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How does additional diagnostic testing influence the initial diagnosis in patients with cognitive complaints in a memory clinic setting?

Anouk P. Meijs[1], Jurgen A. H. R. Claassen[1,2,3], Marcel G. M. Olde Rikkert[1,2,3], Bianca W. M. Schalk[1,2], Olga Meulenbroek[1,2], Roy P. C. Kessels[1,2,4], René J. F. Melis[1,2,3]

[1]Department of Geriatric Medicine, Radboud University Medical Center, Nijmegen, Netherlands
[2]Radboud Alzheimer Centre, Radboud University Medical Center, Nijmegen, Netherlands
[3]Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands
[4]Department of Medical Psychology, Radboud University Medical Center, Nijmegen, Netherlands

Address correspondence to: Tel: +31 30 274 2684, Anouk Meijs. Email: anoukmeijs@gmail.com

Abstract

Background: patients suspected of dementia frequently undergo additional diagnostic testing (e.g. brain imaging or neuropsychological assessment) after standard clinical assessment at a memory clinic. This study investigates the use of additional testing in an academic outpatient memory clinic and how it influences the initial diagnosis.
Methods: the initial diagnosis after standard clinical assessment (history, laboratory tests, cognitive screening and physical and neurological examination) and the final diagnosis after additional testing of 752 memory clinic patients were collected. We specifically registered if, and what type of, additional testing was requested.
Results: additional testing was performed in 518 patients (69%), 67% of whom underwent magnetic resonance imaging, 45% had neuropsychological assessment, 14% had cerebrospinal fluid analysis and 49% had (combinations of) other tests. This led to a modification of the initial diagnosis in 17% of the patients. The frequency of change was highest in patients with an initial non-Alzheimer's disease (AD) dementia diagnosis (54%, compared with 11 and 14% in patients with AD and 'no dementia'; $P < 0.01$). Finally, after additional testing 44% was diagnosed with AD, 9% with non-AD dementia and 47% with 'no dementia'.
Conclusion: additional testing should especially be considered in non-AD patients. In the large group of patients with an initial AD or 'no dementia' diagnosis, additional tests have little diagnostic impact and may perhaps be used with more restraint.

Keywords: *dementia, memory clinic, MRI, neuropsychological testing, diagnostic accuracy, older people*

Introduction

Despite recent advances in diagnostic tests, the accurate diagnosis of dementia remains challenging as distinguishing between normal ageing and dementia, and between the different nosological forms of dementia can prove difficult in clinical practice. Although no curative treatment exists, an accurate diagnosis at an early stage is becoming increasingly important as treatment options improve [1].

The evaluation of patients suspected of dementia in a typical Dutch memory clinic starts with a standard diagnostic assessment resulting in an initial clinical diagnosis. When the diagnosis remains uncertain, additional tests are performed, e.g. brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) biomarker analysis or extensive neuropsychological assessment (NPA), followed by a final diagnosis. Several studies investigated the diagnostic accuracy of these additional tests in diagnosing dementia. MRI is recommended to demonstrate or exclude cerebrovascular disease and brain atrophy [2], and to exclude potentially reversible causes of dementia. Structural imaging using MRI has been shown to improve early detection of dementia when added to the standard diagnostic assessment [3, 4]. The combination of the CSF biomarkers β-amyloid42, total tau and phosphorylated tau discriminates Alzheimer's disease (AD) from other types of dementia and normal ageing [5–7]. In patients with an

ambiguous clinical diagnosis, phosphorylated tau has an added diagnostic value to the standard assessment in the differentiation of AD from non-AD [8]. NPA contributes to the early diagnosis of dementia and to the differentiation of its various forms, by assessing the profile and extent of the cognitive impairments as well as the influence of potentially confounding factors, such as personality and coping or mood disturbances [3, 9]. Geroldi *et al.* concluded that NPA may have added value to the standard diagnostic assessment [10], not only for the diagnosis but also providing information that can be used in the patient's or caregiver's care or support.

From the studies cited above MRI, CSF analysis and NPA are shown to be valuable in diagnosing dementia and differentiating between subtypes. However, it remains unclear which (combinations of) additional tests are used in clinical practice and how they are used in determining the final diagnosis. Preferably, they should only be applied in patients who benefit from the results as they are in general more burdensome for the patient and require additional resources. Therefore, the aim of this study was to analyse whom of the patients, referred to the memory clinic because of cognitive complaints, receive additional diagnostic tests and how often and how these tests resulted in an adjustment of the initial dementia diagnosis and its nosological classification.

