EBC European Brain Council

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RETHINKING ALZHEIMER'S DISEASE

Detection & diagnosis

Economic evaluation of the implementation of Blood-based biomarker (BBBM) tests for the early diagnosis of Alzheimer's disease at primary care level in the Swedish healthcare setting

Technical report

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March 2023

Background and Objectives

In the context of its 'RETHINKING Alzheimer's Disease' project, the European Brain Council (EBC) has developed a White Paper, in collaboration with the European Federation of Pharmaceutical Industries and Associations (EFPIA), to propose policy recommendations with the aim to make tangible changes to improve the lives of people living with Alzheimer's disease (AD) across Europe. The White Paper presents policy recommendations with a specific focus on the detection and diagnosis of AD. For that purpose, EBC has organised country profiling workshops, an online survey and a webinar to gather the views of experts from the five countries covered by the paper.

The objective of this economic evaluation is to assess the health economic impact of some of the solutions identified during the consultations with the expert working groups which are described in the White Paper.

Scope of the economic evaluation

In line with the conclusions of the expert consultation the scope of this economic evaluation is two-fold:

- To assess the impact of better diagnosis of Alzheimer's disease in Europe by implementing Blood-based biomarker (BBBM) tests (in combination with cognitive tests) to improve triaging at the primary care level;

- To assess the health-economic benefits of early diagnosis for patients with AD receiving current available symptomatic treatment options (Donepezil and Memantine).

Scope of the economic evaluation	
Population	Patients (55+) with MCI seeking evaluation at primary care level
Intervention	Primary care: Cognitive test (MMSE) + Blood-Based biomarkers Secondary Care: Confirmatory test using CSF analysis
Comparator	Primary care: Cognitive test (MMSE) only Secondary Care: Confirmatory test using CSF analysis
Outcome	- Costs (Diagnostic tests, Disease related, Treatment) - QALYs
Country	Sweden as example

Methods

Overview

We developed a Markov model to evaluate the health-economic effects of the implementation of Blood-based biomarker (BBBM) tests (in combination with cognitive tests) to improve triaging at the primary care level, compared to a 'usual' care scenario where these tests are not provided. We assessed the short-term impact on the cost of the diagnostic process and the relative balance of benefits and costs over a predicted time horizon of care needs of 20 years, using the Swedish health-care setting as an example. A recent US study (Mattke et al. 2020) has evaluated the impact of the implementation in primary care of Blood-Based Biomarker (BBBM) tests on the efficiency and waiting times during the diagnostic process. This work builds upon and complements those findings by looking at the potential impact on patient outcome and disease related costs over a 20 years period of time.

Model Structure

The model uses a Markov framework with a 1-year cycle time. A schematic of the model is presented in **Figure 1**. The model simulates the journey of patients seeking evaluation for subjective memory complaints. The model has two interacting layers. The first layer captures a patient's journey through different evaluation stages (cognitive and/or blood-based biomarker testing by a primary care clinician and confirmatory specialist evaluation using biomarker cerebrospinal fluid (CSF) testing at secondary care) depending on the true health states (Cognitively normal, MCI due to AD, MCI due to other causes). Patients with MCI start in the "Assessment primary care" state and if they test (false) positive move forward to "Confirmatory Secondary assessment" to receive a confirmatory test (CSF or PET). If patients with AD are tested negative, they are sent to the second layer which captures the health state and the diagnosis status depending on the assessment results. Patients with AD who tested negative (False negative) at any of the assessment stages are sent to "MCI-AD un-diagnosed" state, while if tested positive (True positive) they are sent to "MCI-AD diagnosed" state. Similar to previously published model-based analyses of AD (Lee et al. 2017), the second layer models the disease progression and the location of care. Individuals who are diagnosed with AD were divided into 14 health states (**Figure 1**) on the basis of the severity of their disease, whether or not they were on treatment, and their location (Community or long-term facility). Patients with AD who did not receive a diagnosis are divided in two health states based on disease severity (MCI-AD, Mild-Ad). The model assumed that patients who progress to Moderate-AD received a diagnosis because symptoms are evident. Patients who did not have AD had another disease-causing stable MCI, so individuals who did not have AD were divided into 4 health states on the basis of whether they were on AD treatment (because of false diagnosis) and their type of residence (**Figure 1**).

