# The Impact of Amyloid PET Disclosure on Quality of Life in Patients With Young Onset Dementia

# The Impact of Amyloid PET Disclosure on Quality of Life in Patients With Young Onset Dementia

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**Introduction:** The impact of amyloid positron emission tomography (PET) imaging on patient health outcomes for individuals with dementia is unknown. In the present study, we explored the association between diagnostic outcome and clinician's level of certainty with quality of life (QoL) after [$^{18}$F]flutemetamol PET results were disclosed in young onset dementia patients in a memory clinic cohort.

**Methods:** In 154 patients suspected of dementia, QoL was measured before and after [$^{18}$F]flutemetamol PET results were disclosed. Multiple regression analyses were conducted with (changed) general and disease-specific QoL measures as dependent factors [QoL-Alzheimer disease (AD) and EQ-5D Dutch tariff] and etiological diagnosis and clinician's certainty as independent factors.

**Results:** (Change in) diagnosis of AD was associated to QOL in 2 of the 4 analyses (utility-based QoL $\beta = 0.15$, $P = 0.010$; disease-specific QoL $\beta = 2.0$, $P = 0.037$). Diagnostic certainty was associated to QOL in 1 of the 4 analyses (generic QoL $\beta = 0.002$, $P = 0.028$).

**Discussion:** The diverse results in this explorative analysis do not reflect a univocal association between diagnosis, certainty, and QoL. Nevertheless, this result could be interpreted as a possible potential for advanced diagnostic technologies for AD, which requires confirmation in future research.

**Key Words:** Alzheimer disease, diagnosis, diagnostic certainty, quality of life, amyloid PET

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Worldwide, care systems are challenged with an increasing prevalence of dementia.[1] At the moment, no cure is available for its etiological causes including the most frequent cause of Alzheimer disease (AD).[2] In 2015, the number of people with dementia worldwide was estimated at 46.8 million, it is expected that this will increase to 74.7 million by 2030.[1] Dementia leads to a loss of independence, functional decline, psychological and behavioral symptoms, diminished quality of life (QoL), caregiver burden, and high levels of health care utilization.[3]

The importance of an early diagnosis of dementia in a mild stage is stressed by international Alzheimer Societies.[4] The National Institute on Aging and the Alzheimer's Association (NIA-AA) revised the diagnostic criteria by inclusion of biomarker enhancements in magnetic resonance imaging, cerebrospinal fluid, and positron emission tomography (PET) for research purposes.[5,6] Appropriate use criteria for amyloid (PET) imaging describe the application for individuals with: (1) a cognitive complaint with objectively confirmed impairment; (2) a possible but uncertain diagnosis of AD after comprehensive evaluation; and (3) an expected increase of diagnostic certainty and change in management after obtaining knowledge on the presence or absence of amyloid-beta pathology.[7] Whether (advanced) diagnostic testing has a positive effect in terms of improved patients' health or well-being is debated.[8–10] Diagnostic testing in general could potentially affect emotional, social, cognitive and behavioral outcomes, and care planning[11,12] Specifically for AD various potential positive (enable preparations for future care, address questions concerning cognitive and functional decline) and negative (stigmatization, anxiety, and uncertainty) effects of (early) diagnostic testing have been discussed.[13] A review by Paulsen et al[14] indicated that such effects could impact a person's QoL. They identified studies that reported no significant negative psychological reactions, testing was considered beneficial, no significant adverse events and no feelings of discrimination. However, none of the included studies examined the association between QoL, and a clinician's certainty of a diagnosis (ie, the clinician's subjective rating of the certainty of the correctness of the patient's etiology), and the diagnostic tests mainly reflected predictive testing for familiar AD using genetic markers rather than advanced diagnostic testing. Such evidence is considered important to explore in what way early AD testing could potentially contribute to improved health.[11] This could support determining its clinical utility and feed discussions on reimbursement decision making.

This study aimed to explore the association between the diagnosis and the clinician's level of certainty of diagnosis with generic and disease-specific QoL instruments in young onset dementia patients.

