Current Capacity for Diagnosing Alzheimer's Disease in Germany and implications for wait times

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Abstract

Background:

Amyloid-targeting therapies for Alzheimer's disease (AD) might become available in Germany soon. The combination of a large pool of prevalent cases and a complex diagnostic process to determine eligibility for these treatments is likely to challenge health systems' capacity.

Objectives:

To analyze Germany's healthcare system capacity to identify treatment-eligible patients in a timely and equitable manner.

Methods:

We modeled patients' diagnostic journey and projects wait times due to capacity constraints for AD specialist visits and PET scans from 2024 to 2043 and their disease progression while on the waiting list. Model parameters were derived from published data and expert input.

Results:

Wait times would be ~50 months over the model horizon, if patients were referred to specialists based on a cognitive assessment in primary care. Wait times for patients with social health insurance are projected to be 1.9 times those of patients with private insurance, with peak wait times of around 76 and 40 months, respectively. Adding a blood test for the AD pathology as additional triage step would reduce wait times to below 24 months.

Conclusions:

In spite of having a well-resourced health system, Germany is projected to be unable to cope with the demand for biomarker-based AD diagnosis, if a disease-modifying AD treatment were introduced. As these treatments might become available by the end of 2024, decisive action, in particular dissemination of high-performing AD blood tests for triage in primary care, will be needed to prevent delays in access and potentially avoidable and inequitable disease progression.

KEY WORDS: Alzheimer's disease, disease-modifying treatment, wait times, specialty care, biomarker, diagnosis, health system preparedness

Introduction

After a positive phase 3 trial[1], lecanemab – a monoclonal antibody that removes beta-amyloid deposits from the brain – became the first drug to receive full approval by the U.S. Federal Drug Administration (FDA) to modify the trajectory of early-stage Alzheimer's disease (AD) on July 6, 2023 and subsequently in Japan, China and South Korea. Donanemab, a drug with a similar mechanism of action, also met its endpoints in a phase 3 trial[2] and was approved in the U.S. on July 2, 2024. Lecanemab is currently being reviewed [3] by the European Medicines Agency (EMA), the European Union (EU) regulator, with an expected decision in the second half of 2024.

In EU countries, regulatory approval is typically followed by a health technology assessment process [4] that may take a year or longer. Germany, however, covers EMA-approved drugs at list price for six months, during which time the eventual price will be negotiated. Put differently, patients in the EU's most populous country would have access to a newly approved AD drug almost immediately. This potentially nearing introduction of disease-modifying AD treatments raises the question how well Germany's healthcare system is prepared to handle the expected increase in patients, who will seek access to treatment. The combination of a large prevalent patient pool, a complex diagnostic process, which involves neurocognitive testing, structural brain imaging and, for the treatment decision, confirmation of AD-related amyloid pathology, and the need to monitor these treatments for side effects with brain MRI, has revealed substantial capacity constraints and projected subsequent wait times in several countries, such as the U.S. [5], Brazil[6], China[7], England[8], and Sweden[9].

Anecdotal evidence [10] from the U.S. after the introduction of AD treatments supports these projection of delays in access to diagnosis and treatment. Such delays diagnoses have long limited the opportunity for patients and families to adopt lifestyle changes that have been shown

to reduce the speed of decline,[11] start symptomatic medication treatment, and consider measures to increase physical and financial safety and security.[12] However, in light of recently published data [13,14] that the treatment effect of amyloid-targeting antibodies diminishes as the untreated disease progresses, such delays could have a deleterious impact on patients. While Germany has a well-resourced healthcare system compared to countries of similar size and economic wealth, with the largest number of practicing physicians and second largest number of hospital beds per 1000 population among the G7 countries [15], the capacity to provide diagnostic assessments for suspected AD, including confirmation of amyloid positivity, has not been analyzed to our knowledge.

Against this background, the objective of this study is to project Germany's capacity to diagnose patients with early-stage AD and determine their eligibility for disease-modifying treatments in relation to expected demand, and to estimate potential waiting times. We are estimating those waiting times for the full population, and differences for individuals with social versus private health insurance, as the latter are known to have faster access to elective specialty care. [16] Of note, these estimates are a first approximation of the magnitude of a potential policy problem rather than an attempt to quantify it precisely.

Methods

Model description

We used a Markov model that has been described in detail in earlier publications[5,17] to estimate wait times in the AD diagnostic process from 2024 to 2043. In short, it simulates the journey of patients seeking evaluation for subjective memory complaints or as part of a preventive exam in primary care with two interacting layers. The first layer captures one of four true health states: cognitively unimpaired, mild cognitive impairment (MCI) due to AD, MCI due to other causes,

and dementia using age and sex-specific estimates for incidence and prevalence of MCI and dementia in the underlying population. The second layer captures a - highly stylized - patient's journey through different evaluation stages: initial evaluation by a primary care physician, a comprehensive assessment by an AD specialist, and confirmatory biomarker testing with positron emission tomography (PET) scanning or cerebrospinal fluid (CSF) testing. The model assumes that AD specialist appointments and PET scans are capacity-constrained, and patients progress while waiting for appointments. A technical description including a model schematic and model parameters are documented in the Appendix.

Parameter identification

We conducted desk research for background information on Germany's population, healthcare system and model parameters, as detailed below. A separate literature review and evidence synthesis was conducted on differential wait times for elective specialty care for individuals covered by social versus private insurance.

To obtain input on model parameters, for which no data were available, such as care seeking behavior along the patient journey and proportion of specialists, who would be qualified to evaluate patients for AD treatment eligibility, we conducted a structured expert consultation process involving seven German experts, geriatric psychiatrists, (n=4) neurologists (n=1), neuropsychologists (n=1) and geriatricians, (n=1)We used a modified Delphi approach[18] to obtain their input, in which they received a briefing on the study's approach and were then asked to provide estimates individually. The answers were compiled and analyzed, and results reported back to the group together with feedback and clarifications, if requested. Subsequently, the experts were given an opportunity to change their estimates, if they considered it appropriate. The median of the final ratings was considered the consensus estimate.