Methods

Data on all consecutive patients who visited the outpatient memory clinic of the Radboud University Medical Center between 1 January 2007 and 31 December 2010 were collected from the department's clinical database.

Diagnosis started with a standard diagnostic assessment including history taking, laboratory tests, physical and neurological examination and the following cognitive screening tests: mini-mental state examination (MMSE) [11], the Dutch version of the revised Cambridge cognitive examination (CAMCOG-R) [12], neuropsychiatric inventory [13], geriatric depression scale [14], auditory-verbal learning test (AVLT) [15], trail making test A (TMT A) [16] and digit span forward and backward [17]. This standard diagnostic assessment was done by a registrar in geriatric medicine and supervised by a geriatrician. Subsequently, during the first multidisciplinary consultation (MDC1), the best possible diagnosis was agreed upon and the need for additional diagnostics was discussed. The MDC team consisted of at least a geriatrician, a neuropsychologist, an occupational therapist and the registrar involved in the assessment. When additional testing was performed, a second MDC resulted in the final diagnosis.

The initial and final diagnoses collected from the memory clinic database were categorised into three groups: (i) AD, including possible and probable AD, mixed AD with vascular dementia and posterior cortical atrophy; (ii) non-AD dementia, including possible and probable vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson dementia, semantic dementia, primary progressive aphasia, Creutzfeldt Jacob disease and dementia not otherwise specified; (iii) no dementia, including mild cognitive impairment, vascular cognitive impairment, neurological and psychiatric conditions and no diagnosis (i.e. patients with subjective cognitive complaints).

Patient characteristics drawn from the database included socio-demographic characteristics, presence of relevant co-morbidity and results of the cognitive screening during the first visit. Data on the use (yes/no) of additional tests were collected from laboratory and neuropsychologist's databases.

Statistical analyses

Patients with and without additional tests were compared on baseline characteristics, cognitive screening results and MDC1 diagnosis using independent *t*-tests and Chi-square tests. Further analysis was performed on patients with additional tests. The frequency of a change in the initial diagnosis was calculated for the total group as well as for the three diagnosis groups separately and was compared between these three groups using Chi-square tests.

Subsequently, the types of additional diagnostic tests were taken into consideration. A Venn diagram was made to understand which combinations of additional tests were often performed. On the basis of the frequency of co-occurrence of specific tests, we identified four typical clusters. To compare the change in diagnosis between these additional test clusters pair-wise a closed testing procedure was used [18, 19]. Furthermore, patients with and without a change in diagnosis were compared with regard to patient characteristics using the appropriate statistical procedures.

Results

Over the inclusion period, 767 individual patients were referred to the memory clinic. After excluding 15 patients with an unknown diagnosis at MDC1, data of 752 patients were analysed. Of this group 234 did not undergo additional tests, leaving 518 patients with additional tests. Patients with additional tests were older (73.7 ± 9.2 versus 71.5 ± 11.7 years; $P = 0.006$) than patients without additional tests. Furthermore, patients with additional tests more frequently had an initial diagnosis of AD or non-AD dementia and were less frequently in the 'no dementia' group ($P < 0.001$). For more results see Supplementary data available in *Age and Ageing* online, Table Appendix S1.

Change in initial diagnosis

Overall, the initial diagnosis changed in 17.2% ($n = 89$) of the patients with additional testing. This included 11.4% of the patients with an initial AD and 13.9% of the patients with an initial 'no dementia' diagnosis. The highest frequency of change was observed in the non-AD group where 53.6% of the patients had a change in diagnosis (compared with the other diagnosis groups, $P < 0.001$, Table 1). Finally, following additional testing 231 patients (44.6%) were diagnosed with AD, 45 (8.7%) with non-AD and 242 (46.7%) with 'no dementia'. An important note is that 29 (53.7%) of the 54 patients with an initial possible AD changed to probable AD, and therefore

Table 1. Change frequency of the initial diagnosis, in total and per cluster of additional tests