## METHODS

This research is part of The Dutch Flutemetamol study, a prospective dual-center cohort study held in the Alzheimer centers of the VU University Medical Center (VUmc) and the Maastricht University Medical Center+ (MUMC+).[15] The study aimed to investigate the clinical value of the PET tracer [$^{18}$F]flutemetamol. According to data collection framework of the Dutch String of Pearls Initiative,[16,17] 211 participants were enrolled and screened. Inclusion criteria were: suspected of dementia for whom, after routine workup, no firm diagnosis could be made or diagnostic uncertainty persisted (operationalized as a clinician rating the diagnostic certainty regarding etiology before [$^{18}$F]flutemetamol PET between 50% to 90% on a visual analog scale ranging from 0 to 100[18]), mentally competent [Mini-Mental State Examination (MMSE) $\geq$18] and a participating informal caregiver were included (see eligibility criteria in supporting information S1 Table, Supplemental Digital Content 1, http://links.lww.com/WAD/A370).

Subjects were excluded because of missing data on QoL at baseline or 3 months follow-up because of admission to a nursing home (n = 2), death (n = 1), unwilling to further participate (n = 7) or another reason (n = 47), which left 154 (73%) participants for analyses. Secondary analyses were based on the complete cases (n = 128) and on imputed data on clinical dementia rating (CDR)-based subgroups (CDR = 0.5 n = 92, CDR $\geq$ 1.0 n = 62).

The Flutemetamol study was approved according to the Declaration of Helsinki by the ethics committee of the VUmc and written informed consent was obtained before inclusion.

### Clinical Data

Patient sociodemographic characteristics were obtained from data on age, sex, educational level, and family history of dementia.

Clinical data were collected by clinical examinations and questionnaires at baseline, and at scheduled follow-up visits after 3 months from 2012 to 2016. Global cognitive function was assessed with MMSE. Behavioral disturbances were measured using the full version of the neuropsychiatric inventory (NPI), based on frequency and severity (mild, moderate, and severe) of 12 important symptoms. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (GDS-15), range 0 to 15, with a score $>5$ indicative of depression. The Disability Assessment for Dementia (DAD) was used to evaluate basic and instrumental activities in daily activities. The Charlson Comorbidity Index, reflects comorbidities and was rated by a researcher using information from the medical records. See Dutch String of Pearls Initiative for details.[16,17]

### Diagnosis and Certainty

Before and after participants went through the full diagnostic process, including the [$^{18}$F]flutemetamol PET scan, a clinician determined the most likely diagnosis (classified as AD, Vascular dementia, Frontotemporal, Lewy Bodies, other neurodegenerative disease, no neurodegenerative disease, and unclear/postponed) and the level of certainty of the diagnosis (rated on a visual analog scale ranged from 0% to 100%). The final diagnosis, which was set after participant had received a [$^{18}$F]flutemetamol PET scan as part of the diagnostic process, was communicated to the participant about approximately half a month after the baseline assessment.

### QoL Instruments

QoL data were collected at baseline (before disclosing the [$^{18}$F]flutemetamol PET-based diagnosis) and at 3-month follow-up (after disclosing the [$^{18}$F]flutemetamol PET-based diagnosis). Two QoL instruments were administered by the informal caregiver as a proxy, Quality of Life-Alzheimer's Disease (QOL-AD) and the EuroQoL EQ-5D's 5-level (EQ-5D) in combination with the Dutch tariff. The QOL-AD is a 13 items questionnaire with 4-point multiple choice options (1 = poor, 4 = excellent), which evaluates the domains of interpersonal relationships, financial difficulties, physical condition, memory, mood, and overall health.[19] An improvement of 3 points on the QOL-AD was considered a clinically relevant improvement of QoL[20] on a scale ranging from 13 (worse QoL) to 52 (best QoL). The EQ-5D-3L contains five domains: mobility, self-care, pain/discomfort, usual activities, and anxiety/depression.[21,22] In order to make the EQ-5D-3L suitable for use in economic evaluations, the health states were valued by Lamers et al.[23] The Dutch tariff represents the preferences of the Dutch population and can be used to estimate the impact of health care interventions on QoL. The scale ranges from worse possible health state (−0.33) to best possible health state (0.93).

