20% from 2009 to 2015, substantial reforms were implemented to ensure the sustainability of the system, such as substantial budget cuts, increased co-payments for prescription drugs, more centralized decision making and priority setting, and restrictions on the Autonomous Regions' discretion on spending. In addition, a new System for Promotion of Personal Autonomy and Assistance for Persons in a Situation of Dependency (SAAD) was introduced in 2006 to cover social services (Peña-Longobardo, Oliva-Moreno, García-Armesto, &

THE ENTRY POINT INTO THE HEALTHCARE SYSTEM ARE PRIMARY CARE PROVIDERS, WHO TYPICALLY PRACTICE IN CARE TEAMS AS SALARIED EMPLOYEES OF PUBLIC FACILITIES.

Hernández-Quevedo, 2016). It is funded by contributions from the Autonomous Regions (62%), the Central Government (18.1%) and beneficiaries (19.9%) and also affected by the austerity measures, which resulted in benefit cuts and wait times for eligible beneficiaries to gain access to the scheme.

Governance of the healthcare system is shared between the central government with the Ministry of Health and its subordinate institutions and the health authorities of the autonomous regions. The central government sets the overall framework and the common benefits package, whereas the regional health authorities are responsible for financial and

infrastructure planning and services provision. Regional health authorities may offer benefits in addition to the common benefits package, depending on financial resources, which can result in interregional variation of management, quality and coverage of services.

Regional health authorities contract for services with public and private providers through global budgets that are on projected cost and quality of service volume. Services are free of charge at the point of service apart from co-payments for outpatient prescription drugs that are included in the common benefits package. Out-of-pocket contributions is regulated to be up to one-third of the retail price of the drug, with exemptions for chronic conditions. Around 20% of the population hold supplemental private insurance policies that provide faster access to care and coverage of some additional benefits, such as dental and eye care.

The entry point into the healthcare system is primary care providers, who typically practice in care teams as salaried employees of public facilities. Their salary may be complemented by pay-for-performance contributions. For example, in Catalonia variable payment schemes based on quality and volume targets have been introduced for primary care providers.

(Benavent et al., 2009) Access to specialist care in outpatient clinics and hospitals usually requires a referral, but there are several pilot projects on integrated care models for chronic conditions that either introduce standardized patient pathways or combine primary and specialty care in one organization (Nuño, Sauto, & Toro, 2012).

DEMENTIA PLANNING

The government of Spain approved in 2016 a national plan for neurodegenerative diseases (Ministerio de Sanidad, 2017), which provides a general framework from early detection to chronic care. Implementation, resource planning and budget allocation is in the hands of the Autonomous Regions that all have their own plans and regional guidelines for dementia care, albeit with varying levels of comprehensiveness and currency, according to the below-mentioned expert review (Mateos, Franco, & Sanchez, 2010).

In addition to governmental efforts, an independent expert group has been established in 2016 supported by an unrestricted grant from Eli Lilly Spain (Martinez-Lage, Martin-Carrasco, Arrieta, Rodrigo, & Formiga, 2018). It has taken the initiative to review currently available dementia plans at the national and regional levels, to assess gaps and to develop recommendations to align dementia services with current evidence. The final report of this project specifically discusses the health system implications of implementing disease-modifying treatment for Alzheimer's disease.

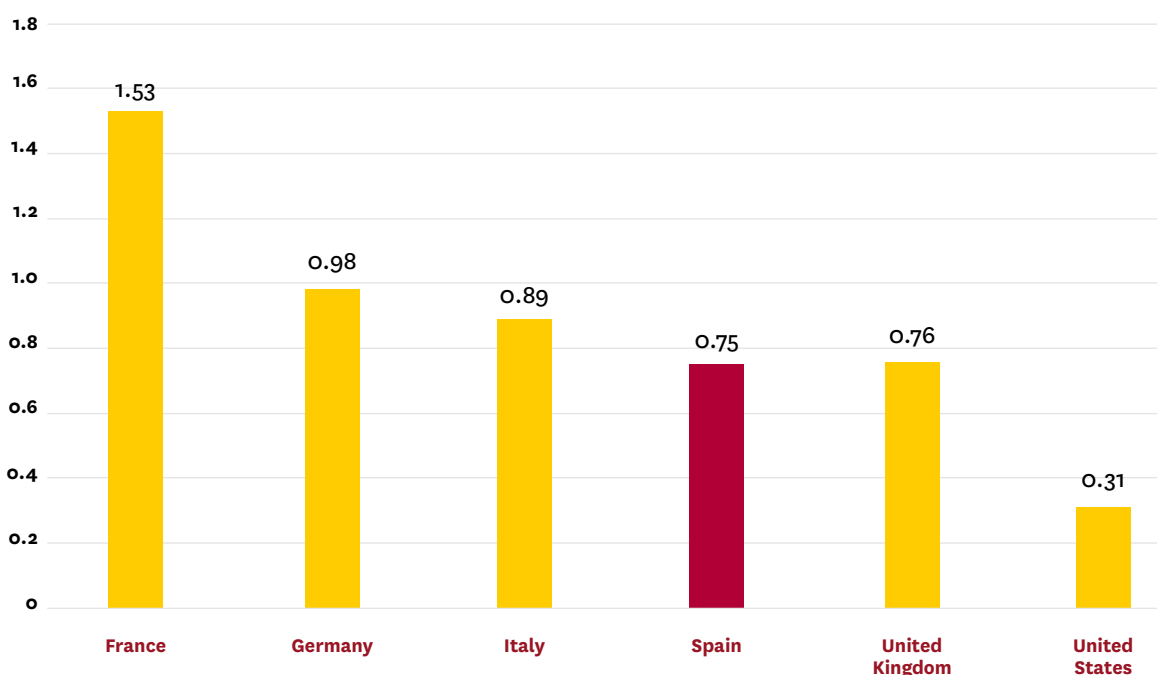
MCI SCREENING

Systematic screening for cognitive impairment or dementia in primary health care is currently not included in the national benefits package, nor is it part of any regional dementia plans and guidelines. However, the 2016 national plan for neurodegenerative diseases has, as one of its objectives, the improvement of early detection (Ministerio de Sanidad, 2017). Implementation would require incorporation into regional plans and corresponding resource allocation, which may prove difficult for several reasons.

The main issue is that freeing up the required capacity in primary care offices would be challenging. First, Spain relies heavily on primary care for coordination and delivery of services, but only has an average density of providers (**Figure 19**). Second, primary care physicians are mostly salaried civil servants and have limited incentive and control to adjust workloads and workflow. Third, limited training and awareness of memory disorders, as well as a lack of standardized assessment tools, might lead to a high number of unnecessary specialist referrals. Thus, a screening program would require capacity increases in primary care, potentially complemented by pay-for-performance schemes.

Figure 19: Density of primary care providers in Spain.

GPs per 1,000 population [2016]



Data from OECD Health Statistics (2019).

Several regional initiatives (such as STOP ALZHEIMER 2020 in the Basque region) have started awareness campaigns to educate about dementia and to address the common misconception that dementia is part of normal aging.

CASE FINDING

Evaluation of a patient presenting with self- or family-identified memory complaints in primary care is a covered benefit under the national health system and access to primary care is not capacity constrained at current levels of demand for services. However, the capability of primary care physicians to conduct an initial evaluation of memory complaints is reportedly limited, partly because of limited tools and protocols. In addition, there is skepticism about the benefit of correctly diagnosing and quantifying cognitive decline and investigating its etiology because of the perceived lack of therapeutic consequences (Martinez-Lage et al., 2018). As a result, patients are either referred to specialists with limited diagnostic work-up or, more commonly, not at all. To improve detection rates and quality of initial evaluation, the MapEA Expert Group recommends continuous medical education for primary care physicians and development of tools and protocols for primary care settings, such as simple cognitive tests and blood-based biomarkers for Alzheimer's disease.

SEVERAL REGIONAL INITIATIVES (SUCH AS STOP ALZHEIMER 2020 IN THE BASQUE REGION) HAVE STARTED AWARENESS CAMPAIGNS TO EDUCATE ABOUT DEMENTIA AND TO ADDRESS THE COMMON MISCONCEPTION THAT DEMENTIA IS PART OF NORMAL AGING.