Initial diagnosis	Final diagnosis	Number of patients (%[a])				
		Total (n = 518)	MRI[b] (n = 190)	NPA[c] (n = 76)	MRI + NPA[d] (n = 156)	Other tests (n = 96)
AD		*n = 210*	*n = 114*	*n = 16*	*n = 31*	*n = 49*
	AD	186 (88.6)	107 (93.8)	9 (56.2)	24 (77.4)	46 (93.9)
	Non-AD	12 (5.7)	6 (5.3)	2 (12.5)	2 (6.5)	2 (4.1)
	No dementia	12 (5.7)	1 (0.9)	5 (31.3)	5 (16.1)	1 (2.0)
Non-AD		*n = 56*	*n = 21*	*n = 9*	*n = 16*	*n = 10*
	AD	17 (30.4)	8 (38.1)	3 (33.3)	4 (25.0)	2 (20.0)
	Non-AD	26 (46.4)	11 (52.4)	3 (33.3)	6 (37.5)	6 (60.0)
	No dementia	13 (23.2)	2 (9.5)	3 (33.3)	6 (37.5)	2 (20.0)
No dementia		*n = 252*	*n = 55*	*n = 51*	*n = 109*	*n = 37*
	AD	28 (11.1)	5 (9.1)	4 (7.8)	18 (16.5)	1 (2.7)
	Non-AD	7 (2.8)	2 (3.6)	2 (3.9)	2 (1.8)	1 (2.7)
	No dementia	217 (86.1)	48 (87.3)	45 (88.3)	89 (81.7)	35 (94.6)
Total change		89 (17.2)	24 (12.6)	19 (25.0)	37 (23.7)	9 (9.4)

AD, Alzheimer's disease; MRI, magnetic resonance imaging; NPA, neuropsychological assessment.
[a]Percentages are column percentages.
[b]MRI but no NPA, with/without other tests.
[c]NPA but no MRI, with/without other tests.
[d]MRI and NPA, with/without other tests.

remained in the AD group but increased in diagnostic certainty. See Supplementary data available in *Age and Ageing* online, Table Appendix S2 for an extensive description of changes.

Types of additional diagnostic tests

Of the total group of patients with additional tests, 66.8% (n = 346) underwent MRI, in 44.8% (n = 232) NPA was performed, and 13.7% (n = 71) had CSF analysis. Overall, 216 (41.7%) patients had more than one of these additional diagnostic tests. Based on the frequency of co-occurrence of tests, patients were grouped into four clusters (Figure 1). These clusters were the following: MRI but no NPA (with/without other tests); NPA but no MRI (with/without other tests); MRI and NPA (with/without other tests); any (combination of) other tests. Included under the heading 'other tests' were CSF analysis, occupational therapy diagnostics (28.1%; n = 102), computed tomography scan of the brain (4.4%; n = 16) and assessment by a social psychiatric nurse (4.1%; n = 15).

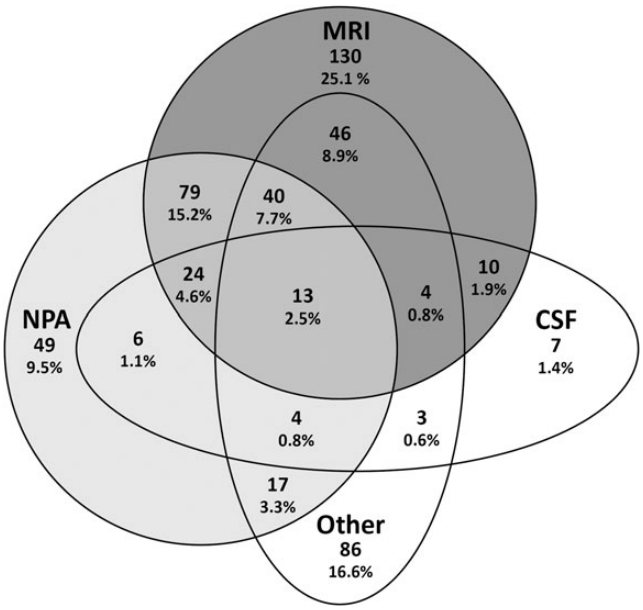

Figure 1. Venn diagram, combinations of additional diagnostic tests (n = 518). Results are displayed as: number of patients, percentage. Grey shades represent the grouping for further analysis: MRI but no NPA (with/without other tests) (n = 190, 36.7%); NPA but no MRI (with/without other tests) (n = 76, 14.7%); both MRI and NPA (with/without other tests) (n = 156, 30.0%) and any (combination of) other tests (n = 96, 18.6%). MDC, multidisciplinary consultation; MRI, magnetic resonance imaging; NPA, neuropsychological assessment; CSF, cerebrospinal fluid.