### Analyses

Missing data on covariates and QoL were imputed by multiple imputation using the software program Stata version 15, creating 10 imputed data sets. Missing values on QoL were only imputed if either the EQ-5D utility, VAS or QOL-AD was available, either at baseline or at 3 months follow-up.

In total, 4 multiple regression analysis were performed on generic and disease-specific QoL: (1) general, generic HRQoL, adjusted for potential confounders; (2) general, disease-specific QoL, adjusted for potential confounders; (3) [$^{18}$F]flutemetamol PET-specific, generic HRQoL, change scores; (4) [$^{18}$F]flutemetamol PET-specific disease-specific QoL, change scores.

In model 1 and 2, a multiple regression analysis was performed to estimate the effect of a diagnosis and its certainty on QoL, adjusted for potential confounders. First, possible confounding factors were selected if their association with QoL has been reported in previous research, if they were correlated to (certainty of the) post [$^{18}$F]flutemetamol PET diagnosis or to QoL at 3 months follow-up, or if they were considered a potential confounder by expert opinion. These included age,[24–27] sex,[26,28] education level,[26,27] MMSE,[28–31] GDS,[32,33] CDR,[25] and NPI.[24,29,31] Second, of this selection only those significant at $P<0.10$ in bivariate analysis to QoL at 3 months follow-up (education, DAD, NPI, GDS) were included in all the multiple regression analyses (see Results section, Table 3). Third, in an automated backward selection procedure only those who remained significantly associated to QoL 3 months after baseline were left in the multiple regression model. Fourth, the post [$^{18}$F]flutemetamol PET diagnosis and certainty of that diagnosis were added to this model.

In model 3 and 4, the change in QoL because of the [$^{18}$F]flutemetamol PET results was explored between baseline and 3 months follow-up. This was done in a multiple regression using change in QoL as dependent and both change in diagnosis as well as change in certainty of the diagnosis as independent factors.

In all 4 models the diagnosis and certainty of the diagnosis were forced entered into the model. Coefficients

and standard errors were adjusted for the variability between imputations according to the combination rules by Rubin.

A secondary analysis was based on cases with complete data on covariates and QoL to address the consistency of the results (n = 128), and CDR-based subgroups on imputed data (CDR = 0.5 n = 92, CDR ≥ 1.0 n = 62) for explorative purpose.

## RESULTS

Demographic and disease characteristics of the cohort at baseline are presented in Table 1. The participants had a mean age of 62 and about half was male (58%). The CDR represented very mild dementia (0.5) in 55%, mild dementia in 33% and moderate dementia in 4%. AD was with 101 cases the most occurring post [$^{18}$F]flutemetamol PET etiological diagnosis and 14 participants were diagnosed with other than a neurodegenerative disease. In 15 cases the post [$^{18}$F]flutemetamol PET etiological diagnosis was different from the pre [$^{18}$F]flutemetamol PET diagnosis (see Table 2). The mean clinician's level of certainty of the diagnosis after [$^{18}$F]flutemetamol PET was 89%. The mean QoL on the disease-specific instrument QoL-AD, at baseline and after 3 months follow-up (SD), was 33 (6). The mean (SD) score on the generic QoL instrument EQ-5D tariff changed from 0.74 (0.22) at baseline to 0.77 (0.20) at 3 months.

The first 2 multiple analyses only showed a significant effect of the diagnosis on the utility-based QoL after 3 months ($\beta = 0.15$, $P = 0.010$). Clinician's diagnostic certainty after [$^{18}$F]flutemetamol PET was not associated to QoL after 3 months (for both $\beta = -0.001$, $P = 0.967$, $P = 0.258$). Clinical symptoms in terms of function (DAD) and behavior (NPI and GDS) were significantly associated to both QoL instruments after 3 months (see Tables 3 and 4 for details).

The multiple regression analysis on change in QoL indicated a significant association ($\beta = 2.019$, $P = 0.037$) with change in diagnostic certainty only for the utility-based instrument and change in diagnosis only for the disease-specific instrument (Table 5). Results in presented table were based on multiple imputed data sets.

