DOI: 10.1002/gps.6126

RESEARCH ARTICLE

Costs of diagnosing early Alzheimer's disease in three European memory clinic settings: Results from the precision medicine in Alzheimer's disease project

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Funding information

Helse-Nord; the Swedish Research Council; Ministry of Education, Science and Sport, Republic of Slovenia; JPND/PMI-AD

Abstract

Objectives: The implementation of disease-modifying treatments for Alzheimer's Disease (AD) will require cost-effective diagnostic processes. As part of The Precision Medicine In AD consortium (PMI-AD) project, the aim is to analyze the baseline costs of diagnosing early AD at memory clinics in Norway, Slovenia, and the Netherlands.

Methods: The costs of cognitive testing and a clinical examination, apolipoprotein E, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), positron emission tomography and blood-based biomarkers (BBM), which are used in different combinations in the three countries, were analyzed. Standardized unit costs, adjusted for GDP per capita and based on Swedish conditions were applied. The costs were expressed in euros (\in) as of 2019. A diagnostic set comprising clinical examination,

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. © 2024 The Author(s). International Journal of Geriatric Psychiatry published by John Wiley & Sons Ltd. cognitive testing, MRI and CSF was defined as the gold standard, with MRI mainly used as an exclusion filter.

Results: Cost data were available for 994 persons in Norway, 169 in Slovenia and 1015 in the Netherlands. The mean diagnostic costs were 1478 (95% confidence interval 1433–1523) € in Norway, 851 (731–970) € in Slovenia and 1184 (1135–1232) € in the Netherlands. Norway had the highest unit costs but also the greatest use of tests. With a uniform diagnostic test set applied, the diagnostic costs were 1264 (1238–1291) €, in Norway, 843 (771–914) € in Slovenia and 1184 (1156–1213) € in the Netherlands. There were no major cost differences between the final set of diagnoses.

Conclusions: The total costs for setting a diagnosis of AD varied somewhat in the three countries, depending on unit costs and use of tests. These costs are relatively low in comparison to the societal costs of AD.

KEYWORDS

Alzheimer's disease, cost analysis, costs, dementia, diagnosis, diagnosis costs

Key points

- The introduction of blood-based biomarkers for detecting Alzheimer's Disease (AD) can change the diagnostic process.
- Given the expected demands for treatment of cognitive disorders such as AD, the costs and capacity of the diagnostic work-up are of great importance for care funders and planners.
- Our study incorporating diagnostic costs from three distinct European regions provides valuable inputs for cost-effectiveness studies.

1 | INTRODUCTION

Alzheimer's Disease (AD) is a devastating and incurable brain disorder causing the majority of dementia cases.¹ AD slowly impairs memory, thinking and other cognitive skills, leading to the need for support from family or health care services and finally to death. AD is defined by common biological and clinical criteria and progresses on a continuum where the disease course also includes a preclinical period which starts long before criteria for a dementia syndrome are fulfilled.² Genetic risks and disease pathways (mechanisms and cellular responses) differ between AD subgroups^{3,4} and precision-medicine (PM) approaches are required to develop successful interventions. The Precision Medicine Interventions in AD Consortium (PMI-AD) explores technologies and competencies to stratify early-stage AD patients using novel mechanistic pathways to therapeutic algorithms to develop costeffective, pathway-adapted diagnostics and early interventions to delay disease onset.⁵

Two disease-modifying targets (DMTs) have shown statistically significant effects on cognition in randomized controlled trials: lecanemab and donanemab.^{6,7} Lecanemab is approved by the Food and Drug Administration (FDA) in the US, in Japan and in China, and the process for its eventual approval has started by the European Medical Agency (EMA). In the case of donanemab, the approval process is

currently underway in the US. However, there is debate regarding the magnitude of its effects and their clinical significance,^{8,9} alongside concerns about side effects such as ARIA.^{8,10} Furthermore, the long-term effects beyond clinical trial periods are also unknown,¹¹ and there is ongoing discussion about the pricing of DMTs.^{11,12}

Due to the long disease course, cost-effectiveness analyses of DMTs in AD are challenging. Initial costs for diagnostics and treatment costs with DMTs are high, while potential economic benefits might occur later in the course of the disease. Thus, within-trial cost effectiveness analysis will unlikely show results that favor diseasemodifying treatments (DMT). Costs impact many societal sectors and vary depending on how care is organized and financed in different countries. A significant portion of care in AD is provided by unpaid, informal caregivers, such as family members. Identifying individuals with early-stage AD (here defined as AD due to mild cognitive impairment (MCI) and mild dementia due to AD is vital for the economic evaluations assessing the cost-effectiveness of DMT's. There is no simple diagnostic test to set a definite diagnosis of AD, and there are discussions about whether AD should be defined as a clinical or biological entity.¹³ A variety of methods are available, and the final diagnosis is based on a synthetic diagnostic approach. There are also differences between these methods in terms of sensitivity, specificity, logistics and costs. It is crucial not only to accurately identify individuals with AD (true positive, TP) and those without AD

(True negative, TN), but also to avoid incorrect diagnoses of AD (false positive, FP) and missed diagnoses of AD (false negative, FN).

Blood-based biomarkers of AD (BBMs)^{14,15} have been introduced as effective, easily managed and rather cheap complements to the existing more complex tests such as cerebrospinal fluid (CSF),¹⁶ positron emission tomography (PET)¹⁷ and Magnetic resonance imaging (MRI).¹⁸ Currently, the focus is on people with cognitive impairment (that is, MCI due to AD and dementia due to AD) and not on preclinical AD. The use of BBMs is still at a research level in Europe but will probably soon be part of clinical practice. The costs of these diagnostic tests vary, making it essential to include the expenses associated with AD diagnostic procedures in a cost-effectiveness analysis of DMT. In Norway, Slovenia and the Netherlands, the costs of the diagnostic work-up for AD is part of the general health system and fully reimbursed (there may be out-of-pocket small fees). Besides the possibility of getting access to DMT (if approved), another advantage of an early AD diagnosis is that families will have more time for planning ahead of the consequences of AD.

As part of the PMI-AD project, the aim is to analyze the baseline costs of diagnosing early AD at memory clinics in Norway, the Netherlands and Slovenia. These three countries represent three regions in Europe (Northern, Western and Central) with somewhat different health and care systems.

2 | MATERIAL AND METHODS

2.1 | Datasets

Three datasets from memory clinics have been used: 994 participants at five memory clinics in Norway, 169 participants in Slovenia from the Center for cognitive impairments, Department of Neurology, University Medical Center, Ljubljana and 1015 in the Netherlands from the Amsterdam Dementia Cohort from the Alzheimer Center Amsterdam, Amsterdam University Medical Center (Table 1), consisting in total of 2179 (Table 1) persons. There were significant differences between the countries in age, gender, education and Mini mental state examination (MMSE).¹⁹

There were no major differences between the whole data set and those whose cost data and diagnostic subtypes were available.

TABLE 1 Study populations.

2.2 | Diagnostic tests

Besides cognitive testing and a clinical examination, the use and costs of the following diagnostic tests have been analyzed: Apolipoprotein E (APOE), MRI, CSF, PET and blood-based biomarkers (BBM) with somewhat various compositions in the three countries. Only a single use of each test was used for the cost calculations.

For the purpose of this project, outcomes of the tests were dichotomized: code 0 for results that do not support an AD diagnosis and code 1 for supporting an AD-diagnosis (see Supporting Information S1).

2.3 | Settings

2.3.1 | Norway

The Dementia Disease Initiation (DDI) is a national, multi-center Norwegian study focused on incipient dementia-related diseases. The DDI cohort consists primarily of non-demented individuals between 40 and 80 years of age, primarily recruited from memory clinics and advertisements in local news media.²⁰

2.3.2 | Slovenia

Cohort consists primarily of non-demented individuals between 50 and 80 years of age, primarily recruited from advertisements in local news media and some referrals from general practitioners to memory clinics. The clinical work-up included a physical and neurological examination.

2.3.3 | The Netherlands

The Amsterdam Dementia Cohort is comprised of individuals who visited the Alzheimer Center Amsterdam, which is a tertiary memory clinic. All individuals who visit the center receive standardized diagnostic work-up, including a consultation with the neurologist, neuropsychological examination, neurological examination, assessment

Country	n	Age (SD)*	Gender (female %)*	MMSE (SD)*	Years of education (SD)*
Norway	994	64.4 (9.4)	54.6	26.3 (7.5)	13.6 (3.1)
Slovenia	169	72.2 (5.3)	58.4	27.4 (4.2)	13.5 (2.5)
The Netherlands	1015	63.8 (8.4)	42.1	27.7 (1.9)	11.9 (3.2)
Cost data and diagnostic su	btype available				
Norway	809	64.4 (9.2)	52.7	27.8 (3.5)	13.7 (3.1)
Slovenia	125	72.1 (5.4)	60.2	27.6 (4.0)	13.7 (2.4)
The Netherlands	593	62.7 (7.8)	48.1	27.7 (3.1)	12.0 (3.2)

*p < 0.001 between countries.

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of vital signs, EEG, MRI, blood withdrawal for standard labs and, in many cases, a lumbar puncture.^{21,22}

2.4 | Costs of the diagnostic work-up

In Norway there are no official tariffs or price lists in the health system. In the Netherlands, consultations, scans, treatments etc. are not charged separately. Instead, an average price per diagnosistreatment combination is used. In Slovenia, there were price lists from UMC Ljubljana official Price List of Medical Services and the Health Insurance Institute of Slovenia - Informative Price List of Medical Services. The unit costs also differ between and within countries, since the economic status (such as Gross Domestic Product. GDP) varies. Furthermore, the methods of costing diagnostic tests varies. Methods of including surrounding staff costs, equipment costs and overhead costs of a test may be different between and within countries. To get better harmonized unit costs, we have used a Swedish tariff with information on all used diagnostic tests, based on the price list for the Karolinska University Hospital in Stockholm. Thus all the underlying data on costs relates to Sweden alone, and GDP per capita was used to estimate the costs for the tests for the three countries based on the data for Sweden (Table 2).

Since BBMs are not part of the clinical practice (yet), there is no set price for them, Thus, an estimated price by experienced clinicians and researchers working on the development of the BBMs (and other biomarkers) in Sweden were used. The cost year is 2019, where $1 \in$ corresponded to 10.545 SEK and to 8.955 NOK.

The standardized unit costs were rather similar in Norway and the Netherlands, but lower in Slovenia.

Another cost option is also presented, where it was assumed that a similar basic diagnostic program (clinical examination, cognitive testing, APOE, MRI and CSF) was used. MRI was used from a clinical viewpoint for excluding patients for further diagnostics (and further aiming for DMT) and not primarily for setting an AD diagnosis.

TABLE 2 Unit costs for the used diagnostic tests at memory clinics (\in 2019, GDP per capita adjusted).

	Norway	Slovenia	The Netherlands
Clinical examination	100.96	62.14	90.42
Cognitive screening	84.69	52.13	75.85
APO E	94.43	58.12	84.57
MRI	528.75	325.45	473.56
CSF	554.69	341.42	496.80
PET	1149.09	707.29	1029.17
BBM ^a	186.93	115.06	167.43

^aexpert estimate.

2.5 | Diagnosis

In this project we define a clinical examination and cognitive testing combined with CSF as the gold standard for an AD-diagnosis, where both the cognitive testing and CSF supported that. If CSF supported AD but the cognitive testing was normal, the label was AD-CN, that is diagnosed as pre-clinical AD. While dementia diagnosis was an exclusion criterion in PMI-AD, a small subset of included cases was initially screened as possible MCI but were through clinical assessment diagnosed with dementia. These cases were included in the cost analyses.

2.6 | Statistical methods

Descriptive statistics were applied on country differences. A univariate general linear model was applied in the cost analyzes for each final diagnosis and country, adjusted for country differences in the samples of age, gender, education years and MMSE.

2.7 | Ethical permissions

Norway: PMI-AD was approved by Regional ethical committee in Norway, reference number 2023/50738.

The Netherlands: The study was approved by the medical ethical review board of the VU University Medical Center, approval number 2016.061.

Slovenia: The national ethical committee permission, Nr 0120-539/2020/10.

3 | RESULTS

In Norway and the Netherlands, about 39% got an AD diagnosis, while it was somewhat higher in Slovenia (49%), 35%–57% had some kind of cognitive impairment (due to AD or non-AD) (Table 3). The low proportion of people with dementia can be attributed to the PMI-AD programs' emphasis on early-stage AD, thereby centering the focus specifically on the prevalence of early AD. More diagnostic tests were used in Norway than in Slovenia and the Netherlands (Table 4). In Slovenia and the Netherlands, MRIs were utilized in >90% of cases, with slightly lower usage observed in Norway. Norway reported the highest usage of CSF (88%). PET scans were either infrequently used or not used at all for initial diagnostic work-up. BBMs were employed in both Norway and Slovenia.

The total costs for establishing a diagnosis of AD varied somewhat between the three countries. They were higher in Norway than in Slovenia and the Netherlands (Table 5) (1478 \in , 851 \in , and 1184 \in , respectively). There were no major differences in costs between individuals with or without AD, nor in relation to their cognitive levels, nor in relation to gender or age class. TABLE 3 Final baseline diagnosis at memory clinics in Norway, Slovenia and the Netherlands with cost data, adjusted for age and gender.

	Norway (%)	Slovenia (%)	The Netherlands (%)		
1.AD-CN (AD_SCD)	90 (11.1)	62 (49.6)	68 (11.5)		
2.AD-dementia	13 (1.6)	3 (2.4)	0		
3.AD-MCI	212 (26.2)	8 (6.4)	161 (27.2)		
4.NonAD-CN	254 (31.4)	25 (20.9)	244 (41.1)		
5.NonAD-dementia	4 (0.5)	3 (2.4)	0		
6.NonAD-MCI	236 (29.2)	24 (19.2)	120 (20.2)		
Any AD diagnosis($1 + 2 + 3$)	315 (38.9)	73 (58.4)	229 (38.6)		
Any cognitive impairment (2 + 3 + 5 + 6)	465 (57.4)	38 (30.4)	281 (47.4)		
All	809 (100)	125 (100)	593 (100)		

Abbreviation: CN, cognitive testing normal.

TABLE 4Used diagnostic tests at baseline at memory clinicsin Norway, Slovenia and the Netherlands.

	Norway (%)	Slovenia (%)	The Netherlands
n	994	146	1015
Clinical examination	994 (100)	146 (100)	1015 (100)
Cognitive screening	809 (81.4)	146 (100)	1015 (100)
APO E	911 (91.6)	99 (67.8)	782 (77)
MRI	763 (76.8)	134 (91.8)	919 (90.5)
CSF	871 (87.6)	104 (71.2)	592 (58.3)
PET	58 (5.8)	0	0
BBM	606 (61.0)	43 (29.5)	0

When it was assumed that a similar basic diagnostic program (clinical examination, cognitive testing, APOE, MRI and CSF) was used, the country differences reflected the variations in unit costs. In Norway, there was a trend for the costs associated with non-AD conditions to be somewhat lower (Table 6).

4 | DISCUSSION

4.1 | The results

The profiles of diagnostic tests vary among memory clinics across the three countries. More tests were used in Norway than in the other countries.

The diagnosis profiles are rather similar in Norway and in the Netherlands, while they differ in Slovenia. There were more patients with normal cognition but with subjective cognitive symptoms in Slovenia. The cost for setting a diagnosis at baseline was highest in Norway, due to higher unit costs for each test and the greater array of tests employed. BBMs are yet not in use in clinical practice and PET is rarely used, so when the same set of tests were applied, the cost differences, as expected, reflected the unit costs more closely.

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5 of 9

In relation to the societal costs of dementia, the costs for setting an AD diagnosis, irrespective of the used diagnostic tests, are rather low; in our study estimated around 851-1478€ per case (842-1264 if the same set of tests is applied) in the three countries. In the Norwegian REDIC project, the direct costs per case of dementia (costs of informal care were not included) were estimated at about 360,000 NOK/year in 2013 (about 42,000€ given the € exchange rate that year).²³ The same pattern can be seen in Slovenia, where the annual societal costs of dementia (inflated to 2019) was estimated to be about 13,500 € per case,²⁴ which can be compared to about 800€ for the diagnostic work-up. The higher proportion for diagnostics in Slovenia is mainly due to the lower societal costs of dementia in Slovenia because of the much lower proportion residing in nursing homes. The Slovenian dataset is also from the memory clinic in Ljubljana, which is probably not representative for the whole of country. In the Netherlands the societal cost per case with dementia (including costs of informal care) can be estimated at about 47,000 € per case and year (^{25,26} combined), to be compared with the diagnostic costs of about 1200 €. Furthermore, dataset in the Netherlands corresponds to a tertiary memory clinic setting, which may not accurately reflect the entire population in the Netherlands.

However, this situation may change. Today, most people with predementia states, such as MCI, are not diagnosed since there is no available specific treatment. For example, the prevalence of early AD in Norway can be estimated at about 100,000 persons, which is the potential target population for DMT, if Gustavsson's prevalence Figure²⁷ are applied, and combined with Norwegian population statistics.²⁸ If all these people would undergo diagnostic procedures at a cost of about 1400 \in per case to identify persons suitable for DMT, the diagnostic cost would be considerable, about 140 million \in . Furthermore, the diagnostic costs for all people concerned about having AD (which may be 50% or more of all elderly people²⁹), who also may seek diagnostic evaluations, should also be included in that figure.



TABLE 5 Cost (€2019) of diagnosing patients at memory clinics at baseline in Norway, Slovenia and the Netherlands, adjusted for age, gender, education and MMSE.

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AlonAD-CNNorway14814511526Slovenia_PMLAD839719960the Netherlands116611271205Slovenia_PMLAD8705201220the Netherlands11368051466Slovenia_PMLAD8705201220the Netherlands6 NonAD-MCINorway141513781453Slovenia_PMLAD8153773929the Netherlands119611371545Any AD (1 + 2 + 3)Norway151114771545Slovenia_PMLAD851773929the Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321467Slovenia_PMLAD849751946the Netherlands119411581234Gender femaleNorway146014321500Slovenia_PMLAD845774946the Netherlands119411461222Gender maleNorway146114641220Slovenia_PMLAD852763940the Netherlands118811561220Age-class <71		Slovenia_PMI_AD	857	618	1096
Slovenia_PMLAD8397199601the Netherlands1166112712055.NonAD-dementiaNorway11368051466Slovenia_PMLAD8705201220the Netherlands6.NonAD-MCINorway141513781453Morway141513781453Slovenia_PMLAD853773725Any AD (1 + 2 + 3)Norway151114771545Norway151114771545124Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Slovenia_PMLAD849751966126Gender femaleNorway147114421500Slovenia_PMLAD119411461222150Age-class <71		the Netherlands	1197	1152	1243
InternationInternationInternationInternationInternationInternationShonaD-dementiaNorway1136A051466Shorenia_PMLADA705201220InternationInternationInternationInternationShorenia_PMLADA53736971Shorenia_PMLADA53736971InternationInternationInternationInternationAny AD (1 + 2 + 3)Norway151114771545Shorenia_PMLADA51773926InternationInternationInternationInternationAny cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Shorenia_PMLADA4975194611461221Gender femaleNorway147114421500150Shorenia_PMLADA52763940122Shorenia_PMLADA52763940122Gender maleNorway149611861126Age-class <71	4.NonAD-CN	Norway	1488	1451	1526
ShonAD-dementiaNorway11368051466Slovenia_PMLAD8705201220the Netherlands6.NonAD-MCINorway141513781453Morway1415137814531453Slovenia_PMLAD853736971the Netherlands119611371256Any AD (1 + 2 + 3)Norway151114771545Slovenia_PMLAD851773929the Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321460Slovenia_PMLAD84975194614641224Gender femaleNorway147114421500Slovenia_PMLAD8457749161234Gender femaleNorway147414641224Gender maleNorway147614641526Slovenia_PMLAD852763940the Netherlands118411561220Age-class <71		Slovenia_PMI_AD	839	719	960
Slovenia PMLAD tic Netherlands5701206NonAD-MCINorway141513781453Slovenia PMLAD853736971Ite Netherlands119611371256Any AD (1 + 2 + 3)Norway151114771545Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147114421500Any cognitive impairment (2 + 3 + 5 + 6)Norway147614661526Any cognitive impairment (2 + 3 + 5 + 6)Norway147614661526Any cognitive impairment (2 + 3 + 6)Norway15001		the Netherlands	1166	1127	1205
Intervalue<	5.NonAD-dementia	Norway	1136	805	1466
6 NonAD-MCINorway141513781453Slovenia_PMLAD853766971file Netherlands119611371256Any AD (1 + 2 + 3)Norway151114771545Slovenia_PMLAD851773929file Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Slovenia_PMLAD8497519461234Gender femaleNorway147114421500Norway147114421500124Slovenia_PMLAD845774916Slovenia_PMLAD845774916Slovenia_PMLAD845774916Morway149611841122Gender maleNorway14961464Slovenia_PMLAD852763940Morway150014731527Slovenia_PMLAD831738924Morway150014731527Slovenia_PMLAD831738924Morway142413791469Slovenia_PMLAD832757908AllNorway147814331524AllNorway147814331524AllNorway147814331524AllNorway147814331524AllNorway147814331526Slovenia_PMLAD83275790		Slovenia_PMI_AD	870	520	1220
Slovenia_PMI_AD853736971he Netherlands119611371256Any AD (1 + 2 + 3)Norway151114771545Slovenia_PMI_AD851773929the Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Slovenia_PMI_AD8497519461231Gender femaleNorway147114421500Slovenia_PMI_AD8457749161222Slovenia_PMI_AD8457749161222Gender maleNorway147114421500Norway148411461222120Age-class <71		the Netherlands	-	-	-
He Netherlands119611371256Any AD (1 + 2 + 3)Norway151114771545Slovenia,PMI,AD851773292He Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Slovenia,PMI,AD84975144611221Gender femaleNorway147114421500Slovenia,PMI,AD8457749161222Gender femaleNorway149611841222Slovenia,PMI,AD8527639401220Gender maleNorway150014731220Morway1501118411221200Age-class <71	6.NonAD-MCI	Norway	1415	1378	1453
Any AD (1 + 2 + 3)Norway151114771545Slovenia,PMLAD851773929ite Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Slovenia,PMLAD8497519461231Gender femaleNorway147114421500Gender femaleNorway147114421500Slovenia,PMLAD845774916the Netherlands118411461222Gender maleNorway14961526Slovenia,PMLAD852763940the Netherlands118811561220Gender maleNorway150014731527Slovenia,PMLAD852763940the Netherlands118711581220Age-class <71		Slovenia_PMI_AD	853	736	971
Slovenia_PM_AD651773929He Netherlands116011581234Any cognitive impairment (2 + 3 + 5 + 6)Noway146014321487Slovenia_PM_AD8497519461231Ine Netherlands1194115812311231Gender femaleNorway147114421500Slovenia_PM_AD8457749161222Gender maleNorway149611461222Gender maleNorway149614661526Age-class <71		the Netherlands	1196	1137	1256
He Netherlands119611581234Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321467Slovenia, PML,AD8497519461231Ender femaleNorway147114421500Slovenia, PML,AD8457749161222Gender maleNorway149411661222Gender maleNorway149514641526Slovenia, PML,AD852763940Morway149611681220Age-class <71	Any AD (1 + 2 + 3)	Norway	1511	1477	1545
Any cognitive impairment (2 + 3 + 5 + 6)Norway146014321487Slovenia,PMLAD849751946the Netherlands119411581231Gender femaleNorway147114421500Slovenia,PMLAD845774916the Netherlands118411461222Gender maleNorway147614661526Slovenia,PMLAD852763940the Netherlands118811561220Age-class <71		Slovenia_PMI_AD	851	773	929
Slovenia_PMLAD849751946the Netherlands119411581231Gender femaleNorway147114421500Slovenia_PMLAD845774916the Netherlands118411461222Gender maleNorway149614661526Slovenia_PMLAD852763940the Netherlands118811561220Age-class <71		the Netherlands	1196	1158	1234
InterventionInterventionInterventionInterventionInterventionGender femaleNorway147114421500Slovenia_PMI_AD845774916Intervention118411441222Gender maleNorway149644661526Slovenia_PMI_AD852763940Intervention118811561220Age-class <71	Any cognitive impairment $(2 + 3 + 5 + 6)$	Norway	1460	1432	1487
Gender femaleNorway147114421500Slovenia_PMLAD845774916bovenia_PMLAD845774916the Netherlands118411461222Gender maleNorway149614661526Slovenia_PMLAD852763940the Netherlands118811561220Age-class <71		Slovenia_PMI_AD	849	751	946
Slovenia_PMI_AD 845 774 916 Klovenia_PMI_AD 184 1146 1222 Gender male Norway 1496 1466 1526 Slovenia_PMI_AD 852 763 940 Me Netherlands 1188 1156 1220 Age-class <71		the Netherlands	1194	1158	1231
Initial Instruction <	Gender female	Norway	1471	1442	1500
Gender maleNorway149614661526Slovenia_PMLAD852763940Age-class <71		Slovenia_PMI_AD	845	774	916
Slovenia_PMI_AD852763940the Netherlands118811561220Age-class <71		the Netherlands	1184	1146	1222
Ithe Netherlands 1188 1156 1220 Age-class <71	Gender male	Norway	1496	1466	1526
Age-class <71		Slovenia_PMI_AD	852	763	940
Slovenia_PMI_AD 831 738 924 the Netherlands 1187 1158 1215 Age-class 71+ Norway 1424 1379 1469 Slovenia_PMI_AD 832 757 908 the Netherlands 1185 1124 1246 All Norway 1478 1433 1523 Slovenia_PMI_AD 851 731 970		the Netherlands	1188	1156	1220
the Netherlands118711581215Age-class 71+Norway142413791469Slovenia_PMI_AD832757908the Netherlands118511241246AllNorway147814331523Slovenia_PMI_AD851731970	Age-class <71	Norway	1500	1473	1527
Age-class 71+ Norway 1424 1379 1469 Slovenia_PMI_AD 832 757 908 the Netherlands 1185 1124 1246 All Norway 1478 1433 1523 Slovenia_PMI_AD 851 731 970		Slovenia_PMI_AD	831	738	924
Slovenia_PMI_AD 832 757 908 the Netherlands 1185 1124 1246 All Norway 1478 1433 1523 Slovenia_PMI_AD 851 731 970		the Netherlands	1187	1158	1215
the Netherlands 1185 1124 1246 All Norway 1478 1433 1523 Slovenia_PMI_AD 851 731 970	Age-class 71+	Norway	1424	1379	1469
All Norway 1478 1433 1523 Slovenia_PMI_AD 851 731 970		Slovenia_PMI_AD	832	757	908
Slovenia_PMI_AD 851 731 970		the Netherlands	1185	1124	1246
	All	Norway	1478	1433	1523
the Netherlands 1184 1135 1232		Slovenia_PMI_AD	851	731	970
		the Netherlands	1184	1135	1232

TABLE 6 Cost (€2019) of diagnosing patients at memory clinics at baseline in Norway, Slovenia and the Netherlands with the same program, adjusted for age, gender, education and MMSE.

IdeaIdeaIcover baudUpper bound1.AD-CNNorway1280124313161.AD-CNNorway1280124313161.Bob enhands110014012312.AD-dementia1000100130013012.AD-dementiaNorway122515413073.AD-MCIStowenia,PMI,AD83740010743.AD-MCIStowenia,PMI,AD8467059863.AD-MCIStowenia,PMI,AD8467059863.AD-MCIStowenia,PMI,AD83376212873.Noway1263123130711064.NovAD-CNStowenia,PMI,AD83376213075.Novenia,PMI,AD833762130713065.Novenia,PMI,AD843775130614095.Novenia,PMI,AD843775130614095.Novenia,PMI,AD844775130614096.NovaP12471247124912497.NovaP12611247124912497.NovaP12611261127112497.NovaP12611261127112497.NovaP12611261127112417.NovaP12611261127112417.NovaP12611261127112417.NovaP12611261127112417.NovaP12611261127112417.NovaP1261 </th <th></th> <th></th> <th></th> <th>95% confidence int</th> <th>erval</th>				95% confidence int	erval
Sivenia PMLAD84677789610 katherlands1100114012312AD dementiaNorway12551154135510Norway12521154135510Norway12621258130710Sovenia PMLAD44670598610116511221165121210Norway12821283128710Norway12821283128710Norway128376298610117311001166117310Norway98376298610Norway98376298610Norway983762108010Norway983762128910Norway983762128910Norway12871263128910Norway1281119112910Norway12811299124110Norway12811299124110Norway12811299124111Norway12811299124111Norway12811299124111Norway12811249124111Norway12811249124111Norway12811249124111Norway12811249124111Norway12811241 <th></th> <th></th> <th>Mean</th> <th>Lower bound</th> <th>Upper bound</th>			Mean	Lower bound	Upper bound
InternationInternationInternationInternationInternation2AD-dementiaNorway12511541355Silvenia, PMLADA376001074Bornal, PMLADA376001074AD-MCINorway128212831307Silvenia, PMLAD846705986He Netherlands119211651174AnonAD-ONNorway126512431265Silvenia, PMLAD117311501166Silvenia, PMLAD1647021269Morway9867921269Morway9867921269Morway124712251269Morway124712551269Morway124712251269Morway124811731150Morway124912601300Morway124712551269Morway124811621269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Morway124912691269Mor	1.AD-CN	Norway	1280	1243	1316
2Ab-dementiaNorway125114135Sovenia, PMLAD techesteriads3AD-MCINorway12212381304Solvenia, PMLAD techesteriads112211651219AnonAD-CNNorway126512431287Morway126512431287Solvenia, PMLAD633762040Morway126512431287Solvenia, PMLAD633762040Morway126512431287Solvenia, PMLAD6336371049Morway9867921160Solvenia, PMLAD8436371049Morway124712251269Solvenia, PMLAD843763049Morway124712571269Solvenia, PMLAD1441591229Any AD (1 + 2 + 3)Norway12611169Solvenia, PMLAD845799891Morway126111691214Any AD (1 + 2 + 3)Norway12611161Morway126111691214Morway126111611170Conder temaleNorway12771240Solvenia, PMLAD843793997Solvenia, PMLAD845793997Morway127612641264Gender temaleNorway12771264Solvenia, PMLAD845793997S		Slovenia_PMI_AD	846	797	896
Silveria PMI AD the Netherlands8374001074 143.AD-MCINorway1282125813073.AD-MCINorway128212581307Silveria PMI AD844705986100110211651287Silveria PMI AD833762984AnnAD-CNNorway8667221180Silveria PMI AD8436371196Silveria PMI AD8436371180Silveria PMI AD8447551269Silveria PMI AD8457991261Any Cognitive impairment (2 + 3 + 5 + 6)Norway12611242Silveria PMI AD8457931361Silveria PMI AD136111621264		the Netherlands	1190	1149	1231
InternationInternationInternationInternation3AD-MCINorway128212581307Slovenia, PMLAD846705966Internation119211651219AnonAD-CNNorway126512431307Slovenia, PMLAD833762964Slovenia, PMLAD833762964Slovenia, PMLAD833762964Slovenia, PMLAD833762964Slovenia, PMLAD833762964Slovenia, PMLAD844775913Slovenia, PMLAD844775913Slovenia, PMLAD844775913Slovenia, PMLAD844775913Slovenia, PMLAD8437941267Any AD (1 + 2 + 3)Norway12611269Slovenia, PMLAD842784899Slovenia, PMLAD842784899Internation118111011212Slovenia, PMLAD843773913Slovenia, PMLAD843773914Slovenia, PMLAD843773914Slovenia, PMLAD842784899Internation118111011214Slovenia, PMLAD843773914Slovenia, PMLAD843773914Slovenia, PMLAD843773914Slovenia, PMLAD843773914Slovenia, PMLAD84577391	2.AD-dementia	Norway	1255	1154	1355
Norway12821283107Slovenia, PMLAD846705986ibo venia, PMLAD1192116511924.NarAD-CNNorway126512431267ibo venia, PMLAD833762986ibo venia, PMLAD83376211805.NorAD-dementiaNorway98679211805.NorAD-dementiaNorway98679211806.NorAD-MCINorway1247122512646.NorAD-MCINorway1247125712646.NorAD-MCINorway1280126010006.NorAD-MCINorway1280126010007.Norway1281116912147.Norway1281116912147.Norway1261114311217.Norway1257124012747.Norway1257124012747.Norway1257124012747.Norway1261116212667.Norway1276125912747.Norway1281116212667.Norway1281116212667.Norway1287124012747.Norway1287124012747.Norway1281116212667.Norway1281116212667.Norway128111621266 </td <td></td> <td>Slovenia_PMI_AD</td> <td>837</td> <td>600</td> <td>1074</td>		Slovenia_PMI_AD	837	600	1074
Sloven, PMLAD846705968the Netherlands1192116512194NonAD-CNNorway126512431287ite Netherlands1173115011405NonAD-dementiaNorway9667921145Sovenia, PMLAD8436371049ite Netherlands117311501149ite Netherlands117412251269ite Netherlands119411501269ite Netherlands119411501269ite Netherlands119411501269ite Netherlands119411501269ite Netherlands119411501269ite Netherlands119411501269ite Netherlands119211691264ite Netherlands119211691264ite Netherlands119211691264ite Netherlands119111701264ite Netherlands119111701264ite Netherlands118411621264ite Netherlands118411621264ite Netherlands118411621264ite Netherlands118711691264ite Netherlands118711691264ite Netherlands118711691264ite Netherlands118711691264ite Netherlands118711701264ite Netherlands118711701264		the Netherlands	-	-	-
the Netherlands1192116512194NonAD-CNNorway126512431267Slovenia, PMLAD83376290411001130115011665NonAD-dementiaNorway98679211805NonAD-dementiaNorway98679211806NonAD-MCINorway12471225126910011941159122912696NonAD-MCINorway1280126013007Slovenia, PMLAD84477591310111591229126913007Slovenia, PMLAD8457998817Norway1280126013007Norway1280126312177Norway1261124512177Norway1261124512177Slovenia, PMLAD84278489971191117012127Slovenia, PMLAD8397778817Norway1257124012747Norway1263126912647Norway1267124912647Norway1257124012747Norway1267126912647Norway1267126912647Norway1267126912647Norway1267126912647Norway<	3.AD-MCI	Norway	1282	1258	1307
AlonAD-CNNorway126512431287Slovenia,PMLAD833762904the Netherlands1173115011965.NonAD-dementiaNorway9867921180Slovenia,PMLAD8436371049the Netherlands6.NonAD-MCINorway124712251269Slovenia,PMLAD844757913the Netherlands119411591229Any AD (1 + 2 + 3)Norway128012601300Slovenia,PMLAD845799891the Netherlands119211691214Any cognitive impairment (2 + 3 + 5 + 6)Norway126112451277Slovenia,PMLAD84278489912611245Gender femaleNorway1277124912641206Slovenia,PMLAD84278489912611245Gender femaleNorway127612591294Slovenia,PMLAD8457938971264Gender maleNorway126311691206Age-class <71		Slovenia_PMI_AD	846	705	986
Slovenia_PMLAD8337629041the Netherlands1173115011965.NonAD-dementiaNorway9867921180Slovenia_PMLAD8436371049ibe Netherlands1046371049ibe Netherlands114712251269Slovenia_PMLAD8447759129Any AD (1 + 2 + 3)Norway128012601300Slovenia_PMLAD845799891Any cognitive impairment (2 + 3 + 5 + 6)Norway126112451277Slovenia_PMLAD842784899Any cognitive impairment (2 + 3 + 5 + 6)Norway125712401212Gender femaleNorway125712401274Slovenia_PMLAD8457938971261Any cognitive impairment (2 + 3 + 5 + 6)Norway125712401274Slovenia_PMLAD1843116212061264Gender femaleNorway127612591294Age-class <71		the Netherlands	1192	1165	1219
the Netherlands1173115011615NonAD-dementiaNorway9667221160Slovenia,PMLAD8436371049ihe Netherlands6NonAD-MCINorway124712251269Slovenia,PMLAD8447759131269Any AD (1 + 2 + 3)Norway128012601300Slovenia,PMLAD8457998911214Any cognitive impairment (2 + 3 + 5 + 6)Slovenia,PMLAD842784899Slovenia,PMLAD842784899121411001212Gender femaleNorway1257124012741226Slovenia,PMLAD839797881116111001212Gender femaleNorway1275124012741266Slovenia,PMLAD83979788111611206Gender maleNorway1276125912941206Age-class <71	4.NonAD-CN	Norway	1265	1243	1287
ShonAD-dementiaNorway9867921180Slovenia_PMLAD8436371049the Netherlands6.NonAD-MCINorway124712251269Slovenia_PMLAD8447759131269Any AD (1 + 2 + 3)Norway128012601300Slovenia_PMLAD8457998911241Any cognitive impairment (2 + 3 + 5 + 6)Norway126112451214Any cognitive impairment (2 + 3 + 5 + 6)Norway125712401214Gender femaleNorway125712401214Gender femaleNorway125712401274Slovenia_PMLAD83979788111621206Gender femaleNorway127612591294Slovenia_PMLAD84579389712641206Gender femaleNorway127612591294Slovenia_PMLAD83177788111691206Gender maleNorway128012651296Slovenia_PMLAD83177788611871169Age-class <71		Slovenia_PMI_AD	833	762	904
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	All	Norway	1264	1238	1291
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		the Netherlands	1184	1156	1213

4.2 | Methodological considerations

Clinical data from memory clinics, such as in this project, has the advantage of representing how the diagnostic process works in clinical settings. The great drawback is, of course, the non-controlled design. Thus, several questions arise: Are the datasets representative of memory clinics in each country, and are the comparisons between the countries valid? How representative is the age distribution in our predementia samples versus the corresponding persons in the general population? Are the datasets comparable internally, that is, there exists unknown missing data? The recruitments process also varied between the countries since part of the study populations in Norway and Slovenia were recruited via advertisements. Probably, it does not affect the diagnostic costs, but it may interfere of the outcome of the diagnostic work-ups in terms of for example, predictive values.

The baseline cost-calculations are based on a single use of each diagnostic test. In the long-run, people with normal cognitive testing, but with subjective symptoms, probably will need re-exams (and resulting increasing costs), which will not be the case for those with a confirmed diagnosis.

Comparing unit costs for diagnostic tests between countries is complicated. First, unit costs may vary within countries at different labs etc. Second, what is included in a unit cost at different labs, clinics? How are the prices set concerning budget principles for different countries, regions, etc. Third, diagnostic capacity, diagnostic culture, reimbursement principles and economic strength vary between countries which also may impact diagnostic costs. In many countries, there are price lists in use, but this was not the case in Norway. Our approach for standardizing the costs, based on using unit costs from a part of Sweden and then adjusting for GDP per person, is transparent, but its validity may be questioned. In the ACTIF-Care project, great efforts were undertaken to get countryspecific costs for different care resources based on multi-country price estimates and expert opinions,³⁰ illustrating the complexity of comparing countries.

BBM so far have no price in clinical praxis, but we regard our estimate as reasonable, and it is obvious that the price of BBM will be much lower than the costs, for example, for CSF and PET, particularly if the costs for the logistics around these tolls are considered.

Our study cannot answer questions of cost-effectiveness of the diagnostic tests and pathways, since it is a descriptive cost-analysis. In our view, cost-effectiveness discussions regarding diagnostic tests and pathways must be linked to some kind of treatment with different arms.

4.3 | Conclusions

If DMTs become available for treating of AD, the diagnostic process will be even more important. The capacity of the diagnostic infrastructure is a great challenge.³¹ No simple test can be used to set an AD diagnosis. To make the diagnostic process cost-effective, both the number of tests, the sequence in which they are used, and the ending accuracy of a package is crucial.³² Furthermore, it can be questioned if diagnostic workups are cost-effective per se. The key issue is the link between diagnostic work-up and treatment which can result in benefits for patients and society. These aspects will be explored in greater depth in another section of PMI-AD.

ACKNOWLEDGMENT

This study has been funded by the Norwegian Research Council, JPND/PMI-AD (NRC 311993). The Swedish part of the project has been funded by the Swedish Research Council (2019-03393). BEK was supported by a grant from Helse-Nord (HNF1540-20). MGK, AE, AS and JB were supported by funding from Ministry of Education, Science and Sport, Republic of Slovenia for JPND PMI-AD.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL STATEMENT

Norway: PMI-AD was approved by the Regional Ethical Committee in Norway, reference number 2023/50738. The Netherlands: The study was approved by the medical ethical review board of the VU University Medical Center, approval number 2016.061. Slovenia: The national ethical committee permission, Nr 0120-539/2020/10.

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SUPPORTING INFORMATION

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

How to cite this article: Wimo A, Kirsebom B-E, Timón-Reina S, et al. Costs of diagnosing early Alzheimer's disease in three European memory clinic settings: results from the precision medicine in Alzheimer's disease project. *Int J Geriatr Psychiatry*. 2024;e6126. https://doi.org/10.1002/gps.6126