JAMA Neurology | Original Investigation

# Interpreting Biomarker Results in Individual Patients With Mild Cognitive Impairment in the Alzheimer's Biomarkers in Daily Practice (ABIDE) Project

Ingrid S. van Maurik, MSc; Marissa D. Zwan, PhD; Betty M. Tijms, PhD; Femke H. Bouwman, MD, PhD; Charlotte E. Teunissen, PhD; Philip Scheltens, MD, PhD; Mike P. Wattjes, MD, PhD; Frederik Barkhof, MD, PhD; Johannes Berkhof, PhD; Wiesje M. van der Flier, PhD; for the Alzheimer's Disease Neuroimaging Initiative

**IMPORTANCE** Biomarkers do not determine conversion to Alzheimer disease (AD) perfectly, and criteria do not specify how to take patient characteristics into account. Consequently, biomarker use may be challenging for clinicians, especially in patients with mild cognitive impairment (MCI).

**OBJECTIVE** To construct biomarker-based prognostic models that enable determination of future AD dementia in patients with MCI.

**DESIGN, SETTING, AND PARTICIPANTS** This study is part of the Alzheimer's Biomarkers in Daily Practice (ABIDE) project. A total of 525 patients with MCI from the Amsterdam Dementia Cohort (longitudinal cohort, tertiary referral center) were studied. All patients had their baseline visit to a memory clinic from September 1, 1997, through August 31, 2014. Prognostic models were constructed by Cox proportional hazards regression with patient characteristics (age, sex, and Mini-Mental State Examination [MMSE] score), magnetic resonance imaging (MRI) biomarkers (hippocampal volume, normalized whole-brain volume), cerebrospinal fluid (CSF) biomarkers (amyloid-β1-42, tau), and combined biomarkers. Data were analyzed from November 1, 2015, to October 1, 2016.

**MAIN OUTCOMES AND MEASURES** Clinical end points were AD dementia and any type of dementia after 1 and 3 years.

**RESULTS** Of the 525 patients, 210 (40.0%) were female, and the mean (SD) age was 67.3 (8.4) years. On the basis of age, sex, and MMSE score only, the 3-year progression risk to AD dementia ranged from 26% (95% CI, 19%-34%) in younger men with MMSE scores of 29 to 76% (95% CI, 65%-84%) in older women with MMSE scores of 24 (1-year risk: 6% [95% CI, 4%-9%] to 24% [95% CI, 18%-32%]). Three- and 1-year progression risks were 86% (95% CI, 71%-95%) and 27% (95% CI, 17%-41%) when MRI results were abnormal, 82% (95% CI, 73%-89%) and 26% (95% CI, 20%-33%) when CSF test results were abnormal, and 89% (95% CI, 79%-95%) and 26% (95% CI, 18%-36%) when the results of both tests were abnormal. Conversely, 3- and 1-year progression risks were 18% (95% CI, 13%-27%) and 3% (95% CI, 2%-5%) after normal MRI results, 6% (95% CI, 3%-9%) and 1% (95% CI, 0.5%-2%) after normal CSF test results, and 4% (95% CI, 2%-7%) and 0.5% (95% CI, 0.2%-1%) after combined normal MRI and CSF test results. The prognostic value of models determining any type of dementia were in the same order of magnitude although somewhat lower. External validation in Alzheimer's Disease Neuroimaging Initiative 2 showed that our models were highly robust.

**CONCLUSIONS AND RELEVANCE** This study provides biomarker-based prognostic models that may help determine AD dementia and any type of dementia in patients with MCI at the individual level. This finding supports clinical decision making and application of biomarkers in daily practice.

*JAMA Neurol*. 2017;74(12):1481-1491. doi:10.1001/jamaneurol.2017.2712
Published online October 16, 2017.

Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The members of the Alzheimer's Disease Neuroimaging Initiative are listed at the end of this article.

**Corresponding Author:** Ingrid S. van Maurik, MSc, Department of Neurology and Alzheimer Center, Amsterdam Neuroscience, VU University Medical Center, De Boelelaan 1118, 1081 HZ Amsterdam, the Netherlands (i.vanmaurik@vumc.nl).

Alzheimer disease (AD) has a long predementia phase that is often referred to as mild cognitive impairment (MCI). The cumulative progression incidence from MCI to dementia is approximately 50% over 3 years.[1,2] This finding simultaneously implies that the other half of patients with MCI will remain clinically stable or return to a normal state. Therefore, there is an urgent need for individualized risk assessments in patients with MCI.[3]

Identification of abnormal biomarkers in patients with MCI helps to identify individuals at high risk of progression to AD dementia.[4] Atrophy on brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) concentrations of amyloid-β1-42 (Aβ1-42) and tau protein are among the most widely used AD biomarkers and are associated with an increased risk of AD dementia at follow-up.[5-10] These findings resulted in the National Institute on Aging and Alzheimer Association (NIA-AA) criteria, stating that biomarker evidence enhances the pathologic specificity of the diagnosis of AD dementia and MCI due to AD dementia, facilitating an accurate and early diagnosis.[3,11,12] However, these criteria do not specify how to deal with conflicting or borderline biomarker results and how to take patient characteristics into account. Moreover, although MRI and CSF are increasingly used in clinical practice, their diagnostic and prognostic value is not perfect. Therefore, optimal use of these biomarkers in daily clinical practice is challenging.[3,13] We aimed to construct prognostic models based on MRI measures and CSF biomarkers for patients with MCI, taking into account patient characteristics to obtain individualized probabilities of progression.