In total, diagnosis was significantly associated to QOL in 2 of the 4 analyses. Certainty was significantly associated to QOL in 1 of the 4 analyses.

The R2 (mean of the separate regressions on each of the imputed data sets) was 0.31, 0.26, 0.02, and 0.03 for the utility T3, QoL-AD T3, utility change, and QoL-AD change regression model, respectively.

Visual interpretation of the normality plots indicated a moderate to weak indication of normally distributed residual for both utility-based models. VIF was lower than 6, indicating no strong sign of multicollinearity.

In the sensitivity analysis on complete case analysis, none of the significance levels changed (Tables S2 and S3, Supplemental Digital Content 1, http://links.lww.com/WAD/A370).

In the post hoc CDR subgroup analyses part of the significance levels changed compared with the primary analyses. For the main predictors (ie, not considering the possible confounders) in the subgroups CDR = 0.5 and CDR ≥ 1, in model 1 (QoL-AD at 3 mo), diagnosis was not significant and clinician's diagnostic certainty was significant (Table S4, Supplemental Digital Content 1, http://links.lww.com/WAD/A370). In model 3 (QoL-AD change) change in diagnosis was not significant and change in certainty was significant (Table S6, Supplemental Digital Content 1, http://links.lww.com/WAD/A370); in the subgroup CDR ≥ 1 in model 2 (EQ-5D at 3 mo) etiology was not significant (Table S5, Supplemental Digital Content 1, http://links.lww.com/WAD/A370), in model 3 (QoL-AD

**TABLE 1.** Demographic and Disease Characteristics at Baseline (n = 154)

| Characteristic | Mean (SD) | N (%) | Missing, n (%) |
|---|---|---|---|
| Age | 62 (5.7) | | 0 |
| Female sex | | 65 (42) | 0 |
| High educational level | | 91 (59) | 1 (1) |
| Positive family history | | 71 (46) | 3 (2) |
| Charlson Comorbidity Index | | | 7 (5) |
| 0 points | | 103 (67) | |
| 1 or 2 points | | 40 (26) | |
| 3 or 4 points | | 4 (3) | |
| Clinician's certainty diagnosis pre-PET | 70 (12) | | 0 |
| Clinician's certainty diagnosis post-PET | 89 (14) | | 0 |
| MMSE [0-30] | 23.5 (3.4) | | 1 (1) |
| CDR [0-3] | | | 13 (8) |
| Score of 0.5 | | 84 (55) | |
| Score of 1 | | 51 (33) | |
| Score of 2 | | 6 (4) | |
| GDS < 4 depressive symptoms [0-15] | | 104 (74) | 13 (8.4) |
| DAD [0-100] | 82 (17) | | 24 (16) |
| NPI [0-144] | 16 (14.7) | | 26 (17) |
| EQ-5D Dutch tariff (proxy rated) [1-1] | 0.74 (0.22) | | 0 |
| EQ-5D Dutch tariff (proxy rated) 3 mo follow-up | 0.77 (0.19) | | |
| QoL-AD patient (proxy rated) [13-52] | 33 (6) | | 4 (3) |
| QoL-AD patient (proxy rated) 3 mo follow-up | 33 (6) | | |

CDR indicates clinical dementia rating [0-3]; DAD, disability assessment for dementia [0-100]; EQ-5D, EuroQol-5 dimension Dutch tariff [-1,1]; GDS, geriatric depression scale [0-15]; MMSE, mini-mental state examination [0-30]; NPI, neuropsychiatric inventory [0-14]; PET, positron emission tomography; QoL-AD, Quality of life-Alzheimer Disease [13-52].

