JAMDA 25 (2024) 105040

JAMDA

journal homepage: www.jamda.com

Original Study

# The Association of Ancillary Diagnostic Tests With Outcome in Dementia

Josephine E. Lindhout MD [a,b,*], Edo Richard MD, PhD [a,b], Melanie Hafdi MD [c], Marieke Perry MD, PHD [d,e], Eric Moll van Charante MD, PhD [b], Willem A. van Gool MD, PhD [a,b]

[a] Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition, and Behavior, Nijmegen, The Netherlands
[b] Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[c] Department of Neurology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[d] Radboudumc Alzheimer Center, Radboud University Medical Center, Nijmegen, The Netherlands
[e] Department of Primary and Community Care, Donders Institute for Brain, Radboud University Medical Center, Nijmegen, The Netherlands

*Keywords:*
Dementia
Diagnostic testing
Health care costs
Institutionalization
Survival

A B S T R A C T

*Objectives:* Dementia is a clinical diagnosis without curative treatment. It is uncertain whether ancillary testing is beneficial for patients. This study investigates the association between use of diagnostic tests and time to poor outcome and health care costs.
*Design:* Nationwide register-based cohort study using health care reimbursement data in the Netherlands.
*Setting and Participants:* All Dutch hospitals, including 13,312 patients diagnosed with dementia in 2018.
*Methods:* Diagnostic testing included computed tomography or magnetic resonance imaging (CT/MRI), neuropsychological examination (NPE), nuclear imaging (PET/SPECT), electroencephalography (EEG), and cerebrospinal fluid (CSF) testing. We compared time to poor outcome (institutionalization or death) and costs per month from 2018 to 2021 between those who underwent a specific diagnostic test in previous years to controls, propensity score matched for age, sex, type of hospital, and comorbidity.
*Results:* Time to poor outcome in those who underwent CT/MRI, EEG, or CSF testing was similar to those who did not, but was longer for those who underwent NPE. Time to poor outcome was shorter in patients who underwent PET/SPECT. Patients who underwent CSF testing or PET/SPECT had higher mean total health care costs as compared to controls (CSF €248, 95% CI 64-433; PET/SPECT: €315, 95% CI 179-451). NPE during the diagnostic trajectory was associated with lower total health care cost (−€127, 95% CI −62, −193).
*Conclusion and Implications:* NPE was associated with longer time to poor outcome and lower health care costs, potentially due to confounding by indication. Patients who underwent neuroimaging (CT, MRI, SPECT/PET), CSF testing, or EEG for dementia diagnostics did not experience a longer time to poor outcome or lower health care costs. This emphasizes the importance of clinical examination as anchor for the diagnosis of dementia.



Clinical guidelines across the globe emphasize the need for a timely diagnosis of dementia.[1–3] The diagnostic trajectory may involve several diagnostic tests, to test differential diagnostic hypotheses, to rule out rare reversible causes of cognitive decline, and to diagnose subtypes of dementia with more certainty.[4] Brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is recommended as part of investigations of people with suspected dementia in a specialist care setting in UK,[2] European,[3] and US[5] guidelines. Additional available tests include positron emission tomography (PET), single-photon emission CT (SPECT), cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), and detailed neuropsychological examinations (NPE).

Diagnosis may relieve uncertainties about one's cognitive impairments and may pave the way for access to appropriate care, including advance care planning.[6] The right timing and setting for diagnosis

* Address correspondence to Josephine E. Lindhout, MD, Department of Public and Occupational Health, Amsterdam University Medical Center, University of Amsterdam, Meibergdreef 9, 1100 DD, Amsterdam, The Netherlands.
*E-mail address:* j.e.lindhout@amsterdamumc.nl (J.E. Lindhout).

https://doi.org/10.1016/j.jamda.2024.105040

relies heavily on patient and caregiver preferences.[7] In younger patients, broad differential diagnostic testing in a specialized memory clinic may be warranted; however, in older patients, the added value of diagnostic testing may be limited because of overlapping pathologies and absence of curative options.[8–12] This raises the question if patients benefit from extensive diagnostic testing compared with more restrictive testing. Diagnostic studies often focus on diagnostic accuracy, whereas clinical utility and patient benefit are of equal importance in the evaluation of diagnostic testing.[13–16] In the Netherlands, dementia is diagnosed in a hospital setting in 58% of cases,[17] and use of ancillary tests for dementia varies substantially across hospitals.[18] Clinical utility of ancillary diagnostic testing heavily relies on improving decision making and, consequently, patient health outcomes.[19] In absence of cure, a diagnosis may still impact health outcomes such as daily functioning or health care costs by facilitating improved disease management through the arrangement of formal or informal care that better aligns with a patient's individual needs. In this study, we investigate whether patients who received a dementia diagnosis in a hospital and underwent an ancillary diagnostic test have a different outcome compared with those diagnosed without that specific ancillary test. We aim to go beyond the point of diagnostic accuracy and focus on a pragmatic clinical outcome; how long is a patient able to live at home following a diagnosis of dementia and is this altered by using ancillary tests?