The first layer uses sensitivity and specificity of the assessment tests to calculate the transition probabilities between assessment states and the second layer. The second layer is guided by disease progression, treatment discontinuation and re-initiation rates. Each year, patients may die, progress or regress in terms of disease severity, discontinue or reinitiate treatment, transition from living in the community to living in a long-term care facility, or stay in the same health state. In the model, patients living in a long-term care facility cannot return to living in community care. As treatment options for patients with AD diagnosis the model considered Donepezil for Mild- and Moderate-AD and Memantine for Severe-AD.

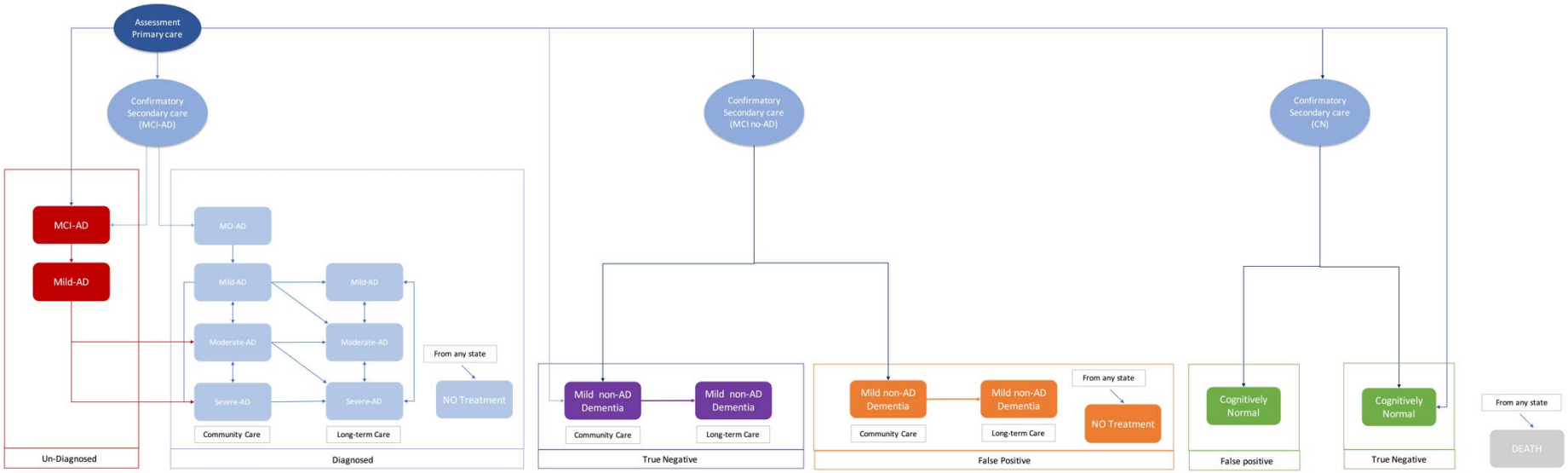

Figure 1. Markov Model Structure. MCI=Mild cognitive impairment; CN= Cognitively Normal

Model inputs

The tables below include the inputs, data sources and assumptions used to infirm the model.

Population		
Start age of the model cohort (Years)	55	("RAND_IG Sweden" 2019)
MCI patients in population visiting primary care	16.60%	
MCI-AD patients in patients with MCI	25.00%	
MCI-AD in the cohort	4.15%	*Calculated*
MCI-NoAD in the cohort	12.45%	*Calculated*
Cognitive Normal in the cohort	83.40%	*Calculated*

Sensitivity	No BBBM	With BBBM	
Cognitive test (CT, MMSE)	82.00%	82.00%	(Mattke et al. 2020)
Blood-based biomarker (BBBMs)	-	89.00%	
Cerebrospinal fluid test (CSF)	91.00%	91.00%	
Specificity			
Cognitive test (CT, MMSE)	73.00%	73.00%	(Mattke et al. 2020)
Blood-based biomarker test (BBBMs)	-	69.00%	
Cerebrospinal fluid test (CSF)	89.00%	89.00%	