**TABLE 2.** Diagnosis Pre-PET and Post-PET (n = 154)

| Diagnosis | n (%) |
|---|---|
| Diagnosis pre-PET | |
| Alzheimer disease | 101 (66) |
| Frontotemporal dementia | 19 (12) |
| Vascular dementia | 2 (1) |
| Lewy bodies | 4 (3) |
| Other neurodegenerative disease | 11 (7) |
| No neurodegenerative disease | 17 (11) |
| Diagnosis post-PET | |
| Alzheimer disease | 101 (66) |
| Frontotemporal dementia | 19 (12) |
| Vascular dementia | 2 (1) |
| Lewy bodies | 7 (5) |
| Other neurodegenerative disease | 11 (7) |
| No neurodegenerative disease | 14 (9) |
| Change in diagnosis (pre-post PET) | 26 (17) |

AD indicates Alzheimer disease; PET, positron emission tomography.

**TABLE 3.** Bivariate Linear Regression Unstandardized β Coefficients (Based on Imputed Data)

| | Unstandardized β Coefficients | |
|---|---|---|
| Characteristic | QoL-AD 3-month FU | EQ-5D Dutch Tariff 3 moFU |
| Sex | 0.677 | 0.039 |
| Educational level Verhage | 0.061 | 0.053* |
| Age | 0.009 | −0.002 |
| Charlson Comorbidity Index | −0.367 | −0.012 |
| MMSE | −0.058 | 0.004 |
| GDS | −0.690** | −0.022** |
| DAD | 0.125** | 0.005** |
| NPI | −0.176** | −0.006** |

*$P < 0.05$.
**$P < 0.01$.
Reference category is no neurodegenerative disease.
AD indicates Alzheimer disease; DAD, disability assessment for dementia; GDS, geriatric depression scale; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; QoL-AD, quality of Life-Alzheimer disease.

change) change in diagnosis was not significant, and in model 4 (EQ-5D change) change in certainty was not significant (Table S7, Supplemental Digital Content 1, http://links.lww.com/WAD/A370).

## DISCUSSION

The main findings of this explorative study were that a diagnosis of AD was significantly associated to QOL in 2 of the 4 analyses, and diagnostic certainty was significantly associated to QOL in 1 of the 4 analyses.

Some speculations could be made on the interpretation of the positive associations, which could be topic for future (qualitative) research.

We hypothesize that the positive association between etiological diagnosis of AD and QoL (compared with no neurodegenerative disorder) could be explained because of feelings clarity about the cause of their cognitive complaints, which might be higher in AD than for other less common causes.

The association between the change in clinician's certainty regarding the etiological diagnosis and the patients' QoL (found in 1 of the 4 analysis) might be related with a better care management decision making, as a result of a more confident diagnosis. In general, patients may have a preference to be treated by more experienced and thus more confident clinicians. Future qualitative research could generate data to identify the presence of these speculated mechanisms.

The clinical relevance of the effects varied. A diagnosis of AD (nonchange model) would predict to affect generic QoL with 0.15 (utility scale worse possible health state −0.33 to best possible health state 0.93), which could be considered moderate to good clinical relevance. However, a change from or to and AD diagnosis would predict a change in disease-specific QoL of 2 points, which was lower than the change considered clinically meaningful. An improvement in certainty of 20 to 30 (around median and third quartile) would predict a change in generic QoL of 0.04 to 0.06, respectively, which could be considered minimally relevant. The analyses on change in QoL could be considered stronger evidence of any potential causal relation compared with the nonchange analysis. Given their effect was weak and only 1 of the 2 QoL instruments showed a significant result it remains uncertain whether the diagnosis and certainty have any effect on QoL.

This study's results raise the question whether additional etiological certainty, as a result of advanced diagnostic testing, is beneficial for patients. Diagnostic certainty might be interacting with key elements (variation in perspectives, expectations, and communication of the diagnosis[34]) in the way patients process medical and diagnostic information.[35] This was not considered in this study. It might also interact with other aspects such as care advice through which it could improve QoL. Another explanation for the weak to moderate results might be that the impact on QoL could be considered a process rather than a single response, with a negative impact on the first days to weeks and an increase over weeks to months because of coping the diagnostic label. Also, a proxy-rating of a patient's QoL by an informal caregiver was possibly influenced by the effects of a caregiver's own emotions on his/her estimation of the patient's QoL and further deluded the association. At last, the model predicting the change in QoL had a low ability to explain the differences in the outcome (reflected by the $R^2$). However, using a change score has possibly over-corrected for the baseline score, as it removes all variation related to the baseline score, also the shared variation that could have been caused by other factors.

