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RESEARCH ARTICLE

Blood-based biomarkers for Alzheimer's pathology and the diagnostic process for a disease-modifying treatment: Projecting the impact on the cost and wait times

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Abstract

Introduction: Concerns have been raised about the limited health system capacity for identification of patients who are eligible for a disease-modifying Alzheimer's treatment (DMT). Blood-based biomarker (BBBM) tests are a promising tool to improve triaging at the primary care level. We projected their impact on cost of and wait times during the diagnostic process.

Methods: We compare four scenarios for triaging patients at the primary care level from the perspective of the U.S. health care system: (1) cognitive test only (Mini Mental State Examination [MMSE]), (2) BBBM test only, (3) MMSE followed by BBBM if positive, and (4) BBBM followed by MMSE if positive.

Results: Referring patients to dementa specialists based on MMSE or BBBM results alone would continuously require more specialist appointments than projected to be available until 2050. Combining MMSE and BBBM would eliminate wait lists after the first 3 years and reduce average annual cost by $400 to 700 million, while increasing correctly identified cases by about 120,000 per year.

Discussion: The combination BBBM with MMSE is projected to increase the efficiency and value of the triage process for DMT eligibility.

KEYWORDS
Alzheimer's disease, blood-based biomarker, disease-modifying treatment, health system capacity, simulation

1 | INTRODUCTION

Several disease-modifying treatments for Alzheimer's disease (AD) are in various stages of clinical development or regulatory review.[1] However, the potential approval of such a treatment will create an enormous challenge for healthcare systems because of the large number of people who are likely to seek out an evaluation for treatment eligibility. Those will include many people without a treatment indication, such as the worried well, those with manifest dementia, and those with cognitive impairment due to other causes.

A previous study analyzed the preparedness of healthcare systems in the United States to handle the potential caseload if a disease-modifying therapy for AD became available in 2020.[2] At current capacity trends, the study estimated an average wait time of 19 months between seeking diagnosis and infusion delivery of the therapy when the DMT might first become available. Because the most pressing rate-limiting step identified was the number of available appointments to see dementia specialists, a logical approach to reducing expected wait time is to improve triage at the primary care level. If primary care clinicians identified more patients to have no

cognitive impairment or cognitive impairment due to other causes, fewer patients without an indication for disease-modifying treatment would be referred to specialist evaluation, hence reducing wait times for everyone.

A recent review evaluated tools to identify early stage AD at the primary care level. The findings suggest that brief cognitive tests, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), are reasonably accurate for the detection of mild cognitive impairment (MCI) but are not designed to distinguish the underlying etiology.[3,4] Although several tests for the pathologic hallmarks of AD, which are suitable for primary care settings, are being developed, only plasma-based biomarker tests currently have sufficient evidence to likely enter routine clinical practice in the foreseeable future.[5,6]

Against this background, we hypothesize that a combination of a brief cognitive test and a blood-based biomarker test can improve triaging of patients at the primary care level and thereby reduce wait times and avoidable cost of specialist evaluation. We use a simulation model to predict the effect of different triaging scenarios at the primary care level from the perspective of the U.S. healthcare system.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched for publications on health system capacity projections to identify and diagnose patients who were potentially eligible for a disease-modifying treatment for Alzheimer's disease (AD) as well as tools to improve this process in PubMed and in references of relevant publications. Previous research points to blood-based biomarkers as a promising tool, but data on their impact on cost and wait times for evaluation were lacking.
2. **Interpretation**: We simulate the cost and wait times for different diagnostic pathways from the perspective of the U.S. healthcare system. We show that a combination of a cognitive screening test and blood-based biomarker test can substantially reduce the number of treatment-ineligible patients referred for specialist evaluation and biomarker testing with positron emission tomography (PET) scan or cerebrospinal fluid (CSF) testing, thereby reducing cost and wait times.
3. **Future directions**: This simulation points to possible solutions for reducing obstacles to access to a disease-modifying treatment. The results will need to be validated empirically.