COGNITIVE TESTING

Upon referral from a primary care provider, further evaluation of memory complaint with cognitive testing is a covered benefit. Testing is conducted in various facilities, depending on regional resources and historic practice patterns. The most common sites are outpatient clinics of hospital-based neurology departments named “Consultas Monograficas de Demencia”, which specialize in memory care. Other sites include psychiatric institutions, such as the psychogeriatric units in the Autonomous Region of Galicia and the Autonomous Region of Zamora, and general neurology clinics. Lastly, there are six multidisciplinary specialized memory units in the autonomous regions of Basque, Valencia and Murcia and a regional center of excellence, the ACE Foundation, in Barcelona. **Figure 20** displays the regional distribution of all kinds of memory services, indicating geographic variability in access.

Importantly, neuropsychologists’ services are not included in the common benefits package, leaving cognitive testing to neurologists and psychiatrists. Some institutions, such as the six specialized memory units and the ACE Foundation, fund neuropsychologists from other sources such as research budgets or charitable giving. Reportedly, testing capacity is adequate at current levels of demand with wait times of about 2–3 months.

Figure 20: Geographic distribution of memory services in Spain.



Source: *Mapa de la enfermedad de Alzheimer y otras demencias en España* (Lilly, 2017).

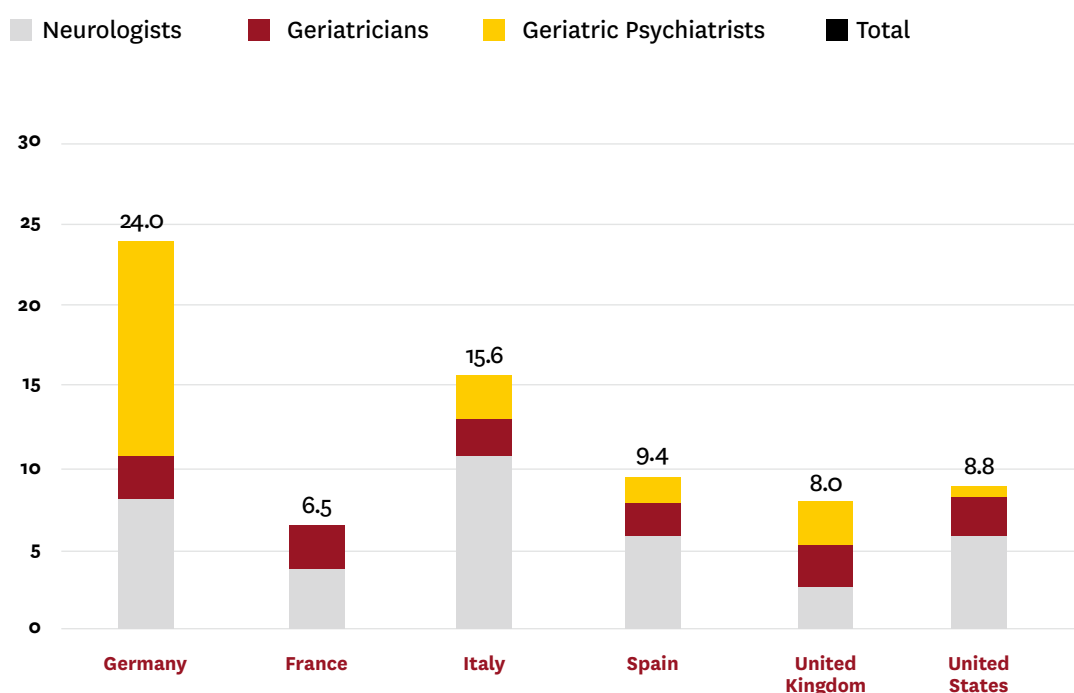
The heterogeneity of institutions providing memory services and the absence of national standards implies substantial variability in scope and quality of the diagnostic work-up work-up of patients with memory complaints. The MapEA expert group (Martinez-

Lage et al., 2018) therefore recommends the creation of multidisciplinary memory centers with standardized patient pathways, to which primary care physicians would refer to directly, a recommendation that is also found in the national plan for neurodegenerative diseases. This would avoid referrals to general neurology and psychiatry clinics that may lack staff and skills to conduct comprehensive evaluations. The group also recommends inclusion of neuropsychologists into the care team, especially in light of the limited number of dementia specialists in Spain (Figure 21).

ACTUAL USE OF BIOMARKER-BASED ALZHEIMER'S DISEASE DIAGNOSIS IS CURRENTLY VERY LIMITED AND VARIES BECAUSE OF DIFFERENCES IN REGIONAL GUIDELINES AND PRACTICES.

Figure 21: Number of dementia specialists per capita in Spain compared to other countries.

Estimated available specialists per 100,000 population



Data from OECD Health Statistics (2019).

BIOMARKER TESTING

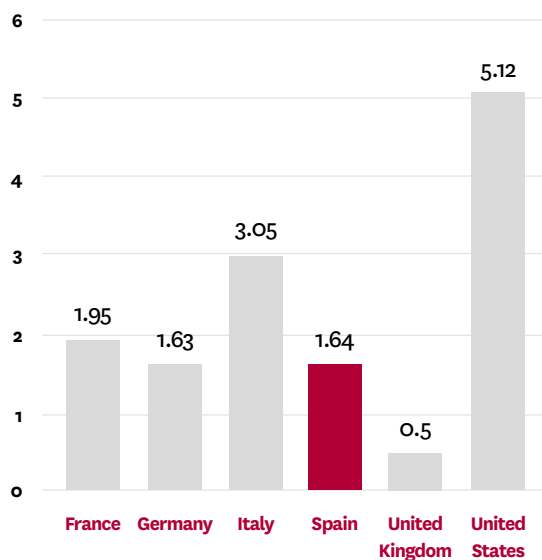
Lumbar punctures and CSF testing for the hallmarks of Alzheimer's disease are routinely covered by the National Health System (SNS), whereas PET scans are reserved to younger patients (age <65 years) and those presenting atypical and rapidly deteriorating dementia. Actual use of biomarker-based Alzheimer's disease diagnosis is currently very limited and varies because of differences in regional guidelines and practices. In some Autonomous Regions, for instance Catalonia, lumbar punctures are routinely

performed, whereas in other regions they are only used in the context of clinical studies. As a result, there is enough capacity to perform lumbar punctures, partly because specialist evaluation is mostly in the hands of hospital-based neurologists, who are well trained in this procedure and have access to the necessary procedure and recovery rooms. Scaling lumbar punctures to other types of specialists and institutions, however, may be challenging. A related concern is that clinical laboratories are not following nationally agreed quality standards for Alzheimer biomarkers (Martinez-Lage et al., 2018), which might limit the validity of test results. In the general public, lumbar punctures are perceived as a risky and uncomfortable, leading to patient reluctance to undergo these procedures (Martinez-Lage et al., 2018).

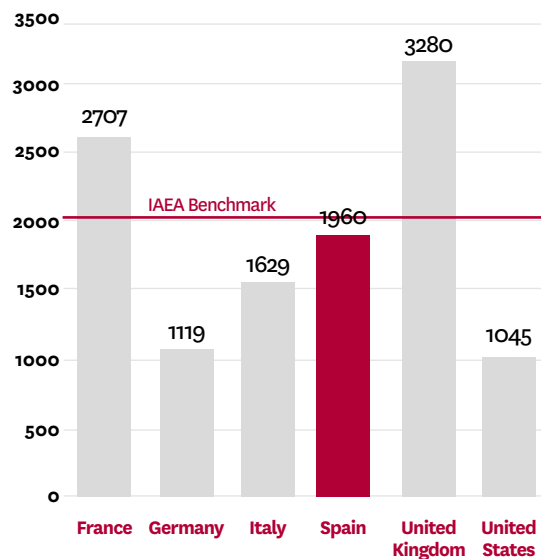
Capacity to conduct additional PET scans in Spain appears limited. While the installed base per population is comparable to that of Germany and France, current utilization rates per device are comparatively high, which limits room to conduct additional scans (Figure 22). Tight public finances and lengthy processes for approval and installation of new imaging equipment make substantial expansion of PET capacity unlikely in the near future. Further, cyclotron facilities are concentrated in the more densely populated areas (Figure 23), which may impose limits to operating PET scanners in the more rural areas of northwestern and central Spain. Combined with the fact that memory care lies largely in the hand of hospital-based neurologists, greater utilization of CSF testing is the likely path in Spain.