If an effective disease-modifying treatment for AD will become available it is most likely that the role of the [$^{18}$F]

**TABLE 4.** Two Final Multiple Regression Models 1 and 2 (Based on Imputed Data)

| | QoL-AD (3 mo FU) | | EQ-5D Dutch Tariff (3 mo FU) | |
|---|---|---|---|---|
| Factor | Unstandardized β Coefficients | *P* | Unstandardized β Coefficients | *P* |
| Etiological diagnosis NND† | Reference category | | Reference category | |
| Etiological diagnosis AD | 0.666 | 0.712 | 0.148 | 0.010* |
| Etiological diagnosis OND | 0.260 | 0.870 | 0.079 | 0.115 |
| Clinician's certainty diagnosis | −0.001 | 0.967 | −0.001 | 0.258 |
| NPI | −0.124 | 0.001** | −0.003 | 0.001** |
| DAD | 0.064 | 0.021* | 0.003 | 0.010* |
| GDS | −0.476 | 0.004** | −0.014 | 0.006** |

*$P < 0.05$.
**$P < 0.01$.
†Reference category is no neurodegenerative disease.
AD indicates Alzheimer disease; DAD, disability assessment for dementia; GDS, geriatric depression scale; NND, no neurodegenerative disease; NPI, neuropsychiatric inventory; OND, other neurodegenerative disease; QoL-AD, quality of life-Alzheimer disease.



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**TABLE 5.** Two Multiple Regression Models 3 and 4 Using Change Scores (Based on Imputed Data)

| | QoL-AD Change Score† | | EQ-5D Dutch Tariff Change Score‡ | |
|---|---|---|---|---|
| Factor | Unstandardized β Coefficients | *P* | Unstandardized β Coefficients | *P* |
| Change in diagnosis | 2.019 | 0.037* | −0.025 | 0.537 |
| Change score clinician's certainty diagnosis | 0.036 | 0.117 | 0.002 | 0.028* |

*$P < 0.05$.
†Change score QoL-AD between FU after 3 months and baseline measurement.
‡Change score EQ-5D between FU after 3 months and baseline measurement.
QoL-AD indicates quality of life-Alzheimer disease.

flutemetamol PET scan will differ from the current situation. It is expected to have a crucial role as a tool to optimize treatment decision making.[36]

The bivariate analyses showed a significant effect of diagnosis and diagnostic certainty while part of the multiple regression analyses did not. Although the multiple regression analyses were adjusted for potential bias, the significance of these factors was not consistent across both the univariate analyses as well as the multiple regression models. This increases the uncertainty whether the adjustment factors were indeed confounders or not.

The sensitivity analysis showed similar results and reflects the robustness of our findings to missing data.

In the CDR-based post hoc analyses different significant levels were observed. Given the various directions and relatively small sample size this argues for future research to distinguish by severity state.

Consistent with previous research we found that dementia patient's QoL is associated with depressive and neuropsychiatric symptoms[28–30,33] and unrelated to age, sex, educational level.[29] In contrast with literature our results did not indicate a significant relation between MMSE and QoL, which might be related to the relatively mild severity of the dementia by the majority having a CDR score of 0.5 or 1. This confirmation of earlier findings supports the validity of the regression models.

## Limitations

This study was subject to limitations. First, the analyses relied on proxy ratings for the QoL of patients rated by their caregivers. Despite there is much debate on the use of patient self-versus proxy ratings, patients in mild dementia would likely have provided a first-hand experience rating of their QoL, and more directly being affected by clinical decisions so therefore possibly stronger associated to the diagnostic characteristics.[25]

Second, clinician's certainty regarding the etiological diagnosis not necessarily reflected the uncertainty as was received by the patient when the diagnosis was communicated. We expect this resulted in a less clear association because of the indirectness of this certainty.