## Methods

### *Study Design and Participants*

We performed a nationwide register-based cohort study on all patients who received a new diagnosis of all-cause dementia in a Dutch hospital in 2018. We used data from the Dutch national health care insurance declaration database (Vektis).[20] In the Netherlands, having health care insurance is mandatory and as a result >99.8% of the population in 2018 was insured for health care costs and is hence included in this database.[21] The cohort included all patients aged >40 years who were newly diagnosed with dementia in the Netherlands in 2018 in a hospital setting, based on (a combination of) health care insurance declarations validated by Vektis for the presence of all-cause dementia.[20] In the Dutch health care system, each new diagnosis is registered for insurance reimbursement purposes.[22] Patients were included in our cohort if they received a dementia diagnosis registered by a neurologist or, alternatively, by a geriatrician, internal medicine specialist, or psychiatrist. In the latter cases, patients had to fulfill a second criterion, which included having declarations for psychogeriatric nursing care, declarations under the long-term care act with a dementia-related care package, or the use of pharmaceuticals exclusively indicated for dementia (ie, galantamine, memantine, rivastigmine, and donepezil). This combination rule to establish the dementia population in the Netherlands is based on a report from the Dutch national statistics office (CBS) to enhance validity of the diagnostic categorization.[23] The methodology is in line with Eurostat Morbidity Statistics, an initiative to collect nationally representative, internationally comparable diagnosis-based information on morbidity for the European Union.[24] Although health care declaration data can indicate the presence of all-cause dementia, it does not allow for accurate nosological diagnoses.

According to Dutch guidelines, a diagnosis of dementia is always based on patient history, informant reports, and objective cognitive testing. Ancillary testing occurs on indication.[25] We compared patients who underwent a specific diagnostic test during the diagnostic trajectory (cases) to patients who did not receive that specific diagnostic test (controls). We also contrasted patients receiving an extensive battery of tests (4 or 5) to patients subjected to restrictive diagnostic testing with none or only 1 ancillary test. Controls were propensity score matched for age, sex, type of hospital, and comorbidity. Type of hospital was operationalized as academic, teaching, or general. Burden of comorbidity was operationalized using pharmacy-based cost group (PCG), which categorizes medication per somatic chronic disease indication and serves as an indicator for the presence of comorbidities.[26] This categorization system is used for risk adjustment by the Dutch health care insurance sector. PCGs are ordinally categorized as 0, 1, 2, or ≥3, reflecting an increasing burden of chronic disease (Supplementary Material 1).

### *Exposure and Outcome*

Exposure of interest was the use of an ancillary test during the diagnostic phase in the years before the diagnosis of dementia: between January 1, 2015, and December 31, 2018 (Supplementary Figure 1). For reimbursement purposes, all health care activities related to diagnosing dementia are defined by the Dutch Healthcare Authority (agency of the Dutch Ministry of Health, Welfare and Sport). To facilitate analysis, 2 experienced neurologists clustered all diagnostic activities in 5 subgroups: (1) structural imaging of the brain using CT or MRI (CT/MRI), (2) neuropsychological examination (NPE), (3) imaging of the brain function using PET or SPECT (PET/SPECT), (4) electroencephalography (EEG), and (5) CSF testing.

We tracked the occurrence of institutionalization or death and health care costs per month alive between January 1, 2018, and December 31, 2021. Primary outcome measure was time to poor outcome, defined as institutionalization in a long-term care facility or death, whichever came first. We expressed the results as median time to poor outcome, referring to the moment at which 50% of the population had experienced the outcome. We also analyzed these 2 poor outcomes separately. Secondary outcome measures were total mean health care costs per month, mean total pharmaceutical costs per month, and mean costs per month for cholinesterase inhibitors (ChEIs). Total mean health care costs were operationalized as direct health care costs, which entails the expenses attributable to medical interventions, treatments, pharmaceuticals, and associated elements, such as hospitalization, clinical consultations, long-term care, and diagnostic assessments based on reimbursement by health care insurances.

### *Statistical Analysis*

We used Kaplan-Meier survival analysis to compare the occurrence of poor outcome between cases and controls during the follow-up period. Time to institutionalization and time to death were examined both separately and as a combined outcome. For mean total pharmaceutical, mean ChEIs, and mean health care costs, we used Welch 2-sample *t* tests. Matching was performed using the matchit package in R. We used a nearest neighbor matching, with a caliper width of 0.2 SD without replacement technique, based on propensity scores using logistic regression.[27] We used a variable control to case ratio with a minimum ratio depending on the number of available cases and a maximum of 3:1 ratio to ensure optimal reduction in bias and maximal gain in precision.[28,29] Statistical analysis was conducted using R, version 4.1.3.

## Results

In 2018, a total of 13,312 patients received a new diagnosis of dementia in a Dutch hospital. The majority were female (51.9%) and the mean age at diagnosis was 77.3 years (SD 8.2), of whom 6.9% were aged <65 years. Comorbidities were present in 73.9% of the population, with 14.1% in the highest ordinal category of medication costs (Table 1). Ancillary testing was performed in 85.6% of the population