2 | MATERIALS AND METHODS

2.1 | Model structure

Our model builds on previous work that combined a Markov model of disease development and progression, a systems dynamics model that uses predicted capacity for specialist visits and confirmatory biomarker testing to estimate wait times, and an accounting facility that tracks associated costs (Supplemental Exhibit 1).[2,7] We improve upon limitations in the previous work in three ways. First, the new model incorporates information on sensitivity and specificity of initial and confirmatory tests to estimate false-positive rates, whereas the previous model assumed "perfect" tests. Second, we account for the fact that cognitively normal but worried patients rather than only those with actual cognitive decline will seek out evaluation. Third, the model now assumes that patients may seek another evaluation after having previously tested negative.

The model simulates the journey of patients seeking evaluation for subjective memory complaints or as part of a wellness exam. The model has two interacting layers. The first layer captures one of four true health states: cognitively normal, MCI due to AD, MCI due to other causes, and dementia. We define AD based on amyloid positivity and cognitive decline. The second layer captures a patient's journey through different evaluation stages: initial evaluation with cognitive and/or blood-based biomarker testing by a primary care clinician, neurocognitive testing by a dementia specialist, and confirmatory biomarker testing with positron emission tomography (PET) or cerebrospinal fluid (CSF) testing. For example, a cognitively normal, but worried patient starts in the "Cognitively Normal - Screening Naïve" state and moves forward to receive evaluation at the primary care setting. If the patient tests (false) positive, they can move to be evaluated by a specialist and then receive a confirmatory biomarker test. If the patient is tested negative during any one of evaluation stages, the patient is sent to the "Cognitively Normal - Screening Experienced" state.

A patient's journey in the model is guided by disease progression rates, the number of available specialist visits and biomarker tests, as well as sensitivity and specificity of initial and confirmatory tests (ie, only the patients who test positive move to the next testing stage). While waiting for evaluation by a specialist and confirmatory biomarker testing, patients can progress from cognitively normal to MCI, and from MCI to dementia. The disease progression rates between the health states were based on previous studies.[8–10] We assume that patients who develop manifest dementia would not receive further evaluation, as they would no longer be eligible for disease-modifying treatment. Death could occur during any stage, but at higher rates for MCI and dementia patients.[11–14] We use age-adjusted mortality rates to account for changes in the age composition of the U.S. population.

The model projects average time elapsed while waiting for the completion of the diagnostic work-up and accounts for the number of patients in the disease states and stages of the evaluation as well as the accrued costs. We compare four scenarios for initial evaluation at the primary care level: (1) cognitive test only; (2) blood-based biomarker test only; (3) cognitive test followed, if positive, by a blood-based biomarker test; and (4) a blood-based biomarker test followed, if positive, by a cognitive test.

2.2 | Model parameters

2.2.1 | Population, disease burden, and available capacity

We use census projections for the U.S. population aged 50 and older, which is the age range typically included in clinical trials for disease-modifying treatments. The model has a time horizon of 30 years, starting in 2020, as the presumptive year of market entry of the first treatment. We use published estimates for prevalence and incidence of MCI and dementia.[15–18] Based on results from the IDEAS study, we assume that 55% of individuals with MCI have AD as the underlying cause.[19]

We assume that 50% of patients who have not been evaluated will seek out an initial cognitive evaluation at a primary care site. This estimate is based on published screening rates for breast, cervical, and colorectal cancer of 81%, 72%, and 63%, respectively, under the assumption that initial uptake will be slightly lower than that for well-established screening programs.[18,20,21] Patients, who test negative during any evaluation stages, have an assumed probability of 10% each year to seek out a repeat evaluation in subsequent years.

Capacity for dementia specialist visits and confirmatory biomarker testing with an amyloid PET scan (assumed to be used in 90% of cases[2]) or CSF testing (assumed to be used in the remaining 10%) is derived from a previous U.S.-based study.[2] Capacity to perform lumbar punctures for CSF testing is assumed to be unconstrained.