Figure 22: Density and utilization of PET scanners in Spain.

PET scanners per 1M population

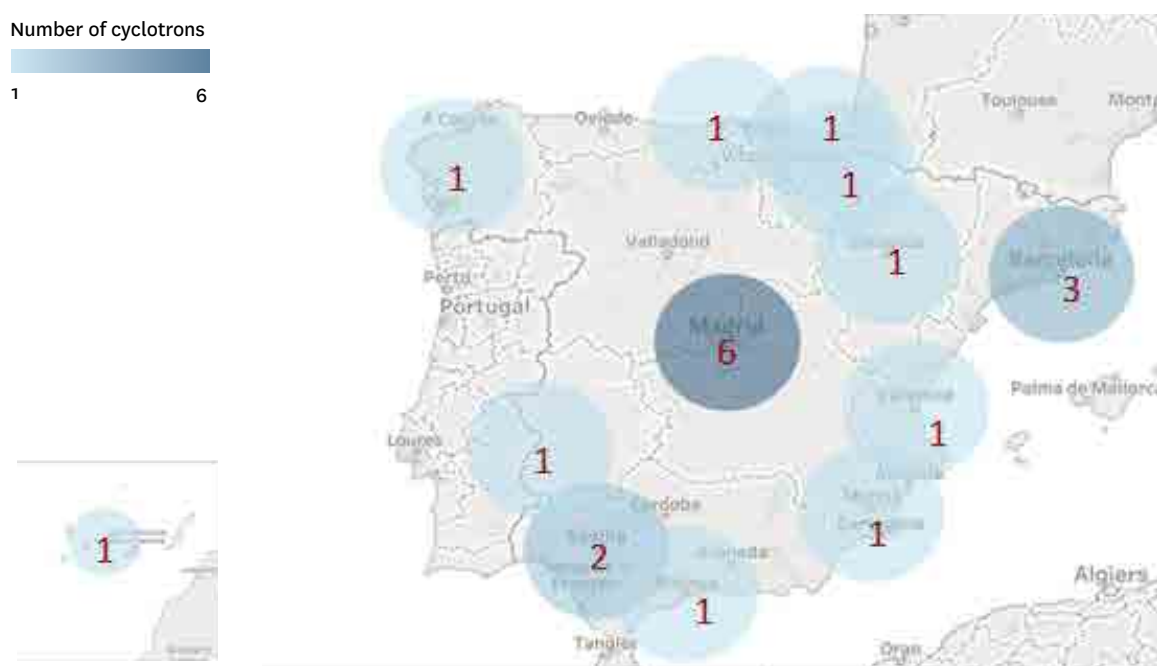


Annual PET scans per device



Data from OECD Health Statistics (2019), The German Society for Nuclear Medicine (DGN) (2019), and NHS England (2019). The International Atomic Energy Association (IAEA) recommends 2000 annual scans per device as minimum threshold for efficient utilization.

Figure 23: Geographic distribution of cyclotrons in Spain.



Source: IAEA (2019). Circles represent 200 km radius around city of device location.

TREATMENT DECISION

The final interpretation of cognitive and biomarker testing results would likely be in the hands of the facility, to which the patient is referred for initial evaluation. Thus, concerns about variability in access and decision making pertain as well, as does the likely solution in form of multidisciplinary memory units.

TREATMENT DELIVERY

It is foreseeable that a disease-modifying treatment would be included in the national benefits package, if approved by the national health authority, which would base its decision on an evaluation of risk–benefit profile and price. Patient cost-sharing will depend on the exact nature of the treatment, as pharmacy–dispensed drugs but not hospital- or clinic-administered drugs are subject to co-payments.

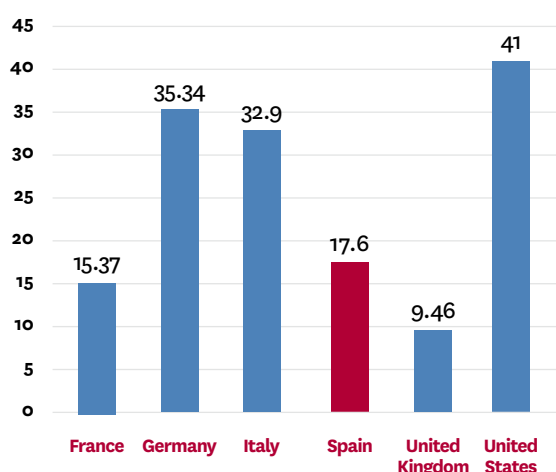
There are no data on capacity for a potential intravenous treatment, but experts do not expect major obstacles to access to arise from infusion capacity. For example, the widespread introduction of oncology day hospitals (Jara, Ayala, & Virizuela, 2017) provides a model for outpatient delivery of complex treatments at scale and under standardized protocols.

MONITORING

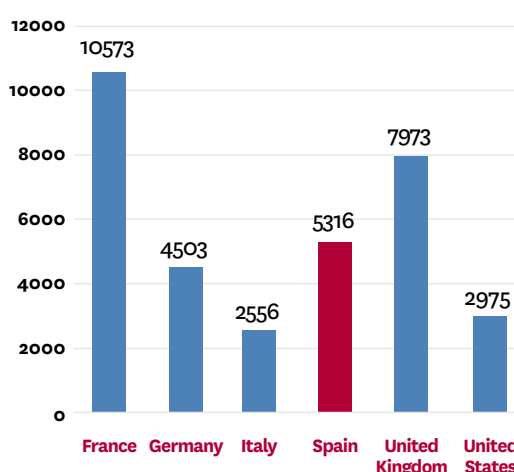
Monitoring of safety and efficacy of treatment would require follow-up appointments with specialists and neuroimaging, which are likely to be covered as part of the standard benefits package. As pointed out above, limited specialist capacity means that follow-up will compound the wait lists for specialist appointments. According to the MapEA group, CT or MRI neuroimaging is regarded as standard of care in dementia evaluation, but with wait times even at today's demand because of limited density and high utilization of installed devices (**Figure 24**). Thus, MRI capacity for post-treatment monitoring would need to be expanded, which will be difficult because of tight public finances.

Figure 24: Density and utilization of MRI scanners in Spain.

MRI scanners per 1M population



Annual MRI scans per device



Data from OECD Health Statistics (2019).

SUMMARY

Among the largest EU economies, Spain is in an unusual situation in that its economic development after World War II started later and was less steady than in countries like Germany and France. Further, the post-2009 financial crisis hit Spain particularly hard because of the dependence of the economy on the property market, resulting in substantial cutbacks in healthcare spending. As a consequence, its health system is more capacity-limited than the current spending levels would suggest, which also translates into bottlenecks in memory services and the longest projected wait times among the EU-5 countries, if a disease-modifying treatment became available.

Planning for dementia care in general and for the advent of a disease-modifying treatment is in early stages. The recently published national plan for neurodegenerative diseases, including dementias, provides a framework, but implementation and resourcing by the Autonomous Regions remains limited. There are no nationally accepted standards and guidelines for the early diagnosis, definitive diagnosis and management of memory disorders. Care practice

varies regionally and by type of institution.

As Spain remains under pressure to contain public spending, substantial increases in funds for a dementia care infrastructure seem unlikely in the near future. There are, however, several opportunities to optimize use of the existing capacity, such as by standardizing and streamlining patient pathways. Greater standardization and the use of multidisciplinary teams might allow for a greater degree of task shifting from specialists to primary care providers and technicians. Leading centers of excellence, such as the ACE Foundation in Barcelona, could become the laboratories for such approaches and the established MapEA expert group could provide guidance. Given the regionalization of implementation decisions, such efforts would need to build on discussions with regional planners and regional pilot projects.

THERE ARE SEVERAL OPPORTUNITIES TO OPTIMIZE USE OF THE EXISTING CAPACITY, SUCH AS BY STANDARDIZING AND STREAMLINING PATIENT PATHWAYS.