**Table 1**
Baseline Characteristics of Total Population and Cases and Controls

| | | CT/MRI[†] | | NPE | | EEG | | CSF | | PET/SPECT | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total population | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| | (N = 13,312) | (n = 7635) | (n = 2545) | (n = 5392) | (n = 5392) | (n = 1018) | (n = 3054) | (n = 541) | (n = 1623) | (n = 1016) | (n = 3048) |
| Female, n (%) | 6911 (51.9) | 4306 (56.4) | 1547 (60.8) | 2655 (49.2) | 2690 (49.9) | 366 (36.0) | 1091 (35.7) | 243 (44.9) | 685 (42.2) | 434 (42.7) | 1282 (42.1) |
| Age, y, mean | 77.3 | 79.5 | 80.7 | 75.2 | 76.1 | 71.8 | 72.0 | 67.9 | 67.8 | 74.3 | 74.4 |
| Hospital, n (%) | | | | | | | | | | | |
| General | 5825 (43.8) | 3196 (41.9) | 1024 (40.2) | 2475 (45.8) | 2469 (45.9) | 452 (44.4) | 1413 (46.3) | 211 (39.0) | 665 (40.1) | 376 (37.0) | 1138 (37.3) |
| Teaching | 6745 (50.7) | 3990 (52.3) | 1366 (53.7) | 2682 (49.7) | 2677 (49.7) | 498 (48.9) | 1467 (48.0) | 275 (50.8) | 840 (51.8) | 570 (56.1) | 1724 (56.6) |
| Academic | 742 (5.6) | 449 (5.9) | 155 (6.1) | 235 (4.4) | 246 (4.6) | 68 (6.7) | 174 (5.7) | 55 (10.2) | 118 (7.3) | 70 (6.9) | 186 (6.1) |
| Comorbidity operationalized as PCG[*], n (%) | | | | | | | | | | | |
| 0 | 3468 (26.1) | 1832 (24.0) | 635 (25.0) | 1461 (27.1) | 1391 (25.8) | 241 (23.7) | 694 (23.7) | 208 (38.4) | 587 (36.2) | 218 (21.5) | 615 (20.2) |
| 1 | 4487 (33.7) | 2592 (33.9) | 859 (33.8) | 1810 (33.6) | 1814 (33.6) | 286 (28.1) | 901 (29.5) | 169 (31.2) | 527 (32.5) | 273 (26.9) | 834 (27.4) |
| 2 | 3480 (26.1) | 2121 (27.8) | 700 (27.5) | 1369 (25.4) | 1463 (27.1) | 282 (27.7) | 892 (29.2) | 106 (19.6) | 336 (20.7) | 271 (26.7) | 891 (29.2) |
| ≥3 | 1877 (14.1) | 1090 (14.3) | 351 (13.8) | 752 (13.9) | 724 (13.4) | 209 (20.5) | 567 (18.6) | 58 (10.7) | 173 (10.7) | 254 (25.0) | 708 (23.2) |

[*]PCG, pharmacy-based cost group (a proxy for burden of comorbidity, a higher number indicates a higher burden of comorbidity).
[†]A total of 10,767 patients received CT/MRI, but only 7635 were included as cases in the analysis, because of a maximum case-control ratio of 3:1. Cases were patients with an ancillary test and controls were patients without that specific test. We used a variable case-control ratio.

during the diagnostic phase of dementia. The most commonly used diagnostic test was CT/MRI (80.9%), followed by NPE (40.5%), PET/SPECT and EEG (both 7.6%), and CSF testing (4.1%). Between January 2018 and December 2021, more than half of those who were diagnosed with dementia in 2018 experienced a poor outcome (54.6%), of whom 40.1% were living in an institution, 32.3% died in an institution and 26.7% died at home.

Time to poor outcome in those who underwent CT/MRI, EEG, or CSF testing was not different from respective controls (Figure 1A, C, and D). For CT/MRI and CSF testing, this was consistent with both time to institutionalization and time to death (Supplementary Figure 2A, D, F, and I). For patients exposed to EEG, we did find a lower risk of institutionalization [relative risk (RR) 0.86, 95% CI 0.77-0.96] but no difference in risk of death (Supplementary Figure 2C and H). Patients subjected to an NPE had a lower risk of experiencing a poor outcome during the follow-up period compared with controls (RR 0.85, 95% CI 0.82-0.88). Median time to poor outcome was 3.1 years (or 1129 days, 95% CI 1102-1161) in matched patients that were not subjected to NPE as compared to a median time to poor outcome of 3.7 years (or 1367 days, 95% CI 1333-1407) in patients who underwent NPE (Figure 1, B). This result was consistent when the outcome was analyzed separately for time to institutionalization and death. Patients who underwent PET/SPECT during the diagnostic phase had a higher risk of experiencing a poor outcome (RR 1.09, 95% CI 1.02-1.17). Median time to poor outcome was 3.2 years (or 1157 days, 95% CI 1090-1261) for patients receiving a PET/SPECT and 3.5 year (or 1274 days, 95% CI 1218-1341) for control patients that did not (Figure 1, E). When analyzed separately, patients who underwent a PET/SPECT had a higher risk of death (RR 1.55, 95% CI 1.40-1.71) but no differences in risk of institutionalization (Supplementary Figure 2E and J). Patients exposed to a combination of diagnostic tests did not have a different time to poor outcome as compared to patients receiving none or only 1 diagnostic test (Supplementary Figure 3).

Total health care costs in those who underwent CT/MRI or EEG did not differ from those who did not (Table 2). NPE as compared to no NPE during the diagnostic trajectory was associated with significantly lower total health care costs per month (difference in mean costs −€127, 95% CI −61 to −193). Significantly higher total health care costs per month were found in patients who underwent CSF testing (difference in mean costs = €248, 95% CI 64-433) or PET/SPECT (difference in mean costs €315, 95% CI 179-451). Mean total pharmaceutical costs per month were comparable for most groups but higher in patients who underwent PET/SPECT as compared to controls (difference in mean costs €15, 95% CI 8-22) (Table 2). The costs for ChEIs per month were significantly higher for patients receiving CT/MRI, CSF testing, and PET/SPECT, but not for patients receiving NPE or EEG (CT/MRI difference in mean costs €0.52, 95% CI 0.33-0.70; CSF testing difference in mean costs €1.40, 95% CI 0.76-2.04; PET/SPECT difference in mean costs €0.64, 95% CI 0.21-1.06) (Table 2).