Population and disease burden estimates

We extracted current estimates and projections for population and mortality [19] by sex and age groups from the Federal Statistics Office. Data for incidence and prevalence of MCI by age group were obtained from prior studies by Gillis et al. [20] and Petersen et al. [21], respectively. Estimates for dementia prevalence were based on Thyrian et al. [22]

Health system capacity

We used the annual Federal census [23] of physicians by specialty and place of occupation (employed in hospital or based in private practice) for counts of physicians with board certification in Geriatrics, Neurology, combined Neurology and Psychiatry, and Psychiatry. We obtained input from the experts, on which proportion of physicians in each of the four groups would have sufficient training to take on the evaluation of patients for eligibility to receive a disease-modifying AD treatment, and used the median of their estimates to calculate the share of AD specialists as 46% of geriatricians, 80% of neurologists, 60% of psychiatrists, and 75% of psychiatrists/neurologists.

The number of available appointments for these physicians was based on a work-time survey conducted by the Federal Statistics Office [19], expert estimates for proportion of time spent on clinical duties, and published estimates for duration of clinic visits for hospital-based [24] and practice-based specialists [8] to arrive at 2,294 and 1,644 visits per year for hospital and practice-based specialists, respectively. Details on the sources and calculations as well as the projection of future capacity are described in the Appendix. Currently available capacity for additional

amyloid PET scans was estimated at 600 per device and year and future capacity based on a linear trend using OECD data [15], as detailed in the Appendix.

Patient journey

Table 1 shows the assumptions based on the expert consultation process described above for the care seeking behavior through the different steps of their journey under the assumption that a disease-modifying AD treatment being widely available.

The simulation prioritizes second specialist visits over first, i.e., slots for first visits are only made available if no patient waits for his or her second visit. At each step, patients can be found not to have MCI due to AD based on test results and exit the queue for that year. We model waiting times over a 20-year horizon from 2024 to 2043, and each year individuals newly aged into the eligible age cohort are entered into the model. Apart from our baseline assumption for PET scans, we explored two alternative scenarios. In the first, PET scan capacity would increase by twice our projection, and in the second, a blood test for the AD pathology with sensitivity and specificity of 80% would be used as triage tool in primary care.

Results

Germany's health and social care system

Germany has a highly devolved healthcare system, in which the Federal government sets an overall framework, and state governments are responsible for capacity planning and public health. The main objectives at the Federal level are the stability of the payroll tax that finances a large part of the system and universal access to a generous benefits package. The most important Federal decision-making body is the Federal Joint Committee (*Gemeinsamer Bundesausschuss*) that is constituted of payer and service provider association representatives as well as

independent members. It determines, for example, the benefits package, fee schedules, and outpatient care capacity and oversees the health technology assessment process for new services, drugs and medical devices. The operational decisions about care delivery and payment within these frameworks are in the hands of regional associations of physicians and payers. Importantly, new drugs approved by the European Medicines Agency are covered [25] at list price for six months, during which the health technology assessment process and price negotiations take place. Manufacturers may withdraw products, if agreement on price cannot be reached.

Health insurance

The financing model traces back to Chancellor Otto von Bismarck, who introduced the world's first national health insurance scheme for workers and their families in 1883. [26] Under this scheme, employees and employers pay into sickness funds (*Krankenkassen*) a contribution of currently 14.6% of wages or salaries to finance medical care. Membership in a sickness fund is mandatory for employees, and self-employed individuals can buy into sickness fund coverage. Historically, membership in a sickness fund was determined by place of employment but free choice of sickness funds was introduced in 1993 [27], which resulted in rapid consolidation from 1221 [28] to around 100 funds [27] today. The sickness funds remain independent not-for-profit carriers with only limited ability to retain surplus premiums. A risk-equalization scheme redistributes contributions based on differences in patient risk to maintain approximately equal contribution rates.

Individuals with a gross salary over 66,000 Euro (in 2023) may opt out of sickness fund coverage and purchase private health insurance policies, which are offered by for-profit insurers and risk rated. Subsequent return into a sickness fund is difficult and near-impossible after age 55. Private health insurance also covers civil servants. The combination of those insurance

schemes means that Germany has almost universal coverage with around 90%% of the population covered by sickness funds, around 10% by private health insurance and others, like the military and civil servants, by separate government programs. [29] Co-payments in the social insurance scheme are limited to small amounts for inpatient care and pharmaceuticals.

Social care insurance

Mandatory social care insurance [30] was introduced in 1995 and individuals are required to enroll with the respective carrier of their health insurance. As the mandatory insurance only covers basic services with substantial cost sharing, supplemental policies are available and may qualify for government subsidies. Social care insurance covers care delivered by community-based professionals and institutional care in nursing homes; it also offers the option of payments to family caregivers. Benefits and payment levels are determined based on an individual's dependency status as determined by a medical review board.

Medical care

Medical care delivered in practices and hospitals is separated from an organizational and financial perspective. Practices are owned and operated by independent physicians, who provide outpatient primary and specialty care. 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 case-mix of the practice and its range of services. Practices 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 for services covered under social insurance, which account for the bulk of their revenues. Practices can augment income with higher margin services for privately insured patients, services not included in the standard benefits package 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 a prospective payment system for medical and surgical 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 admissions and highly specialized services that are not offered in 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 noncommercial objectives, like research priorities.

Privately insured patients largely use the same delivery system as their socially insured counterparts, but often get preferential treatment, such as shorter wait times for elective care

because private carriers pay higher rates and are not subject to the caps imposed by sickness funds.[27]

Social care

Both in-home and institutional social care is delivered by a large number of not-for-profit and for-profit entities. Staffing levels and quality of care are audited by the medical review boards of the local sickness funds.

Current patient journey in memory care

The most typical entry point into the healthcare system for a patient with cognitive impairment remains a patient's primary care physician (*Hausarzt*), with whom particularly elderly individuals often have a long-standing relationship. Proactive identification of cognitive impairment by the physician remains uncommon, even though an annual comprehensive geriatric assessment as well as brief cognitive tests are covered under the standard benefit package. Thus, most cases are detected because of subjective memory complaints or concerns of family members, and often typically at advanced stages.

Further evaluation would be conducted either in primary care or in private specialist practices. Primary care physicians may order additional tests themselves, such as blood work for reversible causes and structural imaging, or refer to specialists. Formal neurocognitive testing, however, is only reimbursed if provided by a certified neuropsychologist or specialist physician. Most memory care specialists are either neurologists or psychiatrists with geriatrics as a relatively new specialty playing a smaller role. While access to specialty care formally requires a referral for patients with social insurance, this requirement is usually not enforced by the sickness funds so that patients may and sometimes do seek out specialists without it. The standard benefits package

currently covers biomarker testing based on CSF analysis but not amyloid PET scans. [31] However, neither is commonly conducted in private practices.