2.2.2 | Performance of diagnostic tests

We base our parameters for performance of the MMSE for cognitive testing on a study by Roalf et al., who demonstrated that the test had a sensitivity and specificity of 0.82 and 0.73, respectively, for distinguishing MCI patients from cognitively normal patients at a cut-off score of 29.[22] We chose the MMSE because it is used more commonly in the United States than the Montreal Cognitive Assessment (or MoCA).[23] The parameters for the blood-based biomarker come from Palmqvist et al., who compared the performance of fully automated plasma assays against CSF assays as a gold standard for detection of amyloid beta 42 and 40 (Aβ42 and Aβ40).[5] We use the sensitivity and specificity of 0.89 and 0.69, respectively, based on their results from their independent validation sample, which is lower than performance reported by specialized laboratories.[20,24]

We assume that neurocognitive testing by a dementia specialist has a sensitivity and specificity of 0.95 and 0.95, respectively, to confirm a finding of MCI.

The sensitivity and specificity estimates for confirmatory biomarker tests come from previous studies. Clark et al. reported the sensitivity and specificity of 0.92 and 0.95, respectively, for amyloid PET imaging by prospectively comparing imaging results with neuropathology findings at autopsy.[25] Hansson et al. investigated concordance between a fully automated CSF immunoassay and amyloid PET scan in the patients from the Swedish BioFINDER study and the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, and reported a sensitivity and specificity of 0.91 and 0.89 at the cut-off ratio of 0.022 for pTau/Aβ(1-42).[26]

2.2.3 | Costs

Our cost estimates are based on billing codes in the 2018 physician service and laboratory fee schedules published by the Centers for Medicare & Medicaid Services, if available. We use the reimbursement rate for a smoking cessation counseling of more than 10 minutes to approximate payment for conducting a cognitive test in the primary care setting, as this test has currently no dedicated reimbursement, but is bundled into the payment for a preventive visit.

Neither the blood-based nor CSF immunoassays for Aβ are currently approved for clinical use in the United States and are therefore not reimbursed. We estimated a payment rate for the blood test at $100 based on a basket of tests used to determine treatment eligibility for high-cost targeted treatment and for screening of common medical conditions (Supplemental Exhibit 2). We assumed that the confirmatory CSF test would be reimbursed at twice the rate of the blood test. All model inputs and their sources are listed in Table 1.

3 | RESULTS

Figure 1 plots the implied demand for dementia-related specialist visits (ie, the number of specialist visits needed) under our four scenarios for evaluation at the primary care level, together with an estimate for the actually available number of specialist visits for the years from 2020 to 2050. Under the scenario that most closely reflects current practice (ie, initial cognitive testing alone), about 23 million specialist visits would be needed in the first year. Although this number is projected to decrease to below 10 million after the first 3 years, it would continue to exceed the availability of the specialists' capacity of about 4 million visits per year. Similarly, referring patients based on a positive blood-based biomarker test alone would result in a demand for specialist visits that vastly exceeds estimated capacity. The combination of initial cognitive and blood biomarker testing, in either order, would reduce the demand for specialist visits by more than 50% to less than 10 million visits in the first year, and the mismatch between supply and demand would be eliminated after the first 3 years.

Figure 2 shows the average wait time to complete both specialist evaluation and confirmatory biomarker testing under our four scenarios based on the estimated capacity for specialist visits and confirmatory biomarker testing. With initial cognitive or blood biomarker testing alone, the expected mean wait times could reach 45 months in 2020 and further increase to 75 or 80 months by 2023, before starting to decline slowly. Following a short period of decline, the expected wait time would likely increase again in the late 2030s and reach up to 75 months in 2050, as population aging leads to growth in demand for specialist visits that outpaces the growth in the number of available specialist visits. With a combination of initial cognitive and blood