## Discussion

Patients with dementia who underwent ancillary investigations including neuroimaging (CT, MRI, SPET, or PET), CSF testing, or EEG examination during the diagnostic phase did not have a different time to poor outcome. Those who underwent PET/SPECT had a shorter time to poor outcome as compared to controls. Undergoing an NPE during the diagnostic phase was associated with a longer time to poor outcome. Total mean health care costs were higher for patients undergoing CSF testing or PET/SPECT scanning. Conversely, patients with an NPE during the diagnostic workup generated lower total mean health care costs. Pharmaceutical costs were similar for most case-control comparisons, only patients with a PET/SPECT scan had higher mean pharmaceutical costs. The fact that many patients did not experience a disadvantageous outcome when dementia was diagnosed without the use of imaging or CSF biomarker corroborates the hypothesis that these tests may not benefit patients with regard to time to institutionalization or death.

Strengths of this study are the large number of patients included, the population-based design, and the complete and long-term follow-up for our outcomes. Our study is based on health care insurance reimbursement data and due to almost complete coverage of the Dutch health care insurance system,[21] the effects of selection bias and loss to follow-up are negligible. However, our study has several limitations. Privacy legislation in the Netherlands prohibited coupling of reimbursement data with specific clinical characteristics, including symptom severity at time of diagnosis. In particular, results with respect to NPE may be influenced by confounding by indication, that is, those in whom NPE is ordered may be in earlier stages of dementia compared with those in whom NPE is not deemed necessary, despite matching for age, sex, type of hospital, and comorbidity.[30] PET/SPECT scanning is mostly used to distinguish between possible cases of frontotemporal dementia or dementia with Lewy bodies and Alzheimer dementia. Frontotemporal dementia and dementia with Lewy bodies typically have a more progressive disease course, more disability and associated costs, and a shorter median survival than AD.[31–34] In a nationwide study, based on health insurance data, potentially relevant questions relating to clinical details remain necessarily unanswered. A second limitation is that the accuracy of identified dementia cases with routinely collected health data varies

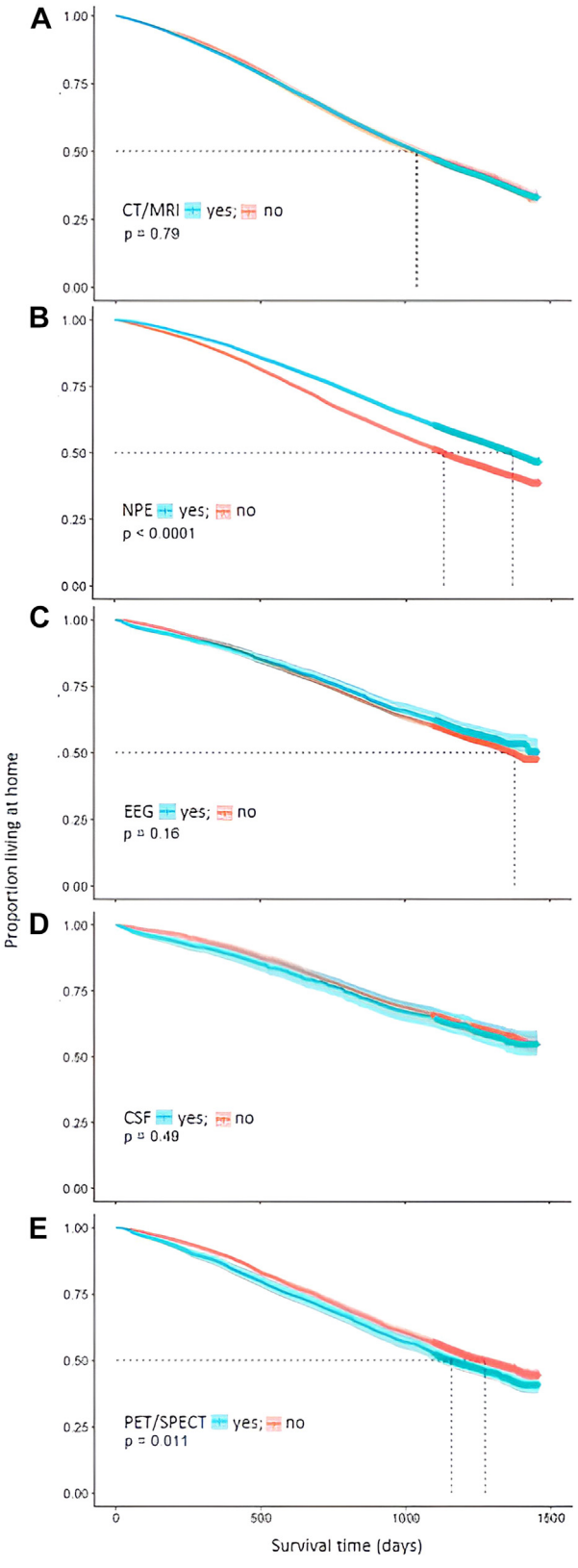



**Fig. 1.** Kaplan-Meier analysis of time to poor outcome (institutionalization or death) in patients receiving an ancillary testing as compared to matched controls. (A) CT/MRI vs controls, (B) NPE vs controls, (C) EEG vs controls, (D) CSF vs controls, (E) PET/SPECT vs controls.

per setting and data source.[35] However, an American study showed that insurance claim data perform relatively well, with a sensitivity of 85% and specificity 89% for all cause dementia.[36]