Consequences of additional diagnostic tests for the initial diagnosis

The frequency of change in diagnosis differed between the additional test clusters (P = 0.002) (Table 1). In the NPA and MRI + NPA clusters, changes in diagnosis occurred more frequently than in the other two clusters. This result was also found (P < 0.001) when tested solely in patients with an initial AD diagnosis. For the non-AD and 'no dementia' group, no such pattern was found (P = 0.58 and P = 0.25, respectively) (Table 2).

Patients with and without a change in initial diagnosis

Analysis of patients with and without a change in the initial diagnosis showed that the patients in the 'no dementia' group with a change in diagnosis were older and performed worse on the MMSE, CAMCOG-R, TMT A and AVLT (Table 2). In contrast, patients in the AD group with a change in diagnosis performed better on the MMSE and the CAMCOG-R than

Table 2. Baseline characteristics, results of cognitive screening and distribution over the additional diagnostic test clusters compared between patients with and patients without a change in diagnosis, per initial diagnosis

Variable	Number of patients (%[a]) or mean ± SD								
	AD			Non-AD dementia			No dementia		
	No change (n = 186)	Change (n = 24)	P-value	No change (n = 26)	Change (n = 30)	P-value	No change (n = 217)	Change (n = 35)	P-value
Age	77.4 ± 7.2	75.0 ± 9.1	0.15	73.6 ± 8.5	74.8 ± 9.0	0.63	70.0 ± 9.7	75.5 ± 7.3	0.002
Female	118 (63.4)	13 (54.2)	0.38	4 (15.4)	18 (60.0)	<0.001	101 (46.5)	20 (57.1)	0.24
Comorbidity	118 (63.4)	12 (50.0)	0.20	20 (76.9)	24 (80.0)	0.78	149 (68.7)	26 (74.3)	0.50
Diabetes	35 (18.8)	4 (16.7)	1.00	5 (19.2)	10 (33.3)	0.36	35 (16.1)	8 (22.9)	0.34
Depression	13 (7.0)	2 (8.3)	0.68	0 (0.0)	2 (6.7)	0.49	31 (14.3)	5 (14.3)	1.00
Cardiovascular comorbidity[b]	106 (57.0)	10 (41.7)	0.16	18 (69.2)	23 (76.7)	0.53	120 (55.3)	20 (57.1)	0.84
MMSE[c]	19.3 ± 4.7	22.4 ± 4.6	0.003	20.0 ± 4.7	20.6 ± 5.2	0.67	26.5 ± 2.7	24.5 ± 3.0	<0.001
CAMCOG-R[c]	71.9 ± 20.3	82. 7 ± 19.4	0.02	77.8 ± 20.7	80.2 ± 19.9	0.66	103.0 ± 14.2	97.1 ± 11.1	0.02
NPI[d]	6.5 ± 5.6	7.6 ± 6.4	0.42	7.9 ± 6.6	5.7 ± 5.2	0.19	4.2 ± 4.5	3.8 ± 4.0	0.70
GDS15[d]	2.7 ± 2.0	3.1 ± 1.3	0.32	3.1 ± 2.2	3.5 ± 2.5	0.59	3.4 ± 2.9	3.2 ± 2.6	0.62
AVLT total[e]	21.4 ± 9.4	23.1 ± 12.8	0.44	26.3 ± 12.1	24.5 ± 14.1	0.66	31.9 ± 11.1	27.9 ± 8.3	0.06
AVLT recall[e]	22.4 ± 6.5	24.4 ± 9.6	0.23	31.2 ± 13.0	28.0 ± 11.8	0.41	32.3 ± 12.8	28.1 ± 10.0	0.09
TMT A[e]	32.4 ± 20.2	31.9 ± 22.8	0.92	25.8 ± 15.0	30.0 ± 24.6	0.50	43.6 ± 14.0	36.5 ± 16.0	0.01
DSF[c]	7.1 ± 1.7	7.3 ± 1.4	0.69	6.5 ± 1.7	6.7 ± 1.4	0.66	7.8 ± 1.9	8.3 ± 2.1	0.20
DSB[c]	3.6 ± 1.7	3.8 ± 1.7	0.62	3.0 ± 1.3	3.4 ± 1.7	0.29	4.8 ± 1.7	4.5 ± 2.2	0.38
Addi tional diagnostic test cluster[f]			<0.001			0.58			0.25
MRI[g]	107 (57.5)	7 (29.2)	0.01[j]	11 (42.3)	10 (33.3)	[j]	48 (22.1)	7 (20.0)	[j]
NPA[h]	9 (4.8)	7 (29.2)	<0.001[j]	3 (11.5)	6 (20.0)	[j]	45 (20.7)	6 (17.1)	[j]
MRI + NPA[i]	24 (12.9)	7 (29.2)	0.03[j]	6 (23.1)	10 (33.3)	[j]	89 (41.0)	20 (57.1)	[j]
Other tests	46 (24.7)	3 (12.5)	0.30[j]	6 (23.1)	4 (13.3)	[j]	35 (16.1)	2 (5.7)	[j]
Number of differential diagnoses	0.9 ± 0.8	1.2 ± 1.0	<0.001	1.3 ± 0.8	1.5 ± 1.0	0.43	1.1 ± 0.9	1.6 ± 0.9	0.003