TABLE 1 Model input parameters

	Value	References
Projected U.S. population (50 years and older)		
2020	119,344,000	17
2025	126,287,000	
2030	132,405,000	
2035	138,792,000	
2040	145,201,000	
2045	151,636,000	
2050	156,729,000	
Initial prevalence		
Cognitively normal	85%	18,20
MCI	9%	18,20
Dementia	6%	19
Proportion of MCI patients with Alzheimer's disease	55%	21
Annual mortality rate by age group (%)		
50-54	0.4	13
55-64	0.9	
65-74	1.8	
75-84	4.5	
85+	13.6	
Hazard ratio for excess mortality		
MCI	1.43	14
Dementia	3.26	15,16
Annual transition probability		
Cognitively normal to MCI	0.030	10
MCI to dementia	0.065	12
% of new MCI patients with Alzheimer's disease	0.55	Assumption based on the IDEAS study
Initial and confirmatory tests		
MMSE – Sensitivity	0.82	22
MMSE – Specificity	0.73	
Blood-based biomarker test (Aβ42/40) – Sensitivity	0.89	7
Blood-based biomarker test (Aβ42/40) – Specificity	0.69	
Confirmatory cognitive testing – Sensitivity	0.95	Assumption
Confirmatory cognitive testing – Specificity	0.95	Assumption
Confirmatory testing with CSF (pTau/Aβ42) – Sensitivity	0.91	25
Confirmatory testing with CSF (pTau/Aβ42) – Specificity	0.89	
Confirmatory testing with PET – Sensitivity	0.92	24
Confirmatory testing with PET – Specificity	0.95	
Proportion of patients receiving amyloid PET scan	90%	Assumption
Proportion of patients receiving CSF testing	10%	Assumption
Annual probability for screening		
Screening naïve	50%	Estimated based on participation rates in cancer screening
Screening experienced	10%	Assumption
Costs (2018 Medicare rates)		
MMSE	$28	Approximated based on comparable service (smoking cessation counseling (CPT: 99407)
Venipuncture	$17	CPT: 36410
Blood-based biomarker assay (Aβ42/40)	$100	Estimated based on Medicare rates for comparable tests
Assessment and care planning by specialist	$242	CPT: 99483
Cognitive performance testing by specialist	$121	CPT: 96125
Diagnostic lumbar puncture	$162	CPT: 62270
CSF assay (pTau/Aβ42)	$200	Estimated as 2x amyloid blood test
Amyloid PET scan - technical component	$1,286	CPT:78811
Amyloid PET scan - professional component	$78	CPT: 78811
Amyloid PET scan - diagnostic radiopharmaceutical	$2,964	HCPCS: A9586

CSF, cerebrospinal fluid, MCI, mild cognitive impairment, MMSE, Mini-Mental State Examination, PET, positron emission tomography

biomarker testing, in either order, the expected wait time would be about 10 months in the first year and gradually begin to decline toward zero after the first 3 years.

Table 2 compares the projected number of correctly identified cases (ie, true positive for MCI due to AD) and expected costs under the four scenarios. With either an initial cognitive test or the blood test alone, we estimate that around 480,000 treatment-eligible patients can be diagnosed each year on average. Combining the two tests would increase that number substantially, to 677,437, if initial cognitive testing were conducted first, and to 607,183, if blood testing were done first, whereas overall annual costs are projected to decline from around

FIGURE 1 Estimated annual demand for specialist visits under different assumptions for testing approaches in the primary care setting