These results underscore the pivotal role of the clinical examination, which is supported by most guidelines. In a systematic review from 2015 on dementia practice guidelines, only 9 of 39 guidelines recommended to perform structural imaging in a specialist care setting.[1] Main argument for the use of neuroimaging or other biomarker tests during the diagnostic phase of dementia is ruling out of reversible causes of dementia and facilitating an early diagnosis. However, actual reversal of dementia is extremely rare (<<1%).[37,38] Moreover, use of diagnostic testing is not without drawbacks. Hospital visits to undergo testing can be burdensome for older patients and the use of biomarkers have potential side effects, including adverse procedural events[39] and the consequences of false positive test results or incidental findings.[40] The rationale behind striving for an "early" diagnosis is the suggestion that it could delay institutionalization by optimizing care and support in the home setting in order for patients to be able to stay at home.[41] This was not confirmed by our findings, although other studies presented conflicting results. A recent non-randomized study compared time to institutionalization or death and health care costs in 2 groups of relatively young patients referred to a tertiary memory clinic, in which the intervention group underwent an amyloid PET scan to facilitate a more precise diagnosis as compared to a propensity score–matched control group.[42] They reported a lower hazard of poor outcome in patients who underwent amyloid PET (hazard ratio 0.54, 95% CI 0.40-0.73). These disparate results are likely attributable to a much younger study population, showing that the clinical utility of amyloid PET may be higher in rare young-onset dementia cases. Another population-based study found a higher rate of institutionalization among patients that consulted a specialist early in the disease course (hazard ratio 2.00, 95% CI 1.09-3.64).[43] However, if more efficacious disease-modifying therapies for Alzheimer disease may become available in the future, this could have an impact on diagnostic procedures.

Our secondary outcome was health care costs. Worldwide, total dementia-related costs are estimated to be around 1% of the global gross domestic product, and 0.65% if informal care costs are excluded.[44] Institutionalization is the main cost driver in dementia care, with on average threefold higher costs for the population living in a long-term care facility. In contrast, in the community-based population, the main cost drivers are pharmaceutical costs and nonmedical support.[45] The use of ancillary testing could influence health care costs in 2 ways. First, by influencing time to institutionalization: an early diagnosis could provide an opportunity for timely interventions to support (in)formal care at home and hence postpone institutionalization. However, as discussed, literature is inconclusive on this part.[42,43] Second, undergoing ancillary testing contributes to health care costs: especially in low- and middle-income countries, direct medical costs add substantially to total health care costs.[44] Critical evaluation of the indication for ancillary testing could contribute to curtailing global dementia costs.

Our study was designed based on the principle that the purpose of diagnostic testing goes beyond an accurate diagnosis. A diagnostic test or procedure should also lead to a measurable improvement of patient's health outcomes to have clinical utility.[13,19] In absence of convincing disease-modifying treatments for dementia, clinical utility of ancillary investigations to facilitate (early) diagnosis is up for debate. Aside from offering treatment options, a diagnosis could influence the outcome for a patient on other levels. For some patients, diagnosis can end the uncertainty of experiencing complaints and facilitate advance care planning. For others, receiving a diagnosis of a

**Table 2**
Health Care Costs per Month in Euros

| | Total Population | CT/MRI | | NPE | | EEG | | CSF | | PET/SPECT | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Total health care costs | 1893 | 2046 | 2017 | 1711† | 1838 | 1826 | 1689 | 1696† | 1448 | 2105† | 1789 |
| Pharmaceutical costs | 45 | 45 | 43 | 45 | 44 | 54 | 51 | 41 | 44 | 69† | 54 |
| Cholinesterase inhibitors costs | 1.76 | 1.73† | 1.22 | 1.92 | 1.83 | 2.13 | 1.86 | 3.22* | 1.83 | 2.38† | 1.73 |

Cases were patients with an ancillary test and controls were patients without that specific test.
*$P < .01$.
†$P < .001$.

progressive disease for which no treatments exist may cause emotional distress and anxiety. Individual patient preferences and the previously mentioned considerations should all be taken into account when finding the right timing for diagnosis.[7,46,47]

The lack of convincing evidence in favor of ancillary testing for dementia diagnosis, confirmed by our study findings, supports guideline recommendations for a strong emphasis on a clinical diagnostic workup in primary care. This may not only decrease diagnostic burden for the individual patient but, in light of the expected global increase in dementia prevalence,[48] facilitate efficient use of specialist diagnostic services.

## Conclusion and Implications

Patients with dementia who underwent ancillary investigations including neuroimaging (CT, MRI, SPECT, or PET), CSF testing, or EEG examinations during the diagnostic phase did not have a different time to poor outcome. Patients who underwent NPE testing had a slightly longer time to poor outcome, potentially due to confounding by indication. Health care expenses were higher in patients who underwent CSF testing or PET/SPECT scanning as part of the diagnostic workup for dementia. The already overburdened health care systems and society as a whole may benefit from reducing the number of ancillary investigations in dementia diagnostics, without harming patients and caregivers. To definitively answer the question if patients who were diagnosed using ancillary investigations fare better than those who were not, a randomized controlled diagnostic trial is required.[13,19]

## Disclosures

The authors declare no conflicts of interest.

## Acknowledgments

We would like to express our appreciation to Vektis for providing us access to their data.