With the recent reforms of the national health system, the central government has taken a greater role in planning decisions, for example for outpatient cancer care. Assuming there is political will to scale up services for Alzheimer's disease treatment, similar centralized decision making and guidance could help accelerate regional implementation of services.



RESULTS

UNITED KINGDOM

HEALTH SYSTEM OVERVIEW

The U.K.'s National Health Service² (NHS) is a tax-funded healthcare system, under which services for all legal residents are covered free of charge, except for a dispensing fee for prescription drugs. Social care is self-funded with means-tested support (Cylus et al., 2015). Policy efforts and pilots are underway to integrate health and social care budgets, such as the Health Innovation Manchester pilot. Health boards in the four countries of the U.K. receive an annual budget from the Treasury and decide on the range of covered services. Actual decisions about the commissioning and funding of services are made by local purchasing bodies, such as the Clinical Commissioning Groups in England, who receive risk-adjusted capitation budgets. While the range of services and capacity can thus differ locally, a substantial degree of standardization exists because of National Service Frameworks and guidance from the National Institute for Health and Care Excellence (NICE), which conducts cost-effectiveness analyses to inform resource allocation. Decisions on capital investment and equipment purchases are also made centrally.

POLICY EFFORTS AND PILOTS ARE UNDERWAY TO INTEGRATE HEALTH AND SOCIAL CARE BUDGETS, SUCH AS THE HEALTH INNOVATION MANCHESTER PILOT.

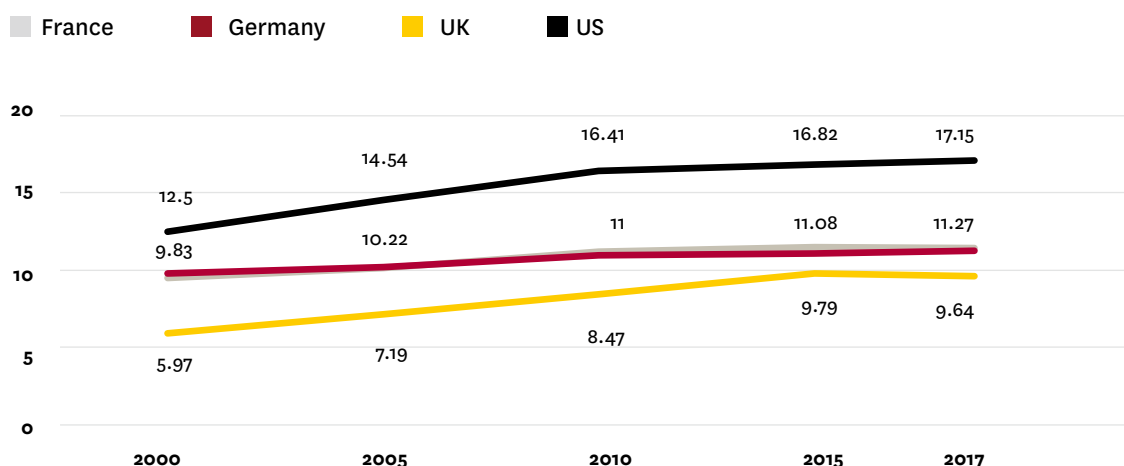
The entry point into the healthcare system is typically the GP, who provides primary care and care coordination services. GPs mostly organize in larger private practices, often referred to as surgeries, with a team-based care model. They contract with local purchasing bodies and receive a risk-adjusted capitation payment with some pay-for-performance bonuses for each patient under their care. GPs serve as gatekeepers for access to specialists and high-cost imaging. Inpatient and outpatient specialty care is provided by salaried staff in hospitals, which are in turn funded based on a combination of budgets and activity-based payments.

SPENDING ON HEALTHCARE PER CAPITA AND AS A SHARE OF GROSS DOMESTIC PRODUCT IN THE U.K. HAS HISTORICALLY BEEN LOWER THAN IN COUNTRIES OF COMPARABLE WEALTH.

Spending on healthcare per capita and as a share of Gross Domestic Product in the U.K. has historically been lower than in countries of comparable wealth, but grew to the EU averages between 2000 and 2010, followed by cutbacks due to the financial crisis (Figure 25). As a result of the constrained funding, capacity tends to be lower than in countries with comparable wealth, and wait times for elective specialty care and imaging are common.

Figure 25: Health spending in percent of GDP in France, Germany, U.K and U.S from 2000 to 2017.

Health spending in percentage GDP



Source: OECD Health Statistics (2019).

DEMENTIA PLANNING

The U.K. has had a national dementia strategy, called “Living Well with Dementia”, since 2009 (U.K. Department of Health, 2009). It was meant to offer a framework for the planning and implementation of dementia services locally. In 2015, then Prime Minister David Cameron set out the Prime Minister’s challenge on dementia 2020 with specific commitments that aim to make England the world-leader in dementia care, research and awareness by 2020, together with an implementation plan with priorities for risk reduction, health and care, awareness and social action and research (U.K. Department of Health, 2015). In addition, there are expert-led efforts to raise awareness and set standards for dementia care, such as the Blackfriars Consensus (Lincoln et al., 2014) on dementia prevention and the Edinburgh Consensus (Ritchie et al., 2017) on preparing for the advent of a disease-modifying treatment.

THERE ARE EXPERT-LED EFFORTS TO RAISE AWARENESS AND SET STANDARDS FOR DEMENTIA CARE, SUCH AS THE BLACKFRIARS CONSENSUS ON DEMENTIA PREVENTION AND THE EDINBURGH CONSENSUS ON PREPARING FOR THE ADVENT OF A DISEASE-MODIFYING TREATMENT.

MCI SCREENING

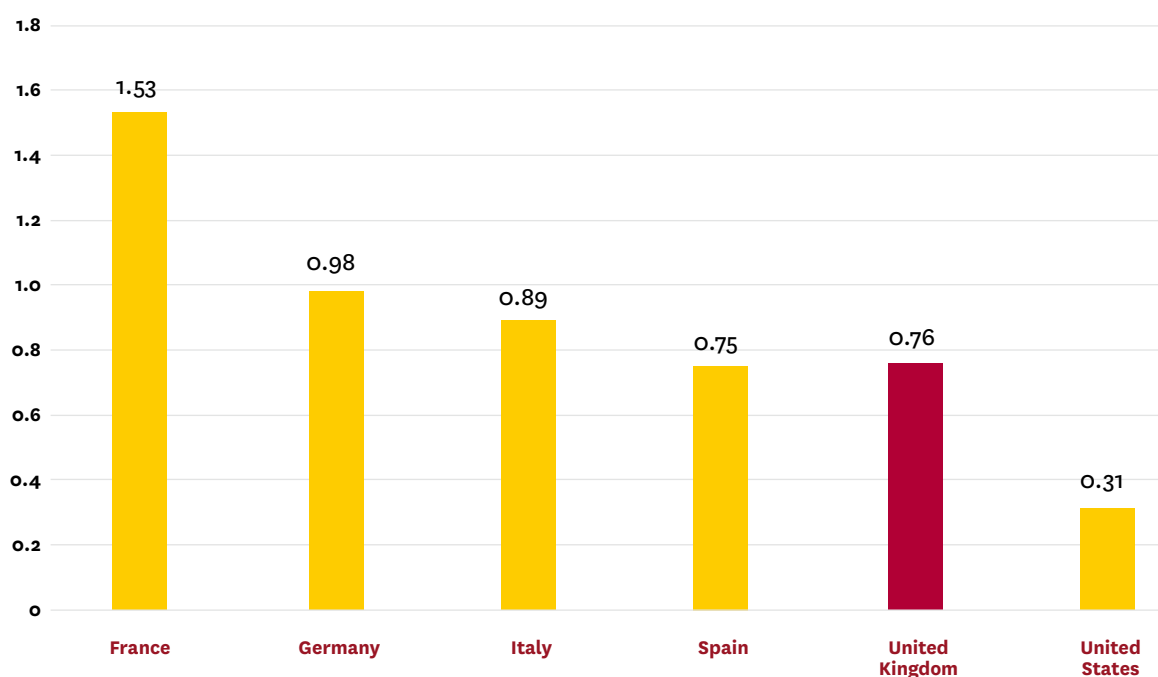
Access to primary care in GP practices is generally seen as adequate with limited wait times (Wise, 2018). While a brief cognitive assessment could be part of preventive visits, the UK National Screening Committee currently advises against systematic screening for mild cognitive impairment for the lack of

benefit in the absence of a disease-modifying treatment (GOV.UK, 2015). Instead, a focus on dementia prevention is encouraged under the Blackfriars Consensus (Lincoln et al., 2014). Correspondingly, the interest of GPs to proactively identify cognitive decline is reportedly limited, as they are concerned about the problem of having to convey bad news with limited options to improve prognosis.