Hospital-based memory clinics, mostly in academic medical centers, serve as institutions for tertiary care and potential clinical trial enrollment. Those clinics, which mostly accept referrals from private specialist practices, provide the full range of diagnostic services, including structural imaging, biomarker profiling with PET scans and CSF analysis, and biobanking as well as clinical trial enrollment. As clinic visits are paid as a partial hospitalization in psychiatric hospitals but only as an outpatient visit in other hospitals, the majority of memory clinics is operated by psychiatry departments.

Wait time projections

The estimated wait times in the diagnostic process under our base case assumptions are shown in Figure 1. Initial wait times in 2024 are projected to be 29 months, increasing to a peak of 65 months in 2028 and then falling to around 50 months for the duration of the simulation. Shortage of AD specialist appointments would account for between 40 and 60% of the wait times.

Figure 1

Figure 2 depicts the effect of our alternative assumption for PET capacity that would increase the number of scans per device from around 1,200 to 1,800, while still using CSF analysis for 80% of cases. Peak wait times would fall to around 40 months and to about 80% caused by wait times for AD specialist appointments.

Figure 2

Figure 3 illustrates the effect of using a blood test for the Alzheimer's pathology as additional triage step in primary care, i.e., only patients with evidence of MCI on a brief cognitive test and the positive blood test would be referred for further evaluation. Confirmatory biomarker testing

would be based on CSF analysis in 80% of cases and PET scan at the baseline capacity assumption in the remain 20%. Overall peak wait times would fall to 23 months on average and to around 17 months by 2043, with a larger contribution of constrained capacity for biomarker testing.

Figure 3

Differences in wait times between social and private health insurance

We identified seven publications that used so-called mystery shopper experiments: Trained callers would contact specialist offices with requests for various elective appointments, such as a gastroscopy or an MRI. In a first wave, they were randomly assigned to represent their insurance coverage as social or private insurance, and in a second wave the other coverage type. The recorded times to first appointments allow then to estimate absolute and relative differences in wait times. The median wait time for 26 elective specialist services was 25 days for social and 11 days for private insurance for an absolute median difference of 17 days and a ratio of wait times of 1.90. Detailed findings are provided in the Appendix.

Figure 4 shows projected wait times for patients in the social insurance scheme. Wait times are estimated to reach a peak of 76 months in 2028 and decline to 56 months by the end of the simulation in 2043.

Figure 4

Figure 5 displays the corresponding estimates for privately insured patients. Wait times are projected to remain below 40 months over the course of the simulation.

Figure 5

Discussion

This study projected wait times in the diagnostic evaluation for eligibility to receive a disease-modifying AD treatment in Germany to start at about 30 months and remain around 50 to 70 for a 20-year period. This projection is comparable to those for the U.S. [5] and Sweden [9] with the qualification that the starting age was 50 years in the U.S. A recently published analysis of England estimated even longer wait times with up to 120 months. [8] An important difference is that wait times for confirmatory biomarker testing cause about a third of overall wait times in Germany, whereas wait times in those other countries are almost exclusively due to scarcity of specialists. This difference is due to a comparatively high number of 17 specialists per 100,000 population compared to Sweden with 13.6, the U.S. with 8.8, England with 5.0 and a G7 average of 11.0.

Wait times for biomarker testing are considerably easier to address. First, the average number of PET scans conducted on each device in Germany is low by international standards because of anecdotally reported shortages of technicians [32] and could be expanded. Second, blood tests for the AD pathology as triage step before ordering testing with PET scans or CSF analysis have been estimated to reduce need for confirmatory testing and cost per case identified[17] and could become routinely available soon. However, the wait time to diagnosis and treatment initiation would remain above two years because of the limited capacity of specialists, which could lead to substantial avoidable disease progression and reduced treatment effectiveness, as recently published data suggest. [14] [13]

Unlike, for example Sweden[9] and the U.K. [33], Germany does not have a formal policy target for wait times for elective specialty care, since wait times have historically been limited, as our above-described literature review findings show. However, the emergence of substantial wait

times to gain access to a disease-modifying treatment for a progressive neurodegenerative disorder might trigger a debate about acceptable wait times.

In addition, the projected differences in wait times between members of social and private health insurance funds raises concerns about equity, as private insurance plans are largely only available to the wealthier segment of the population. While previously reported differences in wait times for elective specialty services of 17 days are not meaningful in absolute terms, those estimates are based on data collected in a situation of ready availability of appointments, and our estimates suggest that the differences could reach years in a situation of scarcity, if the same relative differences in wait times persisted.

Several policy interventions could expand capacity and shorten wait times in the short run, such as loosening the global budget caps for private practices and raising wages for support staff to better utilize existing capacity, but limited economic growth and multiple competing demands on public funds make such changes unlikely. A more affordable option would be better triage technology for primary care to identify and prioritize patients with a likely indication for a disease-modifying AD treatment. Most importantly, blood tests for the AD pathology are reaching accuracy levels comparable to CSF-based tests and could drastically reduce the need for PET scans.[34] Such high-performing blood tests should be cleared for routine care and reimbursed appropriately to promote adoption. Digital cognitive screening tests with higher specificity for MCI could reduce referral of false positive cases to specialists, thereby reducing wait lists. While numerous tests have been developed, evidence for their accuracy in real-world populations is still limited. [35] Professional associations should identify tests with acceptable performance and recommend their routine use, assuming appropriate coverage by sickness funds and private insurers. Adoption of such triage technologies is projected to reduce overall cost of diagnosis.[17]

Limitations

The results should be seen in the context of the limitations of this analysis. Most importantly, modeling does not constitute direct evidence and the results will have to be validated against the actual experience once a disease-modifying AD treatment becomes available in Germany. The model uses a combination of published data and expert input to estimate waiting times and cost. Many of the inputs, especially those relying on expert assumption, are uncertain, including incidence and prevalence estimates for MCI, which rely on global meta-analyses rather than local studies. Lower than expected demand of patients to seek evaluation for an AD treatment could reduce wait times but would not reduce avoidable disease progression. We did not include patients with mild dementia, who could also be treatment eligible, for lack of reliable prevalence data and therefore underestimate wait times. As we argued, better diagnostic technology, such as blood tests for the AD pathology and digital cognitive tests, could replace capacity-constrained services, but those technologies may not be approved or fully adopted in time for use in routine clinical practice, especially in primary care, prior to the launch of an initial disease-modifying AD treatment. Our estimates did not consider constraints on primary care capacity, which might become another bottleneck. Neither did the model consider other health care staff (e.g., neuropsychologists and radiology technicians) who are involved in the diagnostic process. Lastly, we only analyzed capacity and demand for the diagnostic phase; capacity for treatment delivery with infusions and MRI and clinical monitoring might be constrained as well.