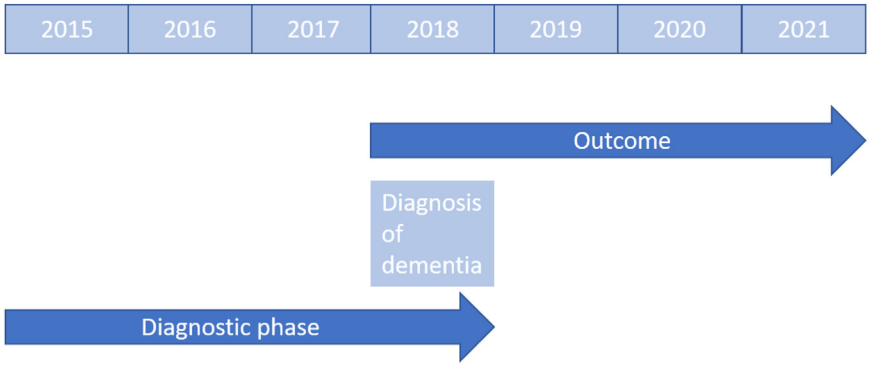
## References

1. Ngo J, Holroyd-Leduc JM. Systematic review of recent dementia practice guidelines. *Age Ageing*. 2015;44:25–33.
2. Pink J, O'Brien J, Robinson L, Longson D, Guideline C. Dementia: assessment, management and support: summary of updated NICE guidance. *BMJ*. 2018;361:k2438.
3. Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *Eur J Neurol*. 2012;19:1159–1179.
4. Elahi FM, Miller BL. A clinicopathological approach to the diagnosis of dementia. *Nat Rev Neurol*. 2017;13:457–476.
5. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:257–262.
6. Robinson L, Tang E, Taylor JP. Dementia: timely diagnosis and early intervention. *BMJ*. 2015;350:h3029.
7. Dhedhi SA, Swinglehurst D, Russell J. 'Timely' diagnosis of dementia: what does it mean? A narrative analysis of GPs' accounts. *BMJ Open*. 2014;4:e004439.
8. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease - lessons from pathology. *BMC Med*. 2014;12:206.
9. Brenowitz WD, Keene CD, Hawes SE, et al. Alzheimer's disease neuropathologic change, Lewy body disease, and vascular brain injury in clinic-and community-based samples. *Neurobiol Aging*. 2017;53:83–92.
10. Lecanemab for Alzheimer's disease: tempering hype and hope. *Lancet*. 2022;400:1899.
11. Golde TE. Disease-modifying therapies for Alzheimer's disease: more questions than answers. *Neurotherapeutics*. 2022;19:209–227.
12. Kaur U, Reddy J, Tiwari A, Chakrabarti S, Chakrabarti SS. Lecanemab: more questions than answers. *Clin Drug Invest*. 2024;44:1–10.
13. Kennedy AG. Evaluating the effectiveness of diagnostic tests. *JAMA*. 2022;327:1335–1336.
14. Agarwal D, Marques G, de la Torre-Díez I, Martin MFA, Zapiraín BG, Rodríguez FM. Transfer learning for Alzheimer's disease through neuroimaging biomarkers: a systematic review. *Sensors (Basel)*. 2021;21:7259.
15. Blennow K, Zetterberg H. Fluid biomarker-based molecular phenotyping of Alzheimer's disease patients in research and clinical settings. *Prog Mol Biol Transl*. 2019;168:3–23.
16. Rossini PM, Di Iorio R, Vecchio F, et al. Early diagnosis of Alzheimer's disease: the role of biomarkers including advanced EEG signal analysis. Report from the IFCN-sponsored panel of experts. *Clin Neurophysiol*. 2020;131:1287–1310.
17. Gruters AAA, Ramakers IHGB, Kessels RPC, et al. Development of memory clinics in The Netherlands over the last 20 years. *Int J Geriatr Psych*. 2019;34:1267–1274.
18. Hafdi M, Richard E, van Gool SE, Moll van Charante EP, van Gool WA. Practice variation in diagnostic testing for dementia; a nation-wide overview. *Ned Tijdschr Geneeskd*. 2021;165:D5315.
19. Gluud C, Gluud LL. Evidence based diagnostics. *BMJ*. 2005;330:724–726.
20. Vektis, Recalibration method determination dementia population. Accessed March 18, 2023. https://www.vektis.nl/herijking-methode-bepaling-dementie populatie
21. Dutch Ministry of Health Welfare and Sport, VWS - healthcare insurance monitor. Accessed March 18, 2023. https://open.overheid.nl/repository/ronl-9345b4f6-22a5-42ff-b5a8-cb7e973554ae/1/pdf/verzekerdenmonitor-2021.pdf
22. Oostenbrink JB, Rutten FFH. Cost assessment and price setting of inpatient care in The Netherlands. The DBC case-mix system. *Health Care Manag Sci*. 2006;9:287–294.
23. Voorrips L, van Oers F. Eurostat morbidity statistics pilot data collection. The Netherlands. Accessed March 18, 2023. https://www.cbs.nl/en-gb/background/2020/44/eurostat-morbidity-statistics-pilot-data-collection
24. Voorrips L, van Oers F. *Eurostat Morbidity Statistics Pilot Data Collection*. the Netherlands: European Union; 2020.
25. Olde Rikkert MG, van Exel E, Knol W, Lemstra AW, Roks G, Verhey FR. Richtlijn diagnostiek en behandeling van dementie [Diagnostic guideline and treatment of dementia]. *Ned Tijdschr Geneeskd*. 2015;159:A8671. Dutch. PMID: 25873222.Geriatrics Dsoc, Guideline Diagnosis and Treatment of Dementia, 2014.
26. Lamers LM, van Vliet RC. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. *Health Pol*. 2004;68:113–121.
27. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–161.
28. Ming KW, Rosenbaum PR. Substantial gains in bias reduction from matching with a variable number of controls. *Biometrics*. 2000;56:118–124.
29. Rosenbaum PR. Modern algorithms for matching in observational studies. *Annu Rev Stat Appl*. 2020;7:143–176.
30. Jacova C, Kertesz A, Blair M, Fisk JD, Feldman HH. Neuropsychological testing and assessment for dementia. *Alzheimer's Dementia*. 2007;3:299–317.
31. Boeve BF, Boxer AL, Kumfor F, Pijnenburg Y, Rohrer JD. Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations. *Lancet Neurol*. 2022;21:258–272.
32. Davison CM, O'Brien JT. A comparison of FDG-PET and blood flow SPECT in the diagnosis of neurodegenerative dementias: a systematic review. *Int J Geriatr Psychiatry*. 2014;29:551–561.
33. Liang CS, Li DJ, Yang FC, et al. Mortality rates in Alzheimer's disease and non-Alzheimer's dementias: a systematic review and meta-analysis. *Lancet Healthy Longev*. 2021;2:e479–e488.