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; CAMCOG-R, Dutch version of the revised Cambridge cognitive examination; NPI, neuropsychiatric inventory; GDS15, geriatric depression scale-15; AVLT, auditory-verbal learning test; TMT A, trail making test part A; DSF, digit span forward; DSB, digit span backward; MRI, magnetic resonance imaging; NPA, neuropsychological assessment.

[a]Percentages are column percentages.

[b]Consisting of hypertension, cardiovascular disease and hypercholesterolaemia/hypertriglyceridaemia.

[c]A low score is abnormal. Range: MMSE (0–30), CAMCOG-R (0–107), DSF (0–16), DSB (0–14).

[d]A high score is abnormal. Range: NPI (0–144), GDS15 (0–15).

[e]Standardized T-scores (normative mean = 50, SD = 10).

[f]Closed testing procedure.

[g]MRI but no NPA, with/without other tests.

[h]NPA but no MRI, with/without other tests.

[i]MRI and NPA, with/without other tests.

[j]P-value for testing the change rate of the specific diagnostic cluster against the change rate among the other three diagnostic clusters combined. If the P-value is not reported, this is because the overall Chi-square test whether change rates differed among the four diagnostic clusters was not significant (closed testing) [18, 19].

AD patients without a change. Typically, AD patients with a changed diagnosis more frequently underwent NPA, whereas the patients with the initial AD without a change more frequently underwent only MRI.

Discussion

The present study investigated the use of additional diagnostic tests and how often and how they changed the initial diagnosis in patients with cognitive complaints referred to a memory clinic. We found that most patients received additional tests. These patients were more frequently diagnosed with dementia (either AD or non-AD) than patients without additional tests. The most frequently applied additional tests were MRI and NPA. Patients with an initial non-AD dementia were most likely to have a change in diagnosis, whereas in patients with the initial AD or 'no dementia' the diagnosis remained mostly unaltered.

Change in initial diagnosis

Additional tests resulted in a change in diagnosis in 17% of the patients. The change was highest in patients with an initial non-AD dementia diagnosis (54%), indicating that this group was most difficult to diagnose with the standard diagnostic assessment. Although the change in diagnosis was low in the AD group, it resulted in more confidence about the diagnosis in more than half of patients with possible AD, as their diagnosis changed to probable AD (Supplementary data available in *Age and Ageing* online, Table Appendix S2).

Our study results are in agreement with a study by Geroldi *et al.* who found a change in diagnosis in 24% of the patients with the initial non-AD compared with 7% in patients with an initial AD diagnosis [10], although their

absolute change percentages were lower. However, the patients in their study were already more severely affected, making it easier to agree upon a diagnosis during standard diagnostic assessment. Furthermore, all their patients received both MRI and NPA regardless of the initial diagnosis, whereas in our study the necessity (most likely based on a lack of diagnostic certainty) of requesting additional tests was considered individually. This probably resulted in the larger percentage of change in diagnosis if additional tests were applied. Our study therefore provides insight in the way additional tests are applied on an individual basis and how they affect the change frequency in an outpatient memory clinic.