Likely, part of the patients visited the tertiary center to obtain a second opinion. Possibly, patients already had received diagnostic information that affected their QoL before entering the study, which would lead to an underestimation of our results. Therefore, the pre [$^{18}$F]flutemetamol PET diagnosis might possible not be the diagnosis that has been disclosed with the patient and its caregiver at first hand and could have affected the possible impact of receiving a change in the diagnosis.

To explore the sensitivity of the results to potentially limited proxy ratings in moderate dementia a post hoc analysis on the subsample of CDR < = 1 indicated the association between QoL-AD change and diagnosis change was no longer significant (the other 3 model coefficient significance remained the same).

## Implications

This study indicated a potential to affect QoL by changes in the diagnosis or diagnostic certainty. this potential could be further investigated by using an improved study design less prone to the limitations by this study as stated earlier. Also, instruments closer to the person with dementia as well as intermediate outcomes between (certainty of the) diagnosis and QoL on the domain of emotional, social, cognitive, and behavioral outcomes[11] could lead to a better understanding of the causal pathway of diagnostic outcomes and patient relevant outcomes in absence of a treatment. In future studies, not only a change in diagnosis but also the correctness of a change in diagnosis should be taken into consideration.

If the causal relation between change (certainty of the) diagnosis and QoL is true, (advanced) diagnostic testing has the potential to improve the QoL of persons with young onset dementia.

Evidence on this causal relation could inform the reimbursement decision-making process of advanced imaging and biomarker technologies for AD.

# CONCLUSIONS

The results of this study's explorative analyses were diverse, and do not reflect a univocal association between diagnosis, certainty, and QoL. Nevertheless, part of the results reflect a possible potential for advanced diagnostic technologies for AD. To confirm this, future studies should empirically assess emotional, social, cognitive, and behavioral outcomes after AD testing.

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## REFERENCES

1. Prince MJ. World Alzheimer Report 2015: The Global Impact of Dementia: an analysis of prevalence, incidence, cost and trends; 2015.
2. Vos SJB, Van Boxtel MPJ, Schiepers OJG, et al. Modifiable risk factors for prevention of dementia in midlife, late life and the oldest-old: validation of the LIBRA Index. *J Alzheimers Dis*. 2017;58:537–547.
3. Fiest KM, Jette N, Roberts JI, et al. The prevalence and incidence of dementia: a systematic review and meta-analysis. *Can J Neurol Sci*. 2016;43(suppl 1):S3–S50.
4. Prince M, Bryce R, Ferri C. *World Alzheimer Report 2011: The Benefits of Early Diagnosis and Intervention*. London: Alzheimer's Disease International; 2011.