Conclusions

In spite of having a well-resourced health system, Germany is projected to be unable to cope with the demand for biomarker-based AD diagnosis, if a disease-modifying AD treatment were introduced. As these treatments might become available by the middle of 2024, decisive action,

in particular dissemination of high-performing blood and digital cognitive tests for triage, will be needed to prevent delays in access and potentially avoidable and inequitable disease progression.

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Figure Legends

Figure 1. Projected wait times in the diagnostic process for determination of eligibility for a disease-modifying Alzheimer's treatment in Germany, 2024 to 2043, base case assumptions.

Figure 2. Projected wait times in the diagnostic process for determination of eligibility for a disease-modifying Alzheimer's treatment in Germany, 2024 to 2043, assuming increased utilization of PET scanners

Figure 3. Projected wait times in the diagnostic process for determination of eligibility for a disease-modifying Alzheimer's treatment in Germany, 2024 to 2043, assuming use of blood test for Alzheimer's pathology as triage step

Figure 4. Projected wait times in the diagnostic process for determination of eligibility for a disease-modifying Alzheimer's treatment in Germany, 2024 to 2043, patients with social health insurance, base case assumptions

Figure 5. Projected wait times in the diagnostic process for determination of eligibility for a disease-modifying Alzheimer's treatment in Germany, 2024 to 2043, patients with private health insurance, base case assumptions

Table 1: Assumptions for patient journey

Step in Patient Journey	Proportion of patients undergoing step
Proportion of individuals of age 60 and above, who have never been evaluated for cognitive decline, undergo a brief cognitive screening, like the Mini-Mental State examination (MMSE) or Montreal Cognitive Assessment (MoCA), in primary care either because of a subjective memory complaint or as part of a routine assessment. Access to these visits is assumed to be unconstrained.	30%
Proportion of of individuals, who were previously screened negative at any stage of their journey, return for a repeated evaluation each year	10%
Proportion of the individuals with suspected MCI based on the brief cognitive assessment are referred to an AD specialist, while the remaining 42% are diagnosed with manifest dementia or cognitive impairment of reversible etiology, such as depression or alcohol use, and treated in primary care settings.	58%
Proportion of individuals, in whom the AD specialist performs a comprehensive assessment, including, neurocognitive testing, in the first visit and are referred to biomarker testing for the AD pathology with confirmed MCI	80%
Proportion of referred individuals who undergo biomarker testing with CSF analysis, which is assumed not to be capacity-constrained,	80%
Proportion of individuals, who return for a second specialist visit to discuss all findings and decide on a care plan	100%

Ethics Approval and Consent Statement

As the study did not constitute human subjects research per U.S. federal regulations (45 CFR 46, 102(f))20, it was exempt from IRB review, consent requirements and registration.

Data availability

Data used in this model were derived from publicly available sources that are documented in the manuscript and appendix.

Declaration of conflicting interests

Outside of the submitted work USC has research agreements, on which Dr. Mattke is PI, with Alzheon, Biogen, C2N, Eisai, Lilly and Roche/Genentech. SM serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AiCure Technologies, AlzPath and Boston Millennia Partners. He has received consulting and/or speaker fees from Biogen, C2N, Eisai, Novartis, Novo Nordisk and Roche/Genentech.

CAFvA received honoraria from serving on the scientific advisory board of Biogen, Roche, Novo Nordisk, Biontech, MinAhead UG and Dr. Willmar Schwabe GmbH &Co. KG and has received funding for travel and speaker honoraria from Biogen, Roche diagnostics AG, Novartis, Medical Tribune Verlagsgesellschaft mbH, Landesvereinigung für Gesundheit und Akademie für Sozialmedizin Niedersachsen e. V., FomF GmbH | Forum für medizinische Fortbildung, MedTrix GmbH and Dr. Willmar Schwabe GmbH &Co. KG and has received research support from Roche diagnostics AG and research funding from the Innovationsfond (Fund of the Federal Joint Committee, Gemeinsamer Bundesausschuss, G-BA Grants No. VF1_2016-201; 01NVF21010; 01VSF21019) and DFG.

LF received honoraria for consulting or lecture fees from Biogen, BioVie, Eisai, Grifols, Janssen Cilag, Neurimmune, Noselab, NovoNordisk, Roche, TauRX, Schwabe; Honoraria for Clinical study committees from Avanir/Otsuka, PharmatrophiX, Charité Berlin, Neuroscios, Vivoryon, and has received Clinical trial honoraria to his institution from Axon Neuroscience, Anavex, Alector, Boehringer Ingelheim, Eisai, Hummingbird, NovoNordisk, Noselab.

TG received consulting fees from AbbVie, Alector, Anavex, Biogen, BMS; Cogthera, Eli Lilly, Functional Neuromodulation, Grifols, Iqvia, Janssen, Noselab, Novo Nordisk, NuiCare, Orphanzyme, Roche Diagnostics, Roche Pharma, UCB, and Vivoryon; lecture fees from Biogen, Eisai, Grifols, Medical Tribune, Novo Nordisk, Roche Pharma, Schwabe, and Synlab; and has received grants to his institution from Biogen, Eisai, and Roche Diagnostics.

OAO received consulting fees from Biogen; lecture fees from Eisai, Boston Scientific, Functional Neuromodulation.

RP has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk, GSK and Tabuk.