Types of additional diagnostic tests and their consequences for the initial diagnosis

MRI and NPA were the most frequently requested tests. Noteworthy is that in more than half of the patients with an initial AD diagnosis MRI was requested as a single test. In this specific group, only 6% had a change in diagnosis, meaning that MRI was confirmatory rather than required to establish the diagnosis. Furthermore, we noticed that patients initially diagnosed with a form of dementia who underwent at least NPA most frequently changed to 'no dementia', whereas patients who only had MRI most frequently switched between AD and non-AD dementia. This difference can be explained by the purpose for which the additional tests are requested. NPA is known for its accuracy in determining the profile and severity of cognitive complaints (differentiate between dementia and no dementia), whereas MRI is used to show structural abnormalities of the brain (distinguish AD from other forms of dementia) [3].

In contradiction to our results, Chui *et al.* [20] found that diagnoses changed more often after neuroimaging (28%) than after NPA (11%). The difference in results can be due to the large number of patients in the study of Chui *et al.* in whom other lesions (e.g. treatable lesions and infarcts) were diagnosed after neuroimaging, making their study population less comparable with ours. Other studies that investigated changes in diagnosis reported values of 26% when NPA and MRI were both added to the standard assessment [3], and 24% for neuroimaging alone [21]. The overall conclusion in these papers was that a standard clinical assessment alone is insufficient for optimal diagnosis in a selection of patients. The current data showed that although additional diagnostics are definitely useful in non-AD, for a large group of patients with AD or 'no dementia' these tests were in practice mainly used to confirm the initial diagnosis.

Patients with and without a change in initial diagnosis

Patients with a change in diagnosis had more atypical results on cognitive screening tests, i.e. better performance than would be expected in patients with an initial dementia diagnosis and worse performance in the 'no dementia' patients indicating a lack of concordance between symptom presentation and cognitive testing. In other words, the diagnostic uncertainty was probably higher in these patients and therefore explained the change in diagnosis. Also, a longer list of differential diagnoses was formulated in patients with a change, which is another indicator of diagnostic uncertainty (Supplementary data available in *Age and Ageing* online, Table Appendix S1). In summary, not only the additional tests but also the diagnostic uncertainty contributed to a change in diagnosis. Therefore, it seems likely that diagnostic uncertainty and the choice of additional tests are associated. In future research, it is thus important to report the level of diagnostic uncertainty as it may be helpful to understand how the diagnostic process results in a certain diagnosis. Furthermore, explicitly taking into account the diagnostic uncertainty in the decision to perform additional testing can increase the awareness of clinicians on why they want additional testing and for which patients it will and for which patients it will probably not be beneficial. The statistically significant difference in sex of patients with initially non-AD type dementia diagnosis has no straightforward interpretation: perhaps it is a chance finding.

Limitations

Although our study design is distinctive from the current literature, using data from a clinical routine database has its limitations as well. First, in patients for whom it was decided that additional testing was unnecessary, the possible influence of additional tests on the initial diagnosis could not be assessed. Especially in the group of patients with a final 'no dementia' diagnosis at MDC1 this could result in denial of early intervention. However, as the decision not to request additional tests in this group was made deliberately by the MDC team, it seems plausible that additional tests would have had a minimal impact on the diagnosis. Furthermore, as none of the diagnoses were validated by post-mortem neuropathological examination [22] or another reference standard, we do not know if the final diagnosis is in fact correct and when the initial diagnosis changed, if it has improved. Nevertheless, for the purpose of this study, these shortcomings do not outweigh the benefits of a database with a study population that resembles the actual patient population and its specific prior probability of dementia [23], and the ability to systematically assess the clinical use of these complex diagnostic tools.

Conclusion

The present study indicated that the occurrence of a change in the initial diagnosis after additional testing differed considerably between groups of memory clinic patients. Additional examination should especially be considered in patients suspected of non-AD, whereas in the large group of patients with an uncomplicated picture of AD or 'no dementia' additional tests may perhaps be requested with more restraint.

Key points

- The majority of patients referred to the memory clinic receive additional diagnostic tests.
- Brain imaging with MRI and NPA are the most frequently requested additional tests.
- After additional tests more than half of patients with an initial non-AD dementia have a change in diagnosis.
- In patients with initial AD or 'no dementia' the diagnosis remains unaltered in most cases after additional tests.

Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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