The introduction of a systematic screening program would be based on a recommendation of the National Screening Committee, which would weigh the evidence, preferably from randomized clinical trials for a net benefit of screening. The actual implementation would require simple tools that could be incorporated into a general practice's workflow as well as greater patient demand to get tested. A related concern is the limited density of GPs compared to other countries and their numerous competing obligations, given their central role in the care pathway (Figure 26).

Figure 26: Density of primary care providers in the U.K.

GPs per 1,000 population [2016]



Data from OECD Health Statistics (2019).

CASE FINDING

Patients with subjective memory complaints would have to seek out their GP for initial evaluation and a possible referral to a memory service for a definite diagnosis. While the initial evaluation is part of covered GP services, the time allotted to a typical visit is only about 10 minutes and GPs have limited familiarity with the diagnosis and differential diagnosis of mild cognitive impairment as well as reluctance to pursue a diagnosis of dementia because of the limited treatment options (Sara Ryan, 2013). NICE has published a pathway for dementia evaluation and diagnosis but no corresponding guidance for MCI. Hence, GPs tend to be reluctant to formally validate the presence of early-stage cognitive impairment

EXPERTS POINTED TO BLOOD-BASED BIOMARKERS FOR ALZHEIMER'S DISEASE AS AN OBVIOUS CHOICE FOR A TOOL THAT COULD HELP TRIAGE PATIENTS AND WOULD EASILY INTEGRATE INTO EXISTING WORKFLOWS.

a pay-for-performance program that ties provider income to national and regional goals (NHS England, 2019a). While diagnosis rates and care planning for dementia are performance measures for the Clinical Commissioning Groups, they are currently not used to reward GPs (NHS England, 2018a). As the Prime Minister's Challenge on Dementia 2020 calls for an increase in dementia detection and for a global leadership role of the U.K (Dementia Policy Team, 2016) in dementia care, the political support for such changes could be available. Further, the so-called Edinburgh Consensus, a position paper of leading academics on the preparedness of the U.K. to deliver a disease-modifying treatment, calls for better tools and cognitive tests for GPs to triage patients into specialist care (Ritchie et al., 2017). Experts pointed to blood-based biomarkers for Alzheimer's disease as an obvious choice for a tool that could help triage patients and would easily integrate into existing workflows.

MMSE and MoCA. Similarly, initial assessment for potential etiologies of cognitive decline is not consistently performed in primary care settings, making referrals to specialists the most common course of action. Some GP practices, like the Gnosall Primary Care Memory Clinic (Greaves et al., 2015), have started to integrate services for cognitively impaired patients with the support of a geriatric psychiatrist. A pilot program for GP-led dementia care was launched in Bristol (Dodd et al., 2014).

Incentives for GPs to devote time and attention to identification and evaluation of MCI could be provided under the Commissioning for Quality and Innovation (CQUIN) scheme,

COGNITIVE TESTING

Upon GP referral, comprehensive neurocognitive testing is available through the memory services, which are specialist-led multidisciplinary clinics that are typically attached to hospitals. These memory services vary in size and skill mix of the staff but are predominately led by geriatric (or old age) psychiatrists (Chrysanthaki, Fernandes, Smith, & Black, 2017), although some are led by neurologists. The care model arose from a realization that a focused, high-throughput service would be required to handle the growing burden of dementia, which was historically in the hands of general mental health specialists (S. Banerjee et al., 2007). Around 220 such memory services are formally accredited by Memory Services National Accreditation Program (2019) maintained by the Royal College of Psychiatrists.

THE CARE MODEL AROSE FROM A REALIZATION THAT A FOCUSED, HIGH-THROUGHPUT SERVICE WOULD BE REQUIRED TO HANDLE THE GROWING BURDEN OF DEMENTIA, WHICH WAS HISTORICALLY IN THE HANDS OF GENERAL MENTAL HEALTH SPECIALISTS.

Wait times for appointments are around five weeks (Royal College of Psychiatrists, 2015).

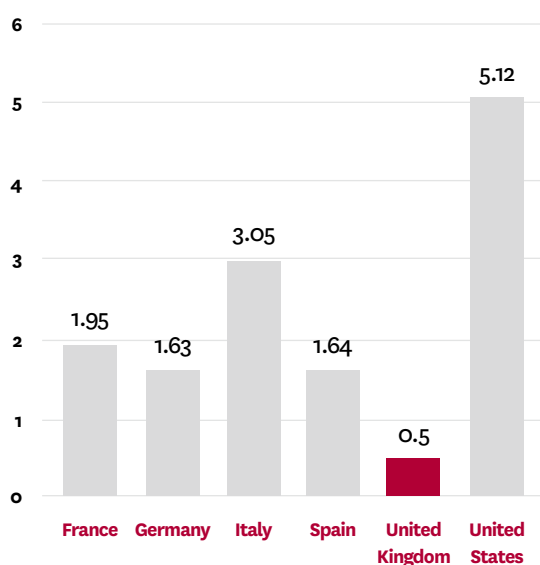
These memory services have been shown to be effective and cost-effective for dementia care (Sube Banerjee & Wittenberg, 2009), but are unlikely to be able to absorb the expected demand for MCI evaluation, if a disease-modifying treatment became available, as they are operating at capacity even today (Ritchie et al., 2017). Substantial additional funding would be required as would extension to less populated regions by tele-consultations. Alternatively, an intermediate service could be introduced, either as a community-based service or integrated into GP offices, handle the initial evaluation of patients with memory complaints and triage those in need for further assessment.

BIOMARKER TESTING

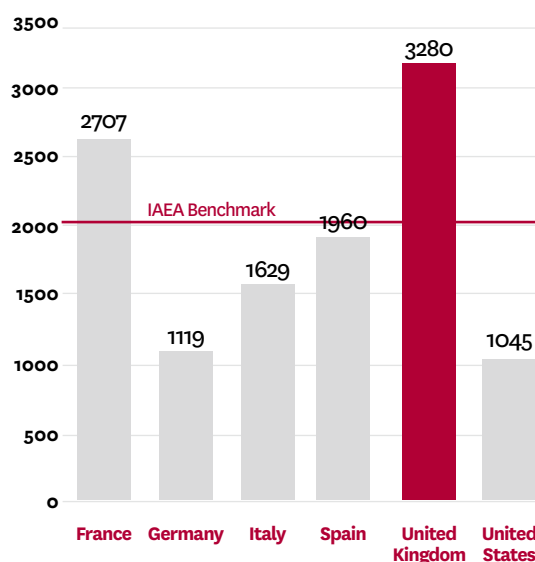
Both CSF testing and PET scans for the detection of amyloid deposits are approved in the U.K., but NICE currently only recommends those tests if the results are likely to change patient management (National Institute for Health and Care Excellence, 2018). NICE also advised against ApoE testing. Geographic coverage with cyclotron facilities to produce the ligand for PET scans is sufficient with gaps in southwestern England and northern Scotland, but PET capacity is quite limited as England has only about one-tenth of the units per 1 million population as the U.S. and one-third of Germany with high utilization of existing devices (Figure 27).

Figure 27: Density and utilization of PET scanners in the U.K.