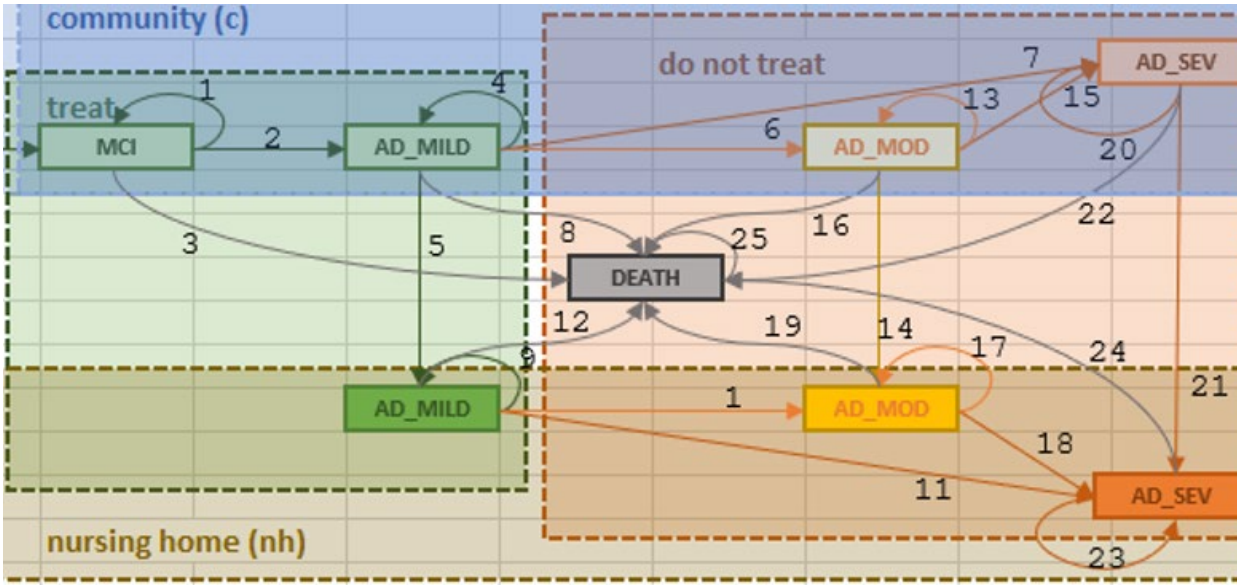
ST. served as member of advisory boards for Lilly, Eisai, and Biogen. He is member of the Independent Data Safety and Monitoring Board of the Study ENVISION (Biogen).

YT, MH, and JT report no disclosures

Technical Appendix

Model description

MCI patients enter the model in the community (c). They may enter nursing homes (nh) while the disease progresses. Patients can die in any health state. Only surviving patients with MCI or mild AD are treated. Patients in all states are accounted for because they incur costs. Patient cohorts move from state j to state i in timestep t according to prob p(j->i).



The process is assumed to be Markov in nature, with health state transitions summarized in a health state transition matrix $\mathbf{T}_k$ with 25 different transition probabilities corresponding to above; h indexes patient cohorts. Transition probabilities are specific to sex and age, therefore transition matrices are specific to sex-age cohorts. Applicable matrices change as cohorts age across the model timeframe. Three indexes are used to organize transition matrices, i = 1 to 8, j = 1 to 8, and k = 1 to 16. k transitions correspond to the entering h sex-age groups.

$\mathbf{T}_k$	**j**							
	1	2	3	4	5	6	7	8
	MCI	AD_MILD_c	AD_MILD_nh	AD_MOD_c	AD_MOD_nh	AD_SEV_c	AD_SEV_nh	DEATH
i MCI	p1							
AD_MILD_c	p2	p4						
AD_MILD_nh		p5'	p9					
AD_MOD_c		p6		p13				
AD_MOD_nh			p10	p14'	p17			
AD_SEV_c		p7		p15		p20		
AD_SEV_nh			p11		p18	p21'	p23	
DEATH	p3	p8	p12	p16	p19	p22	p24	p25
∑	1	1	1	1	1	1	1	1

Transition probabilities are specified by the following formulas. Note that all transition probabilities from a given state (i.e., column sums) sum to 1 (e.g., p1 + p2 + p3 = 1); this observation is used to derive the diagonal (staying in state for the timestep) of the matrix $\mathbf{T_k}$. Transitions to nursing homes (i.e., p5, p14 and p21) are adjusted to allow progression of disease during the transition year. Adjusted transition probabilities are shown with prime (') notation. Transition probabilities are organized in an array p indexed by k and x, where x = 1 to 25.

Parameter	Description	Derivation
p1 =	p(MCI -> MCI)	p1 = 1 - p2 - p3
p2 =	p(MCI -> AD_MILD_c)	
p3 =	p(MCI -> DEATH)	
p4 =	p(AD_MILD_c -> AD_MILD_c)	p4 = 1 - p5' - p6 - p7 - p8
		p5' = p5 * (1 - p6 - p7 -
p5 =	p(AD_MILD_c -> AD_MILD_nh)	p8)
p6 =	p(AD_MILD_c -> AD_MOD_c)	
p7 =	p(AD_MILD_c -> AD_SEV_c)	
p8 =	p(AD_MILD_c -> DEATH)	
p9 =	p(AD_MILD_nh -> AD_MILD_nh)	p9 = 1 - p10 - p11 - p12
p10 =	p(AD_MILD_nh -> AD_MOD_nh)	
p11 =	p(AD_MILD_nh -> AD_SEV_nh)	
p12 =	p(AD_MILD_nh -> DEATH)	
p13 =	p(AD_MOD_c -> AD_MOD_c)	p13 = 1 - p14' - p15 - p16
		p14' = p14 * (1 - p15 -
p14 =	p(AD_MOD_c -> AD_MOD_nh)	p16)
p15 =	p(AD_MOD_c -> AD_SEV_c)	
p16 =	p(AD_MOD_c -> DEATH)	
p17 =	p(AD_MOD_nh -> AD_MOD_nh)	p17 = 1 - p18 - p19
p18 =	p(AD_MOD_nh -> AD_SEV_nh)	
p19 =	p(AD_MOD_nh -> DEATH)	
p20 =	p(AD_SEV_c -> AD_SEV_c)	p20 = 1 - p21' - p22
p21 =	p(AD_SEV_c -> AD_SEV_nh)	p21' = p21 * (1 - p22)
p22 =	p(AD_SEV_c -> DEATH)	
p23 =	p(AD_SEV_nh -> AD_SEV_nh)	p23 = 1 - p24
p24 =	p(AD_SEV_nh -> DEATH)	
p25 =	p(DEATH -> DEATH)	p25 = 1