Diagnostic Transition probabilites (calculated combining sensitivity and specificity and population inputs)				
From	**To**	**No BBBM**	**With BBBM**	
PA	MCI-AD_SA	3.4%	3.7%	*MCI-AD referred to secondary care* *
PA	MCI-Non-AD_SA	10.2%	3.2%	*MCI-NoAD referred to secondary care*
PA	CN_SA	22.5%	7.0%	*Cognitively normal wrongly referred to secondary care*
PA	TN_CN	60.9%	76.4%	*Cognitively normal correctly assessed in primary care*
PA	Undiagnosed_MCI-AD	0.7%	0.5%	*MCI_AD undetected in primary care*
PA	TN_Mild-NonAD	2.2%	9.3%	*MCI-NoAD correctly assessed in primary care*
MCI-AD_SA	Diagnosed_MCI-AD	91.0%	91.0%	*MCI-AD correctly assessed in secondary care*
MCI-AD_SA	Undiagnosed_MCI-AD	9.0%	9.0%	*MCI_AD undetected in secondary care*
MCI-NoAD_SA	TN_Mild-Non-AD	89.0%	89.0%	*MCI_NoAD correctly assessed in secondary care*
MCI-NoAD_SA	FP_Mild-Non-AD	11.0%	11.0%	*MCI_NoAD wrongly assessed in secondary care*
CN_SA	TN_CN	89.0%	89.0%	*Cognitively normal correctly assessed in secondary care*
CN_SA	FP_CN	11.0%	11.0%	*Cognitively Normal wrongly assessed in secondary care*

PA = Primary care assessment; MCI-AD_SA = MCI-AD in secondary care assessment; MCI-Non-AD_SA = MCI-Non-AD in secondary care assessment; CN_SA = Cognitively normal in secondary care assessment; normal True

Negative; TN_Mild-Non-AD = True Negative Mild-NoAD; FP_Mild-Non-AD= False Positive Mild-Non-AD; TN_CN = Cognitively; FP_CN = False Positive Cognitively normal.

[*] *The model assumed that BBBM test is used to confirm AD either in patients with positive or negative cognitive test. Patients with a BBBM positive test are referred to secondary care for confirmatory test.*

Transitions between Health States			
From	**To**		
MCI-AD	Mild-AD	0.21	(Wimo et al. 2020)
Mild-AD	Moderate-AD	0.29	
Mild-AD	Severe-AD	0.00	
Moderate-AD	Severe-AD	0.11	
Moderate-AD	Mild-AD	0.09	
Severe-AD	Mild-AD	0.00	
Severe-AD	Moderate-AD	0.20	

Hazard ratio mortality (HR)[*]			
From	Mild-AD	1.32	(Wimo et al. 2020)
	Moderate-AD	2.42	
	Severe-AD	4.27	
	Mild non-AD Dementia	1.32	

[*]Mortality of patients with dementia was calculated by applying the he hazard ratios to the annual age-specific general population mortality rates (http://www.statistikdatabasen.scb.se) using the formula: 1-exp(-age specific annual death probability *HR)

Transitions to long-term care facilities			
From	Mild-AD	2.08%	(Lee et al. 2017)
	Moderate-AD	6.72%	
	Severe-AD	11.08%	
	Mild non-AD Dementia	1.20%	

Tretament							
	Efficacy		**Discontinuation**		**Re-initiation**		
Donepezil	0.50	Mild to moderate					(Lee et al. 2017)
Donepezil	2.36	Moderate to Mild					
Donepezil	0.37	Transition to long term	0.25	0.46	0.63	0.36	
Memantine	0.37	Transition to long term	0.25	0.46	0.63	0.36	

COSTS				
Yearly drug costs				
Donepezil		415 €		https://www.tlv.se/beslut/sok-i-databasen.html?tab=1
Memantine		379 €		
Disease-related costs				
MCI-AD		1,729 €		
Mild-AD	Community	8,189 €		(Sköldunger, Wimo, and Johnell 2012)*
Moderate-AD		15,039 €		
Severe-AD		20,598 €		
Mild-AD	Long-term Facility	63,670 €		(Handels et al. 2015)
Moderate-AD		63,670 €		
Severe-AD		63,670 €		
Cognitively normal		1,729 €		Assumed to be as MCI-AD
Diagnostic assessment costs				
Primary care visit (2x)		242 €	242 €	(Handels et al. 2015)
Blood-based biomarker test		0 €	100 €	Assumption
Secondary care visit (2x)		832 €	832 €	(Handels et al. 2015)
CSF test		250 €	250 €	Assumption
		No BBBM	**With BBBM**	
Assessment in primary care		242 €	342 €	
Assessment in secondary care		1,082 €	1,082 €	

All costs are converted in Euro (1 euro = 10.90 SEK) and inflated to 2022.