### Key Points

**Question** Magnetic resonance imaging and cerebrospinal fluid measures are associated with an increased risk of progression to Alzheimer disease dementia, but how can we interpret biomarker findings in individual patients with mild cognitive impairment?

**Findings** This cohort modelling study constructed biomarker-based prognostic models (cerebrospinal fluid model, magnetic resonance imaging model, and a combined model) that can be applied in individual patients with mild cognitive impairment, taking into account patient characteristics (age, sex, and Mini-Mental State Examination score). The models show particularly high negative predictive values, and external validation showed that our models were highly robust.

**Meaning** These practical models could support clinical decision making and facilitate application of magnetic resonance imaging and cerebrospinal fluid biomarkers in daily practice.

## Methods

### Participants

This study is part of the Alzheimer's Biomarkers in Daily Practice (ABIDE) project.[14] We included 525 patients with MCI from the Amsterdam Dementia Cohort (eFigure 1 in the Supplement). Inclusion criteria were baseline diagnosis of MCI, availability of Mini-Mental State Examination (MMSE) scores, MRI and/or CSF data, and at least 6 months of follow-up. All patients had their baseline visit in our memory clinic from September 1, 1997, through August 31, 2014. Data were analyzed from November 1, 2015, to October 1, 2016. We obtained written informed consent from all patients. The study was approved by the Medical Ethics Review Committee of the VU University Medical Center, Amsterdam, the Netherlands. All data were deidentified.

Diagnostic workup consisted of a standardized, 1-day baseline assessment. Clinical diagnosis was made by consensus in a multidisciplinary meeting.[15] Until early 2012, the diagnosis of MCI was based on the Petersen criteria.[11] From 2012 onward, we used the core clinical criteria of the NIA-AA for MCI.[3]

The standardized annual follow-up included a visit with the neurologist and neuropsychologist. The diagnosis was reevaluated in a multidisciplinary meeting of the professionals involved. Alzheimer disease dementia was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria or NIA-AA criteria.[12,16] Other types of dementia were diagnosed using established clinical criteria.[17-21]

### MRI Acquisition

Magnetic resonance imaging (available in 456 patients [86.9%]) before 2008 was performed with a 1.5-T MRI scanner (Magnetom Avanto, Vision, Impact, and Sonata, Siemens; Signa HDXT, GE Healthcare). From 2008 onward, MRI of the brain was performed on a 3-T MRI scanner (MR750, GE Medical Systems; Ingenuity TF PET/MR, Philips Medical Systems; and Titan, Toshiba Medical Systems). All images were taken according to a standardized protocol,[22] of which we only used sagittal 3-dimensional T1-weighted images with coronal reformats in this study.

All images were reviewed by experienced neuroradiologists. Visual rating of MRIs was performed according to established, validated semiquantitative visual rating scales (medial temporal lobe atrophy scores, 0-4; global cortical atrophy scores, 0-3).[23,24]

Left and right hippocampal volumes (HCVs) were quantified using FSL FIRST (the integrated registration and segmentation tool of the Oxford Centre for Functional MRI of the Brain) and summed for analysis.[25] Normalized whole-brain volumes (NWBVs) were estimated with Structural Image Evaluation using Normalization of Atrophy Cross-sectional (SIENAX).[26] Volumetric data were available for 394 patients (75.0%).

### CSF Analysis

The CSF samples (available in 417 patients [79.4%]) were obtained by lumbar puncture, collected in polypropylene tubes (Sarstedt), and processed according to international guidelines.[27-29] The CSF biomarkers Aβ1-42 and total tau were measured using sandwich enzyme-linked immunosorbent assays on a routine basis (Innotest, Fujirebio).[9]

### Statistical Analysis

We used Stata 14SE software (StataCorp) for statistical analyses. We used Cox proportional hazards regression analysis to construct prognostic models (determinants as continuous measures; CSF biomarkers were log transformed). The models were based on complete cases only; therefore, the number of patients varied across models (eFigure 1 in the Supplement). The primary clinical end point was probable AD dementia.[12,16] Patients who progressed to dementia not caused

by AD (n = 56) were included in the analysis (non-AD group) and censored at the time of diagnosis of non-AD dementia. Subsequently, we repeated the analysis with conversion to any type of dementia as the clinical end point.