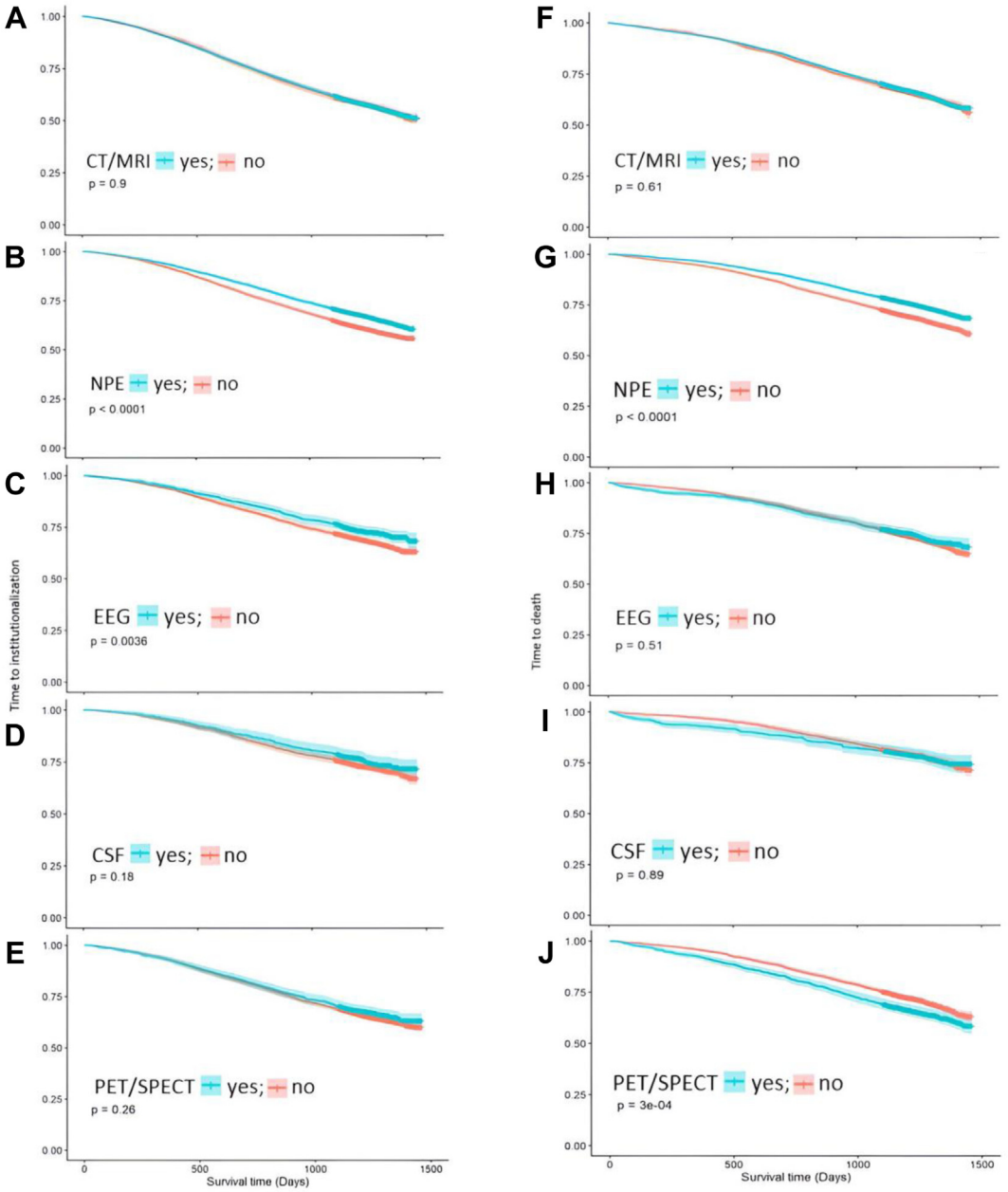
34. Maclin JMA, Wang T, Xiao S. Biomarkers for the diagnosis of Alzheimer's disease, dementia Lewy body, frontotemporal dementia and vascular dementia. *Gen Psychiatr*. 2019;32:e100054.
35. Wilkinson T, Ly A, Schnier C, et al. Identifying dementia cases with routinely collected health data: a systematic review. *Alzheimer's Dementia*. 2018;14:1038–1051.
36. Taylor DH, Ostbye T, Langa KM, Weir D, Plassman BL. The accuracy of medicare claims as an epidemiological tool: the case of dementia revisited. *J Alzheim Dis*. 2009;17:807–815.
37. Clarfield AM. The decreasing prevalence of reversible dementias - an updated meta-analysis. *Arch Intern Med*. 2003;163:2219–2229.
38. Walstra GJ, Teunisse S, van Gool WA, van Crevel H. Reversible dementia in elderly patients referred to a memory clinic. *J Neurol*. 1997;244:17–22.
39. Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: results of the multicenter lumbar puncture feasibility study. *Alzheimer's Dementia*. 2016;12:154–163.
40. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med*. 2007;357:1821–1828.
41. de Vugt ME, Verhey FR. The impact of early dementia diagnosis and intervention on informal caregivers. *Prog Neurobiol*. 2013;110:54–62.
42. van Maurik IS, Broulikova HM, Mank A, et al. A more precise diagnosis by means of amyloid PET contributes to delayed institutionalization, lower mortality, and reduced care costs in a tertiary memory clinic setting. *Alzheimers Dement*. 2023;19:2006–2013.
43. Pimouguet C, Le-Goff M, Rizzuto D, et al. Effect of early referral to specialist in dementia on institutionalization and functional decline: findings from a population-based study. *J Alzheimers Dis*. 2016;49:819–828.
44. Wimo A, Guerchet M, Ali GC, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement*. 2017;13:1–7.
45. Schaller S, Mauskopf J, Kriza C, Wahlster P, Kolominsky-Rabas PL. The main cost drivers in dementia: a systematic review. *Int J Geriatr Psych*. 2015;30:111–129.
46. Brayne C, Kelly S. Against the stream: early diagnosis of dementia, is it so desirable? *BJPsych Bull*. 2019;43:123–125.
47. Linden I, Hevink M, Wolfs C, Perry M, Dirksen C, Ponds R. Understanding patients' and significant others' preferences on starting a diagnostic trajectory for dementia: an integrative review. *Aging Ment Health*. 2022;27:862–875.
48. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7:e105–e125.