5. Jack CR, 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. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263–269.
7. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force (AIT), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer Association (AA). *Alzheimers Dement*. 2013;9:e-1–16.
8. Fox C, Lafortune L, Boustani M, et al. Screening for dementia—is it a no brainer? *Int J Clin Pract*. 2013;67:1076–1080.
9. Le Couteur D, Doust JA, Creasey H, et al. Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis. *BMJ Online*. 2013;347:f5125.
10. Dubois B, Padovani A, Scheltens P, et al. Timely diagnosis for Alzheimer's disease: a literature review on benefits and challenges. *J Alzheimers Dis*. 2015;49:617–631.
11. Bossuyt PM, McCaffery K. Additional patient outcomes and pathways in evaluations of testing. *Med Decis Making*. 2009;29:E30–E38.
12. Lee DW, Neumann PJ, Rizzo JA. Understanding the medical and nonmedical value of diagnostic testing. *Value Health*. 2010;13:310–314.
13. Derksen E, Vernooij-Dassen M, Gillissen F, et al. Impact of diagnostic disclosure in dementia on patients and carers: qualitative case series analysis. *Aging Ment Health*. 2006;10:525–531.
14. Paulsen JS, Nance M, Kim J-I, et al. A review of quality of life after predictive testing for and earlier identification of neurodegenerative diseases. *Prog Neurobiol*. 2013;110:2–28.
15. Zwan MD, Bouwman FH, Konijnenberg E, et al. Diagnostic impact of [(18)F]flutemetamol PET in early-onset dementia. *Alzheimers Res Ther*. 2017;9:2.
16. Aalten P, Van der Flier W, Biessels GJ, et al. Improving diagnosis of dementia in a nationwide setting: first results of the Dutch String of Pearls Initiative on neurodegenerative diseases. *Alzheimers Dement*. 2012;8:P325.
17. van der Flier WM, Pijnenburg YA, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *J Alzheimers Dis*. 2014;41:313–327.
18. Ossenkoppele R, Tolboom N, Foster-Dingley JC, et al. Longitudinal imaging of Alzheimer pathology using [11 C] PIB,[18 F] FDDNP and [18 F] FDG PET. *Eur J Nucl Med Mol Imaging*. 2012;39:990–1000.
19. Logsdon RG, Gibbons LE, McCurry SM, et al. Quality of life in Alzheimer's disease: patient and caregiver reports. *J Ment Health Aging*. 1999;5:21–32.
20. Spector A, Thorgrimsen L, Woods B, et al. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia. *Br J Psychiatry*. 2003;183:248–254.
21. Brooks R, Group E. EuroQol: the current state of play. *Health Policy*. 1996;37:53–72.
22. Versteegh MM, Vermeulen KM, Evers SM, et al. Dutch tariff for the five-level version of EQ-5D. *Value Health*. 2016;19:343–352.
23. Lamers L, Stalmeier P, McDonnell J, et al. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneeskd*. 2005;149:1574–1578.
24. Banerjee S, Smith SC, Lamping DL, et al. Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. *J Neurol Neurosurg Psychiatry*. 2006;77:146–148.
25. Jönsson L, Andreasen N, Kilander L, et al. Patient-and proxy-reported utility in Alzheimer disease using the EuroQoL. *Alzheimer Dis Assoc Disord*. 2006;20:49–55.
26. Matsui T, Nakaaki S, Murata Y, et al. Determinants of the quality of life in Alzheimer's disease patients as assessed by the Japanese version of the Quality of Life–Alzheimer's Disease Scale. *Dement Geriatr Cogn Disord*. 2006;21:182–191.
27. Li XJ, Suishu C, Hattori S, et al. The comparison of dementia patient's quality of life and influencing factors in two cities. *J Clin Nurs*. 2013;22:2132–2140.
28. Mougias AA, Politis A, Lyketsos CG, et al. Quality of life in dementia patients in Athens, Greece: predictive factors and the role of caregiver-related factors. *International Psychogeriatrics*. 2011;23:395–403.
29. Banerjee S, Samsi K, Petrie CD, et al. What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *Int J Geriatr Psychiatry*. 2009;24:15–24.
30. Karlawish J. Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease. *Neurology*. 2011;77:1487–1493.
31. Gómez-Gallego M, Gómez-Amor J, Gómez-García J. Determinants of quality of life in Alzheimer's disease: perspective of patients, informal caregivers, and professional caregivers. *Int Psychogeriatr*. 2012;24:1805–1815.
32. Karlawish JH, Zbrozek A, Kinosian B, et al. Preference-based quality of life in patients with Alzheimer's disease. *Alzheimers Dement*. 2008;4:193–202.
33. Mate KE, Pond CD, Magin PJ, et al. Diagnosis and disclosure of a memory problem is associated with quality of life in community based older Australians with dementia. *Int Psychogeriatr*. 2012;24:1962–1971.
34. van der Flier WM, Kunneman M, Bouwman FH, et al. Diagnostic dilemmas in Alzheimer's disease: room for shared decision making. *Alzheimers Dement*. 2017;3:301–304.
35. Harun N, Finlay A, Piguet V, et al. Understanding clinician influences and patient perspectives on outpatient discharge decisions: a qualitative study. *BMJ Open*. 2017;7:e010807.
36. Handels RL, Joore MA, Tran-Duy A, et al. Early cost-utility analysis of general and cerebrospinal fluid-specific Alzheimer's disease biomarkers for hypothetical disease-modifying treatment decision in mild cognitive impairment. *Alzheimers Dement*. 2015;11:896–905.