We first constructed a prognostic model based on the patient characteristics of age, sex, and MMSE score (demographic model; for comparison). We expanded this model with MRI (HCV and NWBV) or CSF (Aβ1-42 and tau). Finally, we combined the previous 2 models into 1 prognostic model containing CSF biomarkers (Aβ1-42 and tau) and MRI biomarkers (HCV and NWBV) to allow a clinician to appreciate the combined value of both modalities. We focused our report on the volumetric measures and provide a model for visual measurements in the Supplement. In addition, we corrected the volumetric MRI models for field strength. Interaction effects among biomarkers and between biomarker and patient characteristics were included using backward selection. Effects were included in the model if $P \leq .10$. The prognostic accuracy of the model was estimated by the Harrell C statistic.[30] Three-year and corresponding 1-year cumulative progression probabilities with 95% CIs were calculated using the Stata survci command.[31] Because of variation in clinical follow-up visit times, cutoffs were set at 3.5 years for 3-year follow-up and 1.5 years for 1-year follow-up. Specific probabilities of progression with accompanying CIs were read from the survival function for specific patients using the established models. As an example, we determined probabilities of progression for men and women, patients with a younger (60 years) and older (75 years) age, and those with an MMSE score of 29 and 24. We selected the 20th percentile as abnormal and the 80th percentile as normal for each biomarker (for tau, 80th percentile as abnormal and 20th percentile as normal) (eFigure 2 in the Supplement). When these models are used, any value can be entered for the variables, resulting in a personalized value and CI for each patient.

We internally validated the models by 5-fold cross-validation. External validation was performed on the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI-2) cohort (eAppendix and eTable 1 in the Supplement). We fitted the established models to *z* score–converted biomarker values and calculated the Harrell C statistic.

## Results

Of the 525 patients, 210 (40.0%) were female, and the mean (SD) age was 67.3 (8.4) years. During a mean (SD) of 2.4 (1.0) years of follow-up, 201 (38.3%) patients progressed to AD dementia, 52 (9.9%) developed another type of dementia, and 272 (51.8%) remained stable (**Table 1**).[32]

We constructed models to determine AD-type dementia. The variables included in each model (demographic model, CSF model, MRI model, and combined model) and their corresponding regression coefficients are presented in **Table 2**. Risk estimates in the models that included a single biomarker are provided in eTable 2 in the Supplement. Inclusion of field strength only slightly affected the models (eTable 3 in the Supplement). To enable translation of findings to clinical practice, we used the models to determine the risk of progression after a 3-year follow-up, with a corresponding 1-year progression risk. Cumulative progression to AD dementia after 3 years occurred in 162 patients (30.9%) (58 [11.0%] after 1 year). Subsequently, as an example, we estimated risk of progression for men and women with a younger (60 years) and older (75 years) age and an MMSE score of 29 and 24. The model based on sex, age, and MMSE score only identified the highest risk of AD dementia for older women with lower MMSE scores. The 3-year progression risk ranged from 26% (95% CI, 19%-34%) in younger men with an MMSE score of 29 to 76% (95% CI, 65%-84%) in older women with an MMSE score of 24, and the corresponding 1-year progression risk ranged from 6% (95% CI, 4%-9%) in younger men with an MMSE score of 29 to 24% (95% CI, 18%-32%) in older women with an MMSE score of 24 (**Table 3**).

Next, we added biomarker values. For illustrative purposes, we entered the 20th percentile of each biomarker as abnormal and the 80th percentile as normal. With these models, any value can be entered for the continuous variables, resulting in individualized values. The model that included MRI biomarkers showed that the main effects of HCV, NWBV, age, and MMSE score were associated with AD dementia at follow-up (Table 2). In the MRI model, age modified the prognostic value of MRI measures (NWBV × age: β = 0.003, SE = 0.002, $P = .04$). As an example, lower NWBV (20th percentile) increased the 3-year progression risk to 47% (95% CI, 33%-64%; 1 year: 10% [95% CI, 6%-16%]) in younger patients with an MMSE score of 29 but not in older patients (35% [95% CI, 25%-48%]; 1 year: 7% [95% CI, 4%-11%]). By contrast, absence of atrophy (80th percentile) decreased 3-year progression to 18% (95% CI, 13%-27%; 1 year: 3% [95% CI, 2%-5%]) in younger patients with an MMSE score of 29 and to 24% (95%

**Table 1. Patient Characteristics**

| Characteristic | Finding[a] (N = 525) |
|---|---|
| Patients with unfavorable outcome, No. (%) | 201 (38.3) |
| Age at baseline, y | 67.3 (8.4) |
| Female, No. (%) | 210 (40.0) |
| Educational level, y[b] | 5.0 (1.0) |
| MMSE score | 27 (2) |
| Follow-up time, y | 2.4 (1.0) |
| CSF measures, median (IQR) | |
| Aβ1-42 | 584 (441-905) |
| Tau | 396 (261-636) |
| MRI measures | |
| Volumetric measures | |
| HCV, mL | 6.6 (1.1) |
| NWBV, mL | 1417 (80) |
| Visual | |
| MTA score | 0.9 (0.8) |
| GCA score | 0.7 (0.7) |

Abbreviations: Aβ1-42, amyloid-β1-42; CSF, cerebrospinal fluid; GCