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RESEARCH ARTICLE

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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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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 (€) as of 2019. A diagnostic set comprising clinical examination,

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 cost-effective, 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 disease-modifying 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.

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

TABLE 1 Study populations.

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 subtype 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.

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 diagnosis-treatment 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€ 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 (€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

[a]expert 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 €, 851€, and 1184€, 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 4 Used diagnostic tests at baseline at memory clinics in 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.

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 Figure[27] are applied, and combined with Norwegian population statistics.[28] If all these people would undergo diagnostic procedures at a cost of about 1400 € per case to identify persons suitable for DMT, the diagnostic cost would be considerable, about 140 million €. Furthermore, the diagnostic costs for all people concerned about having AD (which may be 50% or more of all elderly people[29]), 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.

			95% confidence interval	
		Mean	Lower bound	Upper bound
1.AD-CN	Norway	1528	1466	1589
	Slovenia_PMI_AD	852	768	936
	the Netherlands	1190	1120	1259
2.AD-dementia	Norway	1501	1330	1672
	Slovenia_PMI_AD	850	447	1252
	the Netherlands	-	-	-
3.AD-MCI	Norway	1519	1478	1560
	Slovenia_PMI_AD	857	618	1096
	the Netherlands	1197	1152	1243
4.NonAD-CN	Norway	1488	1451	1526
	Slovenia_PMI_AD	839	719	960
	the Netherlands	1166	1127	1205
5.NonAD-dementia	Norway	1136	805	1466
	Slovenia_PMI_AD	870	520	1220
	the Netherlands	-	-	-
6.NonAD-MCI	Norway	1415	1378	1453
	Slovenia_PMI_AD	853	736	971
	the Netherlands	1196	1137	1256
Any AD (1 + 2 + 3)	Norway	1511	1477	1545
	Slovenia_PMI_AD	851	773	929
	the Netherlands	1196	1158	1234
Any cognitive impairment (2 + 3 + 5 + 6)	Norway	1460	1432	1487
	Slovenia_PMI_AD	849	751	946
	the Netherlands	1194	1158	1231
Gender female	Norway	1471	1442	1500
	Slovenia_PMI_AD	845	774	916
	the Netherlands	1184	1146	1222
Gender male	Norway	1496	1466	1526
	Slovenia_PMI_AD	852	763	940
	the Netherlands	1188	1156	1220
Age-class <71	Norway	1500	1473	1527
	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	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.

			95% confidence interval	
		Mean	Lower bound	Upper bound
1.AD-CN	Norway	1280	1243	1316
	Slovenia_PMI_AD	846	797	896
	the Netherlands	1190	1149	1231
2.AD-dementia	Norway	1255	1154	1355
	Slovenia_PMI_AD	837	600	1074
	the Netherlands	-	-	-
3.AD-MCI	Norway	1282	1258	1307
	Slovenia_PMI_AD	846	705	986
	the Netherlands	1192	1165	1219
4.NonAD-CN	Norway	1265	1243	1287
	Slovenia_PMI_AD	833	762	904
	the Netherlands	1173	1150	1196
5.NonAD-dementia	Norway	986	792	1180
	Slovenia_PMI_AD	843	637	1049
	the Netherlands	-	-	-
6.NonAD-MCI	Norway	1247	1225	1269
	Slovenia_PMI_AD	844	775	913
	the Netherlands	1194	1159	1229
Any AD (1 + 2 + 3)	Norway	1280	1260	1300
	Slovenia_PMI_AD	845	799	891
	the Netherlands	1192	1169	1214
Any cognitive impairment (2 + 3 + 5 + 6)	Norway	1261	1245	1277
	Slovenia_PMI_AD	842	784	899
	the Netherlands	1191	1170	1212
Gender female	Norway	1257	1240	1274
	Slovenia_PMI_AD	839	797	881
	the Netherlands	1184	1162	1206
Gender male	Norway	1276	1259	1294
	Slovenia_PMI_AD	845	793	897
	the Netherlands	1187	1169	1206
Age-class <71	Norway	1280	1265	1296
	Slovenia_PMI_AD	831	777	886
	the Netherlands	1187	1170	1204
Age-class 71+	Norway	1225	1199	1252
	Slovenia_PMI_AD	829	785	873
	the Netherlands	1181	1145	1216
All	Norway	1264	1238	1291
	Slovenia_PMI_AD	843	771	914
	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 country-specific 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.

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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.

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