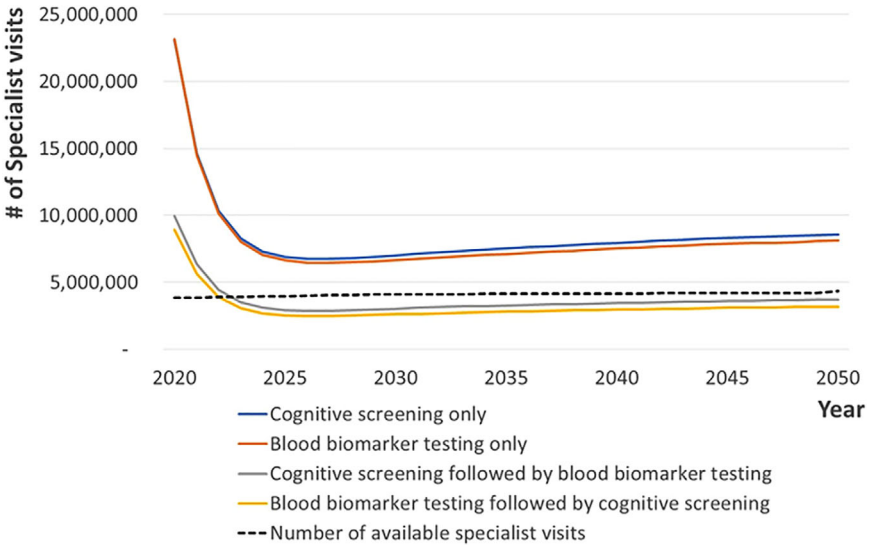
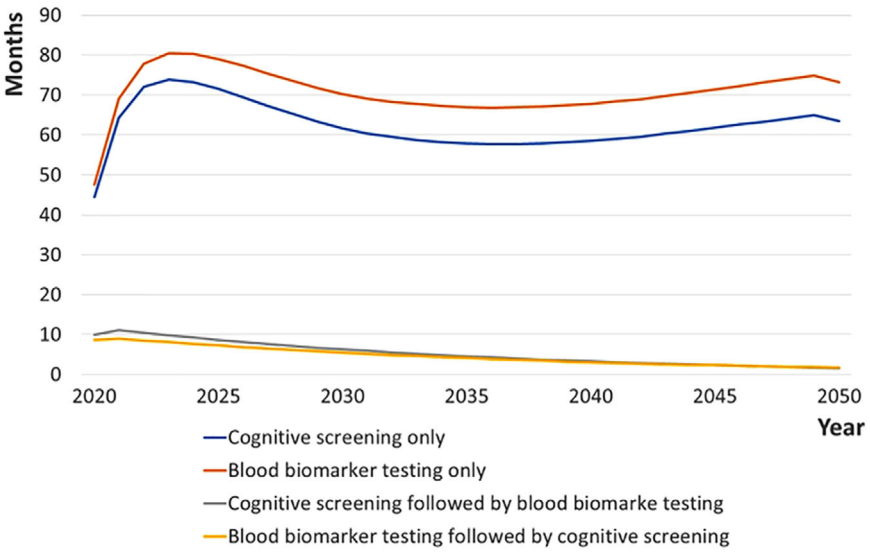


FIGURE 2 Estimated average wait time for completion of diagnostic process by year



$7.2 billion and $7.5 billion for initial cognitive testing and blood assays alone, respectively, to around $6.8 billion. Cost per correctly identified case is projected to be lower for the two tests combined relative to either test in isolation.

Table 3 illustrates the cost implications of the four scenarios by a patient's true health state and evaluation setting. The introduction of a blood-based biomarker test would increase spending at the primary care level by a factor of three to five relative to using only initial cognitive testing, reaching up to $1.4 billion for initial cognitive testing followed by a blood-based test, with concomitant reductions particularly on confirmatory PET or CSF testing. Similarly, a larger proportion of the overall spending is estimated to be devoted to true positive cases (ie,

TABLE 2 Average cost per year for correctly identifying treatment-eligible patient

	Cognitive test only	Blood biomarker test only	Cognitive test followed by blood biomarker test	Blood biomarker test followed by cognitive test
Average annual total cost (millions)	$7,159	$7,492	$6,836	$6,801
Average number of correctly identified cases per year	479,488	483,390	677,437	607,183
Average annual cost per correctly identified case	$14,930	$15,499	$10,090	$11,200

TABLE 3 Average total cost ($ million) per year by health state and evaluation setting

	Cognitive test only	Blood biomarker test only	Cognitive test followed by blood biomarker test	Blood biomarker test followed by cognitive test
By care setting				
Triage at primary care level	$515 (7%)	$2,119 (28%)	$1,351 (20%)	$2,558 (38%)
Formal neurocognitive testing	$1,540 (22%)	$1,540 (21%)	$905 (13%)	$838 (12%)
PET/CSF testing	$5,103 (71%)	$3,833 (51%)	$4,580 (67%)	$3,405 (49%)
By patient health state				
MCI due to AD	$2,404 (34%)	$2,503 (33%)	$3,496 (51%)	$3,168 (47%)
MCI due to other etiology	$2,510 (35%)	$1,122 (15%)	$1,474 (22%)	$502 (7%)
Cognitively normal	$2,244 (31%)	$3,867 (52%)	$1,865 (27%)	$3,131 (46%)