PET scanners per 1M population



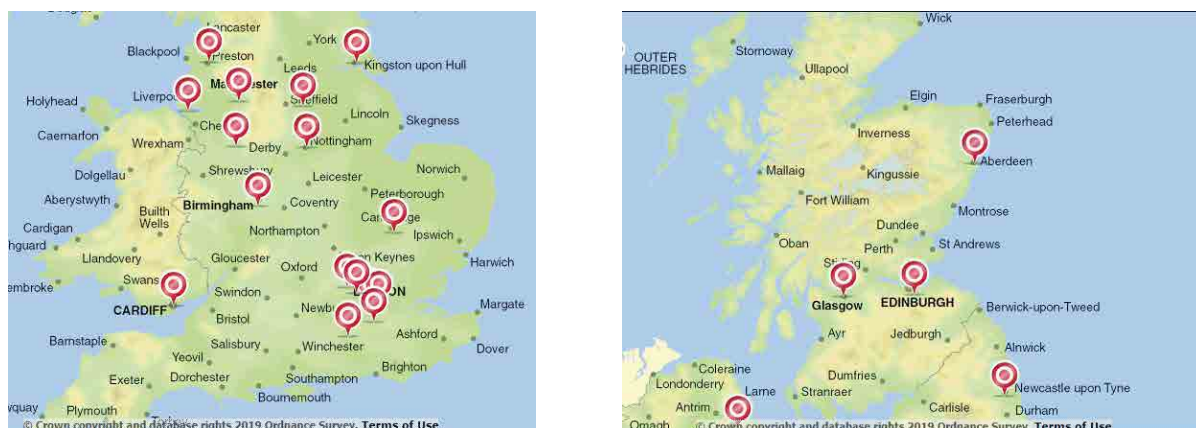
Annual PET scans per device



Data from OECD Health Statistics (2019), The German Society for Nuclear Medicine (DGN) (2019), and NHS England (2019). The International Atomic Energy Association (IAEA) recommends 2000 annual scans per device as minimum threshold for efficient utilization.

Geographic coverage of cyclotrons follows the distribution of the population, which might imply geographical obstacles to access in areas like Northern Scotland and Western England (Figure 28). The distribution of PET scanners follows a similar pattern.

Figure 28: Geographic distribution of cyclotrons in the U.K.



Data from *UK PET Core Lab* (2019).

According to our experts, PET scanners are largely reserved for oncologic cases, whereas use in Alzheimer's patients is exceedingly uncommon outside of clinical trials. Lumbar punctures for CSF testing are also uncommon in routine care, partly because of the NICE guidance and partly because of patients' reluctance to undergo the procedure, and are mostly conducted in early-onset or rapidly progressive dementia to rule out Jakob–Creutzfeldt disease.

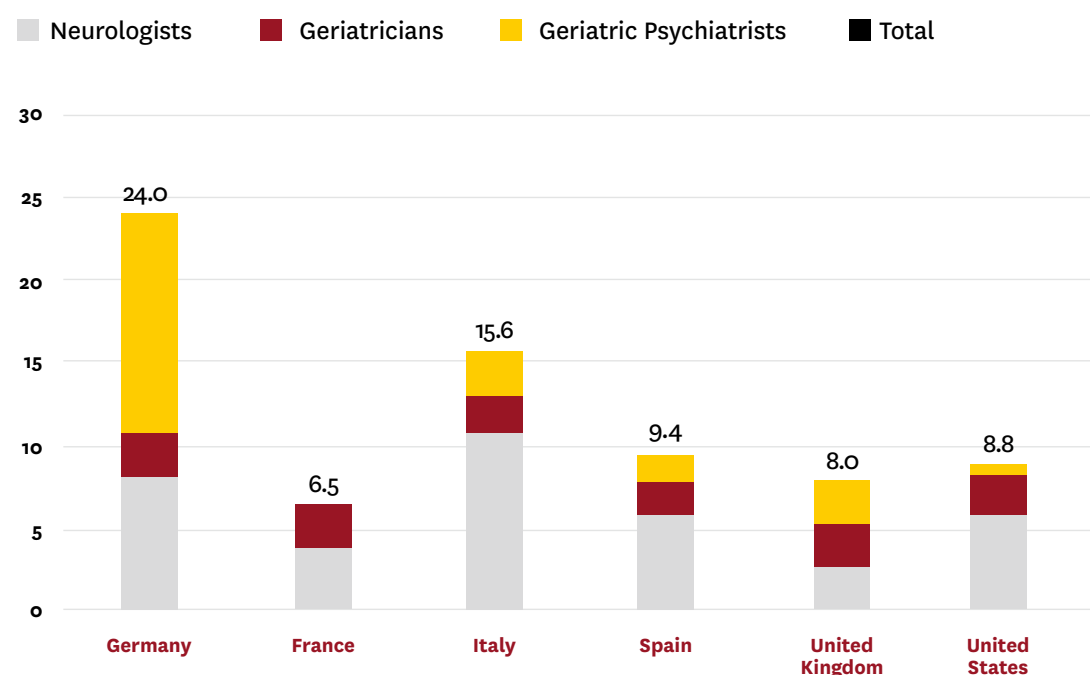
Supportive guidance from NICE and allocation of funding would be a precondition to increase testing capacity. Given the high investment and unit cost of PET scans, the expansion of biomarker testing capacity is likely to rely on CSF testing. As memory services are typically attached to hospitals, they have access to the necessary infrastructure, such as procedure rooms and recovery beds. However, it is unknown whether hospitals could accommodate the required volume of lumbar punctures, and the majority of memory services are led by psychiatrists, who are usually not trained in the procedure.

TREATMENT DECISION

The interpretation of cognitive and biomarker testing results and a decision for or against disease-modifying treatment would again be performed in memory services. Handling patient volume at those institutions, which are already run at capacity, will be challenging for four reasons. First and foremost, a substantial increase in funding would be required. Second, specialists in those clinics are salaried employees of their hospital and have neither the financial incentive to ramp up throughput nor the control over staffing levels for support personnel and space allocation. Third, the U.K has a comparatively low number of dementia specialists from which to draw additional staff (**Figure 29**). Fourth, memory services are currently focused on diagnostic evaluation and counseling. Transforming them to a medicalized operating model that is required for treatment delivery would be challenging, particularly for psychiatry-led clinics.

Figure 29: Number of dementia specialists in the U.K. compared to other countries.

Estimated available specialists per 100,000 population



Data from OECD Health Statistics (2019).

The Edinburgh Consensus (Ritchie et al., 2017) calls for a capability assessment of memory services and the identification of training needs for the delivery of a disease-modifying treatment and surrounding services and for building on the pool of clinicians with experience in biomarker testing and treatment delivery from clinical trials. The authors also recognize the need to reconfigure service models given the traditional focus of these clinics. Proposed models call for greater task shifting to nurses and closer integration with GPs, potentially via so-called General Practitioner with a Special Interest (GPwSI) posts that would focus on memory services (Burns, Wilkinson, & Peachey, 2014). Evidence suggests that GP-led memory services can indeed leverage scarce specialist time effectively, as a review of the Gnosall Surgery, a practice of 8,000 patients, showed that the practice only required the geriatric (specialist) psychiatrist for one 3.5 hour session on site every month and ongoing availability for phone consultations (NHS England, 2015).

TREATMENT DELIVERY

Coverage of a disease-modifying treatment would depend on the assessment by NICE, which uses a strict cost-effectiveness framework. Given the substantial budget implications, our experts believed that NICE would factor the cost and resource requirements for identifying and evaluating potentially treatment-eligible patients into its recommendations. They also argued that NICE might demand data for the effect of the drug on clinical outcomes, such as delay or avoidance of nursing home admissions, rather than merely evidence for slower cognitive decline, to fund a likely expensive treatment. Ten regional Pharmacy Purchasing Groups handle the actual

procurement of prescriptions drugs and funding comes from the budget of the Clinical Commissioning Groups (NHS England, 2018b). No robust data on current capacity to deliver an intravenous treatment exist, but our experts expected that the memory services would be able to scale infusion capacity within a reasonable timeframe, assuming adequate funding. Home infusion services exist mostly in the more populated areas of the country (Figure 30).

Figure 30: Location of home infusion services in the U.K.



GIVEN THE SUBSTANTIAL BUDGET IMPLICATIONS, OUR EXPERTS BELIEVED THAT NICE WOULD FACTOR THE COST AND RESOURCE REQUIREMENTS FOR IDENTIFYING AND EVALUATING POTENTIALLY TREATMENT-ELIGIBLE PATIENTS INTO ITS RECOMMENDATIONS.

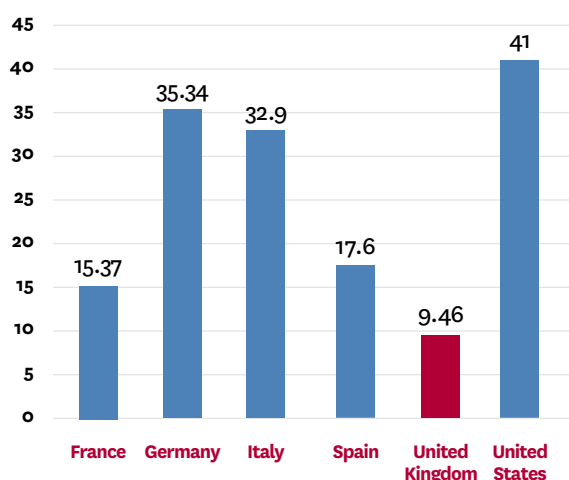
Data from National Infusion and Vascular Access Society (2019).

MONITORING

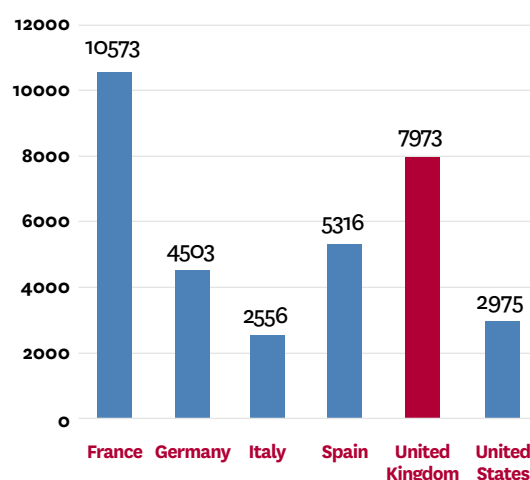
Visits to GPs and memory services as well as imaging to monitor treatment effectiveness and safety will be covered according to the drug label and guidelines. The relatively low density of MRI scanners combined with a high utilization rate in the U.K suggests that MRI capacity might constitute a bottleneck (Figure 31).

Figure 31: Density and utilization of MRI scanners in the U.K.

MRI scanners per 1M population



Annual MRI scans per device



Data from OECD Health Statistics (2019).

Similarly, the need for follow-up visits will compound any capacity constraints for specialist care. GPs might lack the experience and tools to take on a greater role in monitoring treatment effects and detecting and handling adverse effects like ARIA, emphasizing the need for expanding GP capabilities.

SUMMARY

The U.K. has a tax-funded healthcare system that ensures universal access to care with almost no cost-sharing for patients. Decisions on whether to cover new treatments follow a highly structured national health technology assessment process that uses a strict cost-effectiveness framework. In light of the expected budget impact of a disease-modifying treatment for Alzheimer's disease as well as the diagnostic services around such a treatment and an overall budget constraint, substantial scrutiny is to be expected.

GPs in private practice operate as entry point and gate-keepers with limited wait times for primary care services. As the U.K. has historically spent less on healthcare than nations of comparable wealth, however, capacity for specialty care and high-cost diagnostic services tends to be limited and wait times are common. Thus, the system appears ill-equipped to absorb the increase in demand for services that the introduction of a disease-modifying treatment would trigger. Even with a substantial increase in funding, expanding capacity would take years.

THERE IS RECOGNITION OF THE CHALLENGE AND A THOUGHTFUL PUBLIC DISCOURSE ON POLICY INTERVENTIONS AND CARE MODEL INNOVATION TO FACILITATE ACCESS TO DEMENTIA CARE IN GENERAL AND TO A DISEASE-MODIFYING TREATMENT IN PARTICULAR.

At the same time, there is recognition of the challenge and a thoughtful public discourse on policy interventions and care model innovation to facilitate access to dementia care in general and to a disease-modifying treatment in particular. The Edinburgh Consensus, for example, combines recommendations for health system changes with a call to action. Given the central role of GPs in the management of population health, strengthening their role is a common theme in this discourse. Efforts are underway to enable GPs to take on more responsibilities in memory care as are efforts to integrate health and social care budgets that might allow reallocating funds from dementia care to dementia prevention.

SUMMARY

Population aging and a growing burden of disease have made dementia an important policy issue in the EU-5 countries. All countries have crafted or are in the process of crafting a national dementia strategy, often accompanied by regional and/or local guidance for implementation. Those plans tend to focus on identification of and care for patients with manifest dementia. Non-governmental groups, for example in the U.K. and Spain, have assessed health system preparedness to deliver a disease-modifying treatment for Alzheimer's disease, as the most common cause of dementia, and made recommendations. Italy has launched a government-sponsored project on identification of patients who are likely to benefit from such a treatment, but system changes to accommodate the delivery of it have not yet been incorporated into policy decisions.

Against the background of a potential approval of a disease-modifying treatment, this report analyzes how well the EU-5 countries are prepared to make such treatments accessible in order to provide guidance for policymakers and other stakeholders on an action plan. As the current development pipeline suggests that a treatment might be available as early as 2021, the fact that all five countries plan infrastructure investments and operational funding implies the need for a timely discussion.

ALL FIVE COUNTRIES HAVE CRAFTED OR ARE IN THE PROCESS OF CRAFTING A NATIONAL DEMENTIA STRATEGY, OFTEN ACCOMPANIED BY REGIONAL AND/OR LOCAL GUIDANCE FOR IMPLEMENTATION. THOSE PLANS TEND TO FOCUS ON IDENTIFICATION OF AND CARE FOR PATIENTS WITH MANIFEST DEMENTIA.

FINANCIAL PLANNING

Our analysis shows that all five countries functionally operate their healthcare systems under global budgets, either directly as in tax-funded countries, like the U.K. or Italy, or indirectly through a combination of price regulation and volume controls in social insurance countries, like Germany. This approach limits the growth in healthcare spending but makes it difficult for the system to absorb unanticipated substantial increases in demand for services, as the experience of the COVID-19 pandemic has shown. The example of the introduction of directly acting antiviral drugs for hepatitis C has illustrated this problem, and, without advance planning, the advent of a disease-modifying treatment for Alzheimer's might have a much bigger impact because the patient pool is three to five times as large (CDC, 2019). The particular nature of the disease also means that there is less room to manage the market entry of a treatment by prioritizing patients with more advanced disease initially, as was used to limit the immediate budget impact of the hepatitis C drugs. Holding Alzheimer's patients on wait lists might lead to irreversible progression of the disease for many (Hlavka et al., 2019).

Thus, a dialog about the financial implications of an Alzheimer's treatment seems warranted to prepare health systems accordingly. Given the likely size of the immediate budget impact, creative financing approaches may become necessary that would consider the long-term cost offsets and societal benefits of avoiding or delaying the onset of dementia (Mattke & Hoch,

OUR ANALYSIS SHOWS THAT ALL FIVE COUNTRIES FUNCTIONALLY OPERATE THEIR HEALTHCARE SYSTEMS UNDER GLOBAL BUDGETS, EITHER DIRECTLY AS IN TAX-FUNDED COUNTRIES OR INDIRECTLY THROUGH A COMBINATION OF PRICE REGULATION AND VOLUME CONTROLS IN SOCIAL INSURANCE COUNTRIES.

2015). Such approaches would be particularly attractive for countries with long-term care coverage, as actual cost savings would accrue to these programs in the future.

CAPACITY PLANNING – PRIMARY CARE

As memory disorders are population-level diseases, afflicted patients will need to access care via the primary care system for initial evaluation and triage to specialist care. Countries like the U.K. mandate this pathway via gatekeeping roles of GPs, and others, like Germany, recommend it. The challenge is that in all countries of our sample primary care providers are reluctant to proactively identify cognitive decline and even to investigate memory complaints further because of a combination of workload, skills and perceptions.