Table 1: Model parameters and sources

	Value								Source
Initial disease prevalence									
a. MCI									
Age bracket	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>= 85	[21]
MCI prevalence	3.21%	4.43%	6.70%	8.40%	10.10%	14.80%	25.20%	30.53%	
2023 MCI cases	123,130	170,923	227,026	240,042	271,969	341,940	366,599	444,719	
b. Dementia									
Age bracket	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>= 85	[36, 22]
Sex (female)	0.08%	0.16%	0.20%	1.79%	3.23%	6.89%	14.35%	23.19%	
Sex (Male)	0.14%	0.26%	0.90%	1.43%	3.74%	7.63%	16.39%	34.37%	
Annual transition probability									
a. for male									
Age bracket	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>= 85	
mci->mild(p2)	0.187	0.187	0.187	0.187	0.187	0.187	0.187	0.187	
mci->death(p3)	0.0103	0.0156	0.0225	0.0309	0.0449	0.0702	0.1145	0.2367	
nh_mild(p5)	0.0542	0.0542	0.0564	0.0564	0.0586	0.1564	0.061	0.0634	
mild->moderate(p6)	0.323	0.323	0.323	0.323	0.323	0.323	0.323	0.323	
mild->severe(p7)	0.044	0.044	0.044	0.044	0.044	0.044	0.044	0.044	
mild->dead(p8)	0.0107	0.0107	0.0107	0.019	0.019	0.0428	0.0428	0.0428	
nh_moderate(p14)	0.1446	0.1446	0.1504	0.1504	0.1564	0.1955	0.1627	0.1692	
moderate->severe(p15)	0.401	0.401	0.401	0.401	0.401	0.401	0.401	0.401	
moderate->dead(p16)	0.0331	0.0331	0.0331	0.0487	0.0487	0.1062	0.1062	0.1062	
nh_severe(p21)	0.1807	0.1807	0.188	0.188	0.1955	0.061	0.2033	0.2115	
severe->dead(p22)	0.1453	0.1453	0.1453	0.1613	0.1613	0.2331	0.2331	0.2331	[37, 38, 39]
b. for female									
Age bracket	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>= 85	
mci->mild(p2)	0.187	0.187	0.187	0.187	0.187	0.187	0.187	0.187	
mci->death(p3)	0.0064	0.0096	0.0135	0.0195	0.0306	0.05	0.0855	0.2103	
nh_mild(p5)	0.0542	0.0542	0.0564	0.0564	0.0586	0.1564	0.061	0.0634	
mild->moderate(p6)	0.323	0.323	0.323	0.323	0.323	0.323	0.323	0.323	
mild->severe(p7)	0.044	0.044	0.044	0.044	0.044	0.044	0.044	0.044	
mild->dead(p8)	0.006	0.006	0.006	0.0107	0.0107	0.0243	0.0243	0.0243	
nh_moderate(p14)	0.1446	0.1446	0.1504	0.1504	0.1564	0.1955	0.1627	0.1692	
moderate->severe(p15)	0.401	0.401	0.401	0.401	0.401	0.401	0.401	0.401	
moderate->dead(p16)	0.0181	0.0181	0.0181	0.0266	0.0266	0.0589	0.0589	0.0589	
nh_severe(p21)	0.1807	0.1807	0.188	0.188	0.1955	0.061	0.2033	0.2115	
severe->dead(p22)	0.0946	0.0946	0.0946	0.1053	0.1053	0.1546	0.1546	0.1546	
Screening and confirmatory tests									
MMSE - Sensitivity	0.82								[40]
MMSE - Specificity	0.73								
Blood-based biomarker test - Sensitivity	0.89								[41]
Blood-based biomarker test - Specificity	0.69								
Confirmatory cognitive testing - Sensitivity	0.95								Assumption
Confirmatory cognitive testing - Specificity	0.95								Assumption
Confirmatory testing with CSF - Sensitivity	0.91								[42]

Confirmatory testing with CSF - Specificity	0.73	
Confirmatory testing with PET- Sensitivity	0.92	[43]
Confirmatory testing with PET- Specificity	0.95	

Estimation of AD specialist capacity

Number of AD specialists

The Federal Association of Physicians (*Bundesärztekammer*) publishes an annual census[23] of physicians by specialty and place of occupation (employed in hospital or based in private practice). We obtained counts of physicians with board certification in Geriatrics, Neurology, combined Neurology and Psychiatry, and Psychiatry from the 2017 through 2022 census reports. While Germany has separate board certifications for Geriatric Neurology and Geriatric Psychiatry, only one or two physicians were certified in recent years and we subsumed them into Neurology and Psychiatry, respectively. We used linear predictions based on that historic trend to predict future numbers of physicians in those four categories, separately for hospital-based and practice-based physicians. Of note, the combined Neurology and Psychiatry board certification was phased out in 2003[44], which leads to declining numbers in this specialty.

Figure 1: Regression Model for Geriatrics (practices)

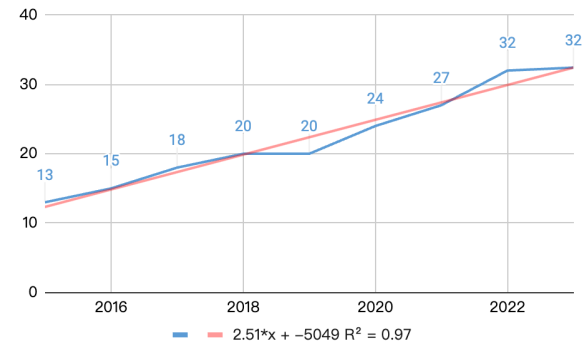


Figure 2: Regression Model for Geriatrics (hospitals)

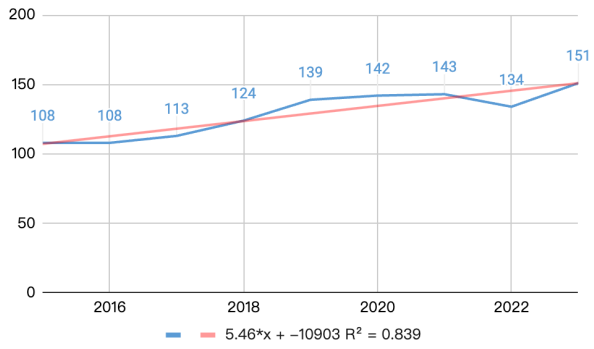


Figure 3: Regression Model for Neurology (practices)