**Supplementary Material 1: Pharmacy-Based Cost Group (PCG).**

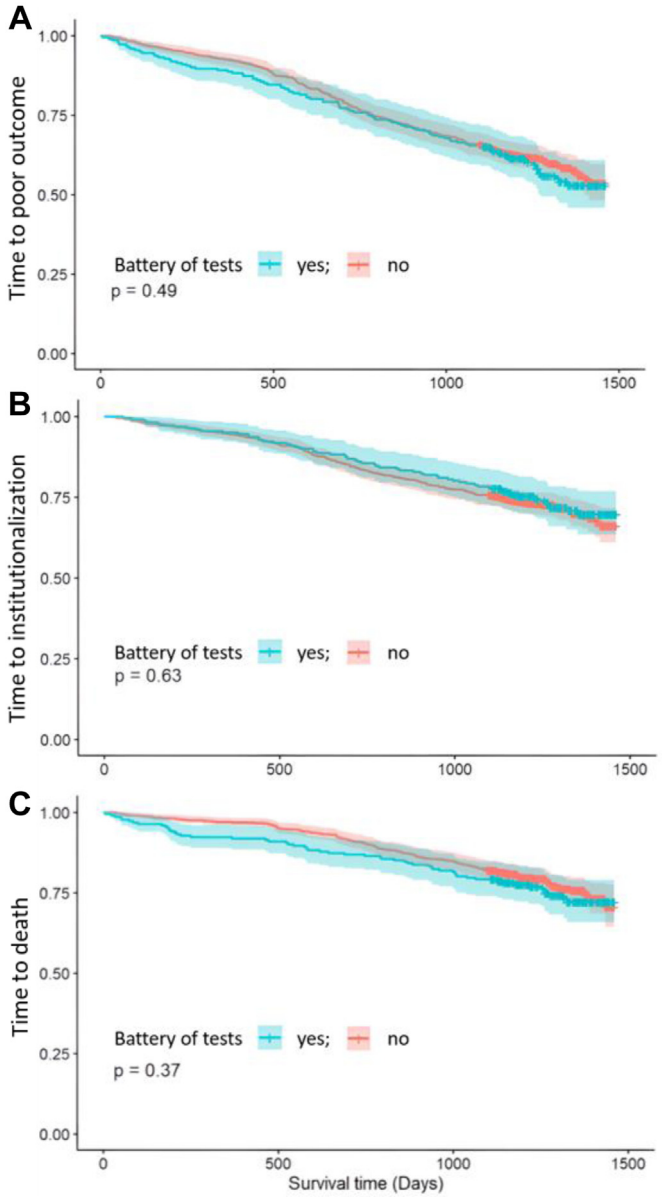
This is a model used in the Dutch health care insurance sector since 2002 for risk-adjusted capitation.[1] Pharmaceuticals prescribed to an individual for more than 6 months in the base year are regarded as markers of an associated chronic condition in that year. PCGs used in this study include only somatic conditions. It is shown that PCGs are good predictors for future direct health care costs.[2] Somatic PCGs in this model include diabetes, cardiovascular, autoimmune, kidney, respiratory, and oncologic diseases.




**Supplementary Figure 1.** Timeline of study. Diagnostic phase between January 2015 and December 2018, diagnosis of dementia between January and December 2018, outcome between January 2018 and December 2021.




**Supplementary Figure 2.** Kaplan-Meier analysis separated for time to institutionalization (left) and time to death (right) in patients receiving diagnostic testing as compared to controls: (A) CT/MRI vs controls, (B) NPE vs controls, (C) EEG vs controls, (D) CSF testing vs controls, (E) PET/SPECT vs controls, (F) CT/MRI vs controls, (G) NPE vs controls, (H) EEG vs controls, (I) CSF testing vs controls, (J) PET/SPECT vs controls.




**Supplementary Figure 3.** Kaplan-Meier analysis comparing patients receiving a battery of tests (4 or 5) to controls receiving none or just 1 test for (A) time to poor outcome, (B) time to institutionalization, and (C) time to death.

## References

1. Lamers LM, van Vliet RC. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. *Health Pol*. 2004;68:113–121.
2. Lamers LM. Pharmacy costs groups - a risk-adjuster for capitation payments based on the use of prescribed drugs. *Med Care*. 1999;37:824–830.