CSF, cerebrospinal fluid, MCI, mild cognitive impairment, PET, positron emission tomography

TABLE 4 Results from univariate sensitivity analysis

RU	MMSE then BBBM					BBBM then MMSE				
Input parameter adjustment	baseline cost	10% decrease	10% increase	10% decrease*	10% increase*	baseline cost	10% decrease	10% increase	10% decrease*	10% increase*
MMSE										
Sensitivity for MCI	6,835,523,746	6,471,673,380	7,181,522,560	-5.3%	5.1%	6,800,725,517	6,554,061,442	7,035,071,294	-3.6%	3.4%
Specificity for MCI	6,835,523,746	7,083,510,131	6,589,152,127	3.6%	-3.6%	6,800,725,517	6,918,177,132	6,659,044,218	1.7%	-2.1%
Cost ($)	6,835,523,746	6,779,196,324	6,891,851,168	-0.8%	0.8%	6,800,725,517	6,781,378,921	6,820,072,112	-0.3%	0.3%
BBBM										
Sensitivity for Amyloid +	6,835,523,746	6,618,919,934	7,036,554,719	-3.2%	2.9%	6,800,725,517	6,580,017,067	7,005,437,630	-3.2%	3.0%
Specificity for Amyloid +	6,835,523,746	7,184,962,227	6,478,336,361	5.1%	-5.2%	6,800,725,517	6,937,879,349	6,646,470,063	2.0%	-2.3%
Cost ($)	6,835,523,746	6,756,787,439	6,914,260,053	-1.2%	1.2%	6,800,725,517	6,564,298,730	7,037,152,303	-3.5%	3.5%
Specialist Evaluation										
Cost ($)	6,835,523,746	6,745,053,843	6,925,993,649	-1.3%	1.3%	6,800,725,517	6,716,924,962	6,884,526,072	-1.2%	1.2%
Confirmatory Biomarker Test										
Cost ($)	6,835,523,746	6,377,505,003	7,293,542,489	-6.7%	6.7%	6,800,725,517	6,460,226,902	7,141,224,131	-5.0%	5.0%

*cell values reflect percent change in cost relative to baseline cost with input parameter adjustment +/-10%

patients in whom MCI due to AD was confirmed), if the two tests are combined. For example, 34% of the spending would go to true positives if only initial cognitive testing were used, whereas 51% would go to true positives if a positive cognitive test were followed by a blood test.

The results of a sensitivity analysis are displayed in Table 4. We varied the values for the input parameters by ±10% and calculated the effect on overall cost of the diagnostic process. No change in the inputs resulted in a change of more than 10% of the overall cost, and parameters for the cost of confirmatory biomarker testing, sensitivity of the MMSE, and cost and specificity of the blood test had the largest effect.

4 | DISCUSSION

Consistent with an earlier study by Liu et al.[2], our findings suggest that the U.S. healthcare system is ill-prepared to handle the likely demand for services should a disease-modifying treatment for AD be approved, assuming currently available technology. However, we project substantially longer wait times of 45 months for the diagnostic workup for treatment eligibility than their estimate of 18 months in the first years. We also find that long wait times of around 60 months would persist for decades in contrast to their prediction of having resolved the backlog of prevalent cases by 2028. The difference stems from our model that incorporates information on sensitivity and specificity of the various tests and allows for cognitively normal patients to seek out evaluation and repeat evaluation after having previously tested negative. These three changes increase the demand for dementia specialist visits substantially, as a large number of false-positive cases are referred, possibly more than once, for cognitive testing and evaluation.

Limited capacity of dementia specialists is not only the most relevant obstacle to access to a possible disease-modifying treatment, but it also the most difficult to address because of long training times for specialists and overall increasing demand for geriatric care because of other age-related conditions in an aging population. In response, several authors have called for greater involvement of primary care providers in the evaluation process.[3,27,28] Primary care–led memory services models have been introduced that could germinate such task shifting [29–31] However, it is not clear that those models, which currently focus on support for dementia patients and coordination with social services, are equipped to handle the medicalized nature of

services around a disease-modifying treatment. Moreover, it might prove difficult to integrate those services into the workflow of primary care settings, which constitute the entry point into the healthcare system for most patients.[32]

Tools are clearly needed to facilitate embedding the initial evaluation and triage of patients with possible early stage ADI into primary care workflows. Blood-based biomarker assays have great potential in that respect, now that they have matured from tests conducted in highly specialized laboratories to automated tests that run at scale on standard equipment.[24] They conveniently fit into primary care workflows, require little time of clinicians and, unlike cognitive tests, do not depend on the user for adequate test performance.