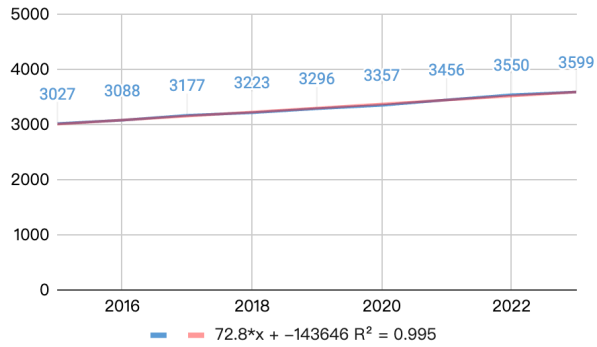
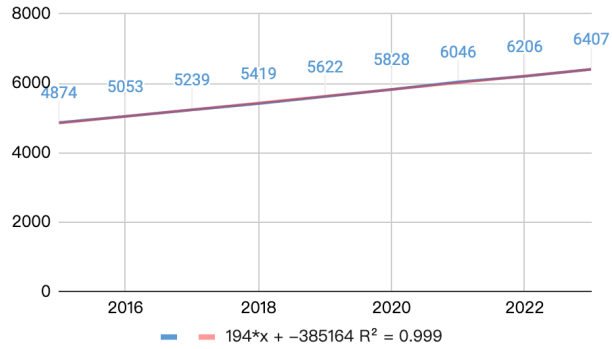


Figure 4: Regression Model for Neurology (hospitals)



Notes: This linear regression model includes Neurology and Geriatric neurology as one group.

Figure 5: Regression Model for Psychiatry (practices)

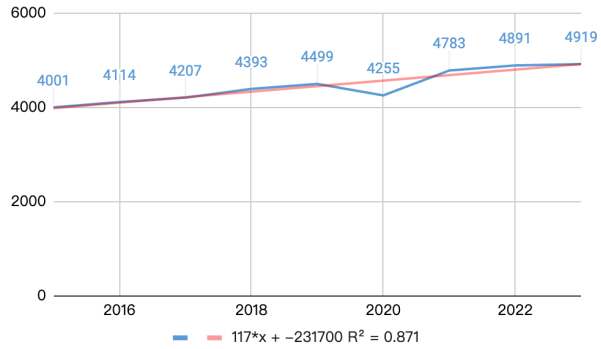
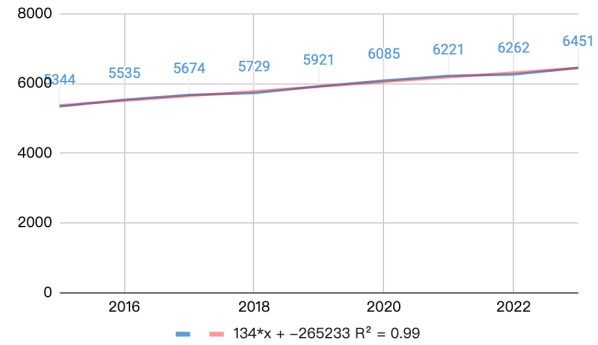


Figure 6: Regression Model for Psychiatry (hospitals)



Notes: This linear regression model includes Psychiatry and Geriatric Psychiatry as one group.

Figure 7: Regression Model for Neurology/psychiatry (practices)

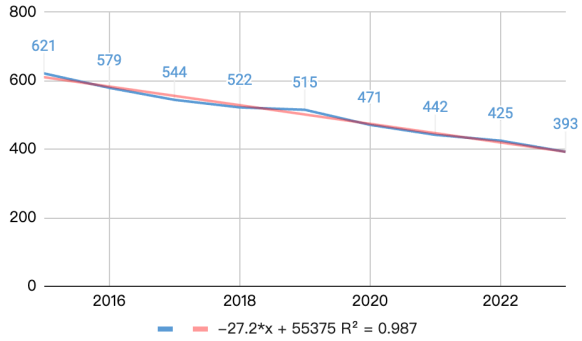
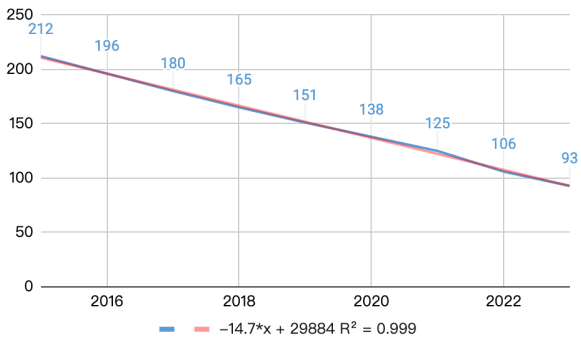


Figure 8: Regression Model for Neurology/psychiatry (hospitals)



AD specialist time available for visits

The Federal Statistics Office (*Bundesamt für Statistik*) conducts a biannual survey on working hours [19] that reports the actually weekly working hours by occupation, which accounts for overtime, time off for holidays, vacation and sick leave, and training time. We obtained the 2022 estimates for physicians specialized in neurology and psychiatry, which reported 32.3 working hours per week for physicians in private practice and 30.4 working hours per week for hospital employees, corresponding to 1,680 and 1,581 hours per year, respectively.

We asked our experts what proportion of time hospital-based and practice-based physicians would devote to patient care versus other tasks, like administration, research and teaching. Their average estimate was 66% and 78% for hospital-based and practice-based physicians, respectively, translating into 1,109 and 1,233 hours of clinical time per year.

Number of available appointments

Time use of AD specialists for the first and second specialist appointment was calculated separately for hospital- and practice-based physicians, because the latter have a broader range of support staff, such as junior physicians, nurses and technicians, to whom tasks can be delegated. Time use estimates for hospital-based physicians came from a study that surveyed 15 memory clinics on staff time required for