*Skodungher et al., 2013 provided aggregate medical, social and informal costs by disease severity. These costs were adjusted to exclude institutional care costs assuming they account 60% of the total costs (Wimo et al., 2016)

Utilities			
Age-related utilities*			
Age Range			
45-64		0.83	(Lee et al. 2017)
65-69		0.82	
70-74		0.81	
75-79		0.79	
79+		0.74	
Disease-related utilities*			
MCI-AD		1.00	(Lee et al. 2017)
Mild-AD	Community	0.68	
Moderate-AD		0.54	
Severe-AD		0.37	

Mild-AD	Long-term Facility	0.71
Moderate-AD		0.48
Severe-AD		0.31
Cognitively normal		1.00
Incremental Utility on Memantine		0.051
Disutility CSF		-0.008

*Age and AD severity-specific utilities were incorporated into the model by multiplying the age-specific utility by the AD severity-specific utility

Results

The value of better diagnosis on patient outcome and costs

The Markov model was used to calculate the Costs and QALYs of patients with Alzheimer disease comparing the two alternative diagnostic assessments with and without the use of blood-based biomarker test in primary care. The use of BBBM in primary care generated 0,033 QALYs and reduced the costs by 1062 € per patient over a time horizon of 20 years. The cost savings is largely driven by a reduction in AD-related costs (including medical, social and informal care). These results indicate that improving AD diagnosis has a value in itself which is independent of the availability of disease modifying treatments and it can provide benefits to patients and society by ensuring early access to current symptomatic treatment.

Cost per AD patient in the cohort	No BBBM	With BBBM	
Diagnostic Assessment Costs*	603 €	473 €	-130 €
AD related costs	161,543 €	160,481 €	-1,062 €
AD Treatment costs	2,427 €	2,463 €	36 €
Total cost	**178,511 €**	**174,346 €**	**-1,156 €**
Outcomes			
LYs accrued by AD subpopulation	13.69	13.70	0.010
QALYs accrued by AD subpopulation	8.34	8.37	0.033

*Cost calculated on the whole cohort

The Impact of BBBM testing on the cost of the diagnostic process

To estimate the impact on the cost of the diagnostic process of the implementation of Blood-based biomarker (BBBM) tests in primary care, we estimate the annual costs for primary and secondary assessment comparing the two alternative strategies with and without the use of blood-based biomarker tests in primary care. The proportion of patients referred to secondary care for confirmatory tests for the two alternative strategies was calculated using the Markov model and combined with the estimated number of people seeking primary care evaluation each year in Sweden. Furthermore, we considered two scenarios. In the first scenario, the population seeking primary care assessment was based on the estimated MCI incident population. The second scenario assumed that more people without MCI will seek primary care assessment once DMT will be available. The details of the calculation are described in the table below.

Calculation Annual Population seeking primary care evaluation		
Population age 55+	**3,300,000**	https://www.statista.com/statistics/521717/sweden-population-by-age/
MCI prevalence	6.6%	*(Overton, Pihlsgård, and Elmståhl 2019)*
Prevalent population with MCI	217,800	
MCI incidence	0.9%	(Overton, Pihlsgård, and Elmståhl 2019)
Incident population with MCI	29,700	
% of non-MCI people seeking assessment	42%	*Estimated based on ("RAND_IG Sweden" 2019) data*
non-MCI people seeking assessment in primary care	1,282,050	

Scenario 1			
Annual incident population seeking primary care diagnostic assessment	**29,700**	*=Incident MCI population + non-MCI population seeking assessment*	
	No BBBM	**With BBBM**	
% of patients referred to secondary care for assessment	36%	14%	-22%
Number of patients referred to secondary care for assessment	10,731	4,110	-6,620
Cost of primary assessment	€ 7,187,400	€ 10,157,400	€ 2,970,000
Cost of secondary assessment	€ 11,610,520	€ 4,447,176	-€ 7,163,344
Annual net saving			**-€ 4,193,344**

Scenario 2			
Annual incident population seeking primary care diagnostic assessment	**1,311,750**	*=Incident MCI population + non-MCI population seeking assessment*	
	No BBBM	**With BBBM**	
% of patients referred to secondary care for assessment	36%	14%	-22%
Number of patients referred to secondary care for assessment	473,935	181,531	- 292,404
Cost of primary assessment	€ 317,443,500	€ 448,618,500	€ 131,175,000
Cost of secondary assessment	€ 512,797,968	€ 196,416,950	-€ 316,381,017
Annual net saving			**-€ 185,206,017**

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