Our simulation results suggest that conducting a blood-based biomarker test in patients with suspected MCI based on a brief cognitive assessment improves the efficiency of the initial evaluation process dramatically, because ≈41% of specialist referrals could be avoided. The improved triage is estimated to nearly eliminate wait times and to allow the detection of more true positive cases, given that specialists are not tied up with examining false-positive cases.

Our results also indicate that a blood-based biomarker test should be used in conjunction with initial cognitive testing, since referring patients to specialists on the basis of a positive blood test alone would lead to similarly long wait times as referrals based on initial cognitive testing results only.

Although overall expected spending on identifying treatment-eligible patients for a disease-modifying treatment for AD decreases only slightly with the addition of a blood-based biomarker assay, the value of money spent increases substantially. Average annual spending on diagnostic services would fall by about 5%, if a blood-based biomarker test were used in patients with a positive cognitive test before a specialist referral. In addition, we project that such a triage process would allow for the correct diagnosis of almost 200,000 additional patients per year on average, reducing the total diagnostic cost per identified case by 32%. The share of spending devoted to patients who will eventually be diagnosed with MCI due to AD would increase from about one third to about one half.

The emergence of predictive models, which estimate a patient's risk of progressing from MCI to dementia due to AD, could further reduce costs and wait times, as they allow triaging patients for specialist evaluation. Such models are currently being tested in the Interceptor Project in Italy and the ADNI.[33,34]

Our analysis is not without limitations. First, we use a stylized patient journey to track patients through various discrete disease stages and diagnostic steps. Although we expect deviations from that journey under real-world conditions, particularly because cognitive decline is gradual and not linear, we consider this simplified pathway to be representative of a typical patient. Second, most but not all of our parameters have an empirical basis. We had to approximate care-seeking behavior from other screening programs but note that assumptions for uptake rates will not affect the outcomes under the four scenarios relative to each other. Third, because several tests are not currently reimbursed in the United States, we had to estimate their costs. Fourth, our estimates provide a national overview and do not account for known regional disparities in access to memory care.[35] Finally, test performance was derived from published studies and may deviate under real-world conditions, especially for user-dependent tests, like brief cognitive testing.

Overall, a simulation study is not direct evidence. It provides directionally correct answers but needs direct empirical validation. The true value of a blood-based biomarker test will also depend on cost and net clinical benefit of an eventual disease-modifying treatment.

Our results confirm earlier findings that demand for services might initially overwhelm health system capacity if a disease-modifying treatment became available, given the large pool of prevalent cases. The introduction of a blood-based biomarker test to detect the Alzheimer's pathology in patients with MCI appears to be a valuable and scalable solution. In light of a potential arrival of a treatment as early as 2021, we hope that our findings will inform a stakeholder dialogue about the organization of and payment for the required diagnostic steps.

AUTHOR CONTRIBUTIONS

Soeren Mattke, Tobias Bittner, and Jakub Hlávka worked on conception and design of the study, whereas Sang Kyu Cho, Tobias Bittner, and Mark Hanson worked on the acquisition and analysis of data. Soeren Mattke and Sang Kyu Cho helped draft a significant portion of the manuscript or figures.

CONFLICT OF INTERESTS

The work was funded under a contract from F. Hoffmann - La Roche, a company that is developing blood-based biomarkers and disease-modifying treatments for Alzheimer's disease, to the University of Southern California. The sponsor had no role in the design of the study, the interpretation of the results, or decision to submit. TB is an Employee of and shareholder in Roche. All other authors report no conflicts related to the work under consideration. Full International Committee of Medical Journal Editors (ICMJE) disclosure forms are available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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