The combination of aging populations and tight finances means that primary care providers have to handle growing needs without commensurate growth in resources. Verifying and quantifying a memory complaint requires in-depth conversations with patients and family members as well as initial cognitive testing, tasks that hardly fit into the usual 10–15-minute slot of an office visit. Preconceived notions that cognitive decline is an inevitable consequence of aging and a perception that diagnosing it formally has no therapeutic consequences, contribute to a lack of willingness to investigate. As a result, providers do not develop or maintain skills and workflows for evaluation of memory complaints, resulting in a vicious cycle of underdiagnosis.

There are encouraging signs that more attention is being paid to early detection and diagnosis of memory disorders, as evidence of therapeutic benefit even in the absence of disease-modifying treatment is emerging. Results from the FINGER study (Ngandu et al., 2015) suggest that risk-factor management and cognitive training can delay disease progression, initial findings from the IDEAS study (Rabinovici et al., 2019) show that an exact diagnosis influences clinical management and researchers have shown potential benefits in terms of reduction of injuries (Härlein, Dassen, Halfens, & Heinze, 2009) and susceptibility to financial scams (Boyle, Yu, Schneider, Wilson, & Bennett, 2019). At least as important is a realization that patients simply have a right to know about their disease and its prognosis, as strongly advocated in the French

VERIFYING AND QUANTIFYING A MEMORY COMPLAINT REQUIRES IN-DEPTH CONVERSATIONS WITH PATIENTS AND FAMILY MEMBERS AS WELL AS INITIAL COGNITIVE TESTING, TASKS THAT HARDLY FIT INTO THE USUAL 10–15-MINUTE SLOT OF AN OFFICE VISIT.

THE NHS FOR ENGLAND AND WALES USES DEMENTIA DETECTION RATES AS A KEY PERFORMANCE INDICATOR FOR PRIMARY CARE TRUSTS TO ENCOURAGE CASE FINDING.

national plan for neurocognitive diseases, just like they would expect for other conditions. Put differently, one would hardly tell a patient with advanced cancer that there is no point in making a formal diagnosis as there are no options to prolong survival.

Primary care providers will need help if they are asked to assume the additional responsibility of detecting and evaluating memory complaints. Apart from education about the benefits of early and accurate diagnosis of the underlying etiology, they need resources and tools. None of the countries in our sample currently has

a population screening program for dementia or cognitive decline that would allocate funding, even though the Interceptor Project in Italy is looking into approaches to identify patients at risk for dementia prospectively. Germany has introduced a comprehensive geriatric assessment, which would include memory complaints, as a sickness fund benefit, and the NHS for England and Wales uses dementia detection rates as a key performance indicator for primary care trusts to encourage case finding. More such initiatives are needed to increase detection and diagnosis rates.

Better tools that are suitable for general practice are dearly needed. Current cognitive assessment tools, like the MMSE or MoCA, require 10–15 minutes to administer and interpret and have limited sensitivity and specificity, especially for the detection of mild cognitive impairment as opposed to detection of manifest dementia. Computerized tools are in development that could facilitate identification and longitudinal tracking of cognitive decline, but none are close to clinical use at this point. Blood-based biomarkers for Alzheimer's disease are showing promise and could facilitate differential diagnosis and triaging in primary care settings (Palmqvist et al., 2019). As such technologies become available for routine clinical use, sufficient allocation of funding will be critical to promote uptake, given the large numbers of patients that might benefit from them.

Making all these changes to primary care may appear like a daunting task, but experience with conditions such as depression and heart failure have shown that, with proper tools and resources, routine management of even complex conditions can be moved into general practice. In fact, primary care-led memory clinics have already emerged in the U.K. (Greaves et al., 2015), Norway (Engedal, Gausdal, Gjora, & Haugen, 2012) and Canada (Lee et al., 2014).

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CAPACITY PLANNING – SPECIALTY CARE

The likely complexity of the first disease-modifying treatments for Alzheimer's disease implies that they will remain in the hands of specialists. Formally diagnosing patients and determining whether they are likely to have a net clinical benefit from a treatment requires the integration of findings from a thorough anamnesis with cognitive testing results, biomarkers and imaging data. Infusion

FUTURE ALZHEIMER'S CARE MODELS WILL HAVE TO EVOLVE FROM THE CURRENT FOCUS ON COUNSELING AND SOCIAL CARE TO RESEMBLE MODELS IN THERAPEUTIC AREAS LIKE ONCOLOGY AND MULTIPLE SCLEROSIS.

delivery may be necessary and safety and efficacy of the treatment will have to be closely monitored. Thus, the future of Alzheimer's care models will have to evolve from the current focus on counseling and social care to resemble models in therapeutic areas like oncology and multiple sclerosis. In light of the scarcity of dementia specialists, care models will have to leverage their time efficiently.

A precondition for this evolution will be creating larger-scale memory services. In countries like Germany and France, patients might be referred to specialists in private practice, who work as solo practitioners or in small groups. Memory clinics in Italy and Spain may also be quite small. The patient volume handled in such practice settings will not support a multidisciplinary team and the

infrastructure necessary to deliver a disease-modifying treatment, because of substantial fixed cost.

First and foremost, future models need to be large multispecialty practices with a team of clinical and nonclinical staff to allow task shifting and “top-of-license” practice (Russell-Babin & Wurmser, 2016), i.e., delegating tasks that do not require specialist medical training to other clinical staff and non-clinical tasks to other team members. For example, cognitive tests can be administered by technicians and interpreted by neuropsychologists, leaving only the integration of testing results with biomarker and imaging results and eventual treatment recommendation to the specialist. Non-clinical tasks, such as coordination with social services, can be delegated to social workers.

Secondly, future care models will need to be more medicalized to reflect the shift from care to cure. In countries like the U.K. and Germany, psychiatrists traditionally play an important role in dementia care. As psychiatry is a relatively large specialty, which helps to expand access to care, many psychiatrists may not have acquired or maintained required skills like administering lumbar punctures or infusion delivery. Conversely, countries that rely more heavily on the smaller specialty of neurology for dementia care, such as Spain and France, have fewer specialists per capita but are better

MEMORY CLINICS WILL NEED TO BE DIFFERENTIATED INTO THOSE THAT HANDLE ROUTINE CASES IN THE COMMUNITY AND REFERRAL CENTERS THAT HANDLE COMPLEX CASES AND RESEARCH, MUCH LIKE IN OTHER THERAPEUTIC AREAS.

equipped to handle the mechanics of a disease-modifying treatment. Co-location of memory clinics with general hospitals, as in the U.K., or inpatient psychiatric facilities, as in Germany, can provide access to the necessary procedural skills and infrastructure, like recovery beds and fluoroscopy.

Third, memory clinics will need to be differentiated into those that handle routine cases in the community and referral centers that handle complex cases and research, much like in other therapeutic areas. Such regionalization has emerged spontaneously, for example in Spain and Germany, or in a planned fashion, such as in France.

Blueprints for such advanced memory care models exist in all five countries both within memory care and in other specialties. In particular, oncology has transformed into a specialty that provides complex care in large outpatient treatment centers. Providers, payers and planners will need to collaborate to codify the lessons learned and best practices from these blueprints into memory care models with standardized staffing, skill mix and processes. Such standardization can be achieved through central planning, as in France, or an accreditation scheme, such as in the U.K. Adequate funding and payment models that reward high-quality care will be crucial.

The experience in other therapeutic areas has shown that such advanced practice models can emerge organically. For example, rheumatology evolved from small clinics to practices with large infusion centers with the advent of immunomodulating drugs. A similar evolution occurred in multiple sclerosis treatment. However, these specialties had the advantage of long having disease-modifying treatments, albeit of limited effectiveness, and could prioritize non-responders while scaling up. Alzheimer's disease is different in that it is one of the last population-level diseases without any disease-modifying treatment. Around 13 million persons in the EU-5 countries are estimated to have mild cognitive impairment (Hlavka et al., 2019) and in over half of them, Alzheimer's disease is the underlying cause (Rabinovici et al., 2019). Identifying, diagnosing and treating those prevalent cases when a treatment first becomes available will require substantial resources and the progressive nature of the disease means that advance capacity planning will be necessary to avoid wait times and unnecessary disease progression. With a treatment potentially becoming available in 2021, it is our hope that this report will trigger a discussion among patient advocates, policymakers, payers, planners and providers about how to make it accessible.

ADEQUATE FUNDING AND
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