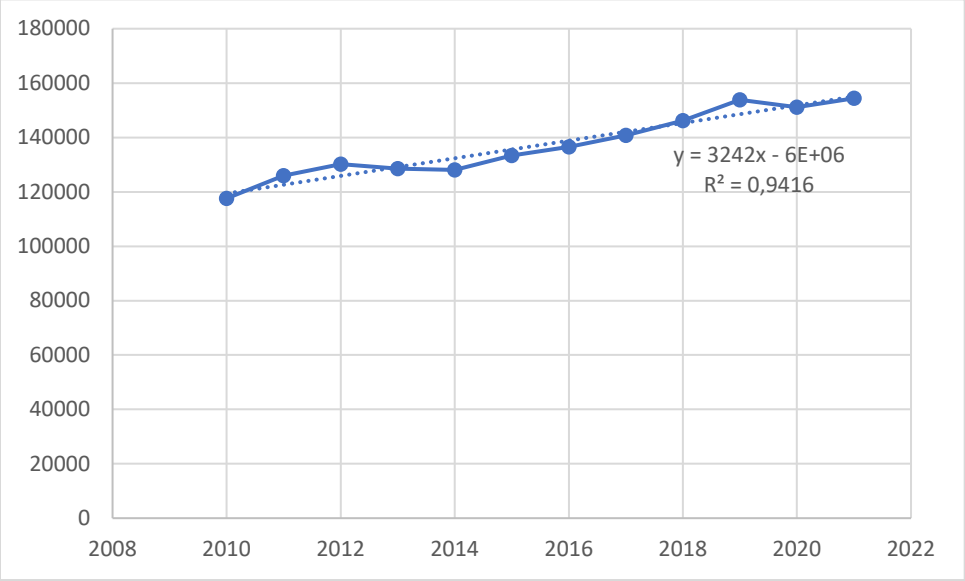
different stages of the diagnostic process[24]. Based on their mid-point estimate, 50.5 and 27.5 minutes would be required for the first and second visit, respectively. The average duration of 39 minutes means that hospital-based specialists could provide 2,294 visits per year.

No corresponding data could be identified for practice-based physicians, and we relied on estimates of our experts that 45 and 45 minutes would be required for the first and second visit, respectively, which is similar to recently published study in England. [8] The average estimated duration of 45 minutes means that practice-based specialists could provide 1,644 visits per year.

Estimation of PET scan capacity

The Federal Government publishes the annual number of imaging devices in hospitals, including PET scanners[45] but not the number of PET scanners operated in private practices. Further, the reported numbers seem unreliable, as the number of reported devices remained largely unchanged around 125 between 2012 and 2018, and even dropped to 102 in 2019, whereas the annual number of scans grew continuously in this time period according to OECD data[15], as shown in Figure 8.

Figure 8: Annual Number of PET Scans in Germany



The only source for PET scanners operated by physicians in private practice is a registry maintained by the German Society of Nuclear Medicine (*Deutsche Gesellschaft für Nuklearmedizin*), which lists PET scan sites in German-speaking countries.[46] While participation in this registry is voluntary, we expect that private practices have an economic incentive to be listed so that patients and referring physicians can find them. We went through the sites listed for Germany manually and identified 79 devices in private practices for 2023. However, this registry does not provide historic counts, which made it impossible to estimate a growth trend.

As the OECD Health Statistics database[15] reports the number of PET scans independent of setting, we used the trend data in Figure 8 to project the future number of scans. We then assume that as many amyloid brain scans can be performed in addition to the projected number, i.e., that the projected devices could handle twice the projected capacity. The assumption seems plausible because the number of scans per device is comparatively low, with less than 1,000 scans for 2020 and 2021, even if only counting the hospital-based devices, and around 600 when adding our estimates for practice-based devices. The IAEA benchmark for efficient device use is at least 2,000 per device and year, and as many as 3,208 scans per year and device were reported for 2019 in the UK.[47] Expanding number of scans tends to be feasible for brain imaging, since those scans are shorter than the ones required for oncology, and can be done late in the day, because patients do not have to be fasting. We also explored a scenario, under which the number of scans per device would triple to 1,800 to get closer to the IAEA benchmark.

Estimation of wait times for patients in social and private insurance

The literature of the mystery shopper experiments showed that the median wait time for elective specialty care for patients with social insurance 1.9 times the one for privately insured patients as summarized in Table 1. Around 85% of German residents are covered by social insurance, and we assume that the remaining 15% have private insurance policies and we assume that age structure and disease burden are identical for both groups. The two data points allows us to set up a system of equations:

$$(Eq.1)\ WaitSI * 0.85 + WaitPI * 0.15 = WaitTotal$$

$$(Eq.2)\ WaitSI = 1.90 * WaitPI$$

Substitute Eq. 2 into Eq. 1

$$1.90 * WaitPI * 0.85 + WaitPI * 0.15 = WaitTotal$$

$$WaitPI = WaitTotal/1.63$$

Solve for WaitSI

$$WaitSI = 1.90 * (WaitTotal/1.63)$$

(WaitSI: wait times for patients with social health insurance; WaitPI: wait times for patients with private health insurance; WaitTotal: overall wait times for all patients)

Table 2: Differential wait times for patients in social versus private insurance based on published mystery shopper studies

Specialty	Publication	Year of data collection	Wait times - public	Wait times - private	Absolute diffs	Relative diffs
Allergology/Pneumology	[48]	2006	19.8	14.6	5.2	0.36
Ophthalmology		2006	24.9	8.5	16.4	1.93
Diagnostic Radiology		2006	18.5	1.1	17.4	15.82
Gastroenterology		2006	40.4	8.2	32.2	3.93
Otorhinolaryngology		2006	6	2.9	3.1	1.07
Ophthalmology	[49]	2014	27.4	12.7	14.7	1.16
Audiology		2014	10	5.4	4.6	0.85
Allergology/Pneumology		2014	21.7	13.7	8	0.58
Allergology/Pneumology		2014	54.4	26	28.4	1.09
Diagnostic Radiology		2014	19.7	16	3.7	0.23
Gastroenterology		2014	52.4	24	28.4	1.18
Ophthalmology		2016	32.8	7.6	25.2	3.32
Audiology		2016	8.4	2.9	5.5	1.9
Allergology/Pneumology		2016	40.7	10.5	30.2	2.88
Allergology/Pneumology		2016	70.2	21.3	48.9	2.3
Diagnostic Radiology		2016	24.4	1.4	23	16.43
Gastroenterology		2016	52	12.9	39.1	3.03
Gastroenterology	[50]	2018	49	18	31	1.72
Allergology/Pneumology		2018	26	12.5	13.5	1.08
Otorhinolaryngology		2018	15	9	6	0.67
Orthopedic surgery	[51]	2007	3.5	0.88	2.62	2.98
Cardiology		2007	10.8	7.6	3.2	0.42
Gynecology		2007	7.11	5.84	1.27	0.22
Dermatology	[52]	2019	48.7	33	15.7	0.48
Neurology		2019	56	40	16	0.4
Median			**24.9**	**10.5**	**17.4**	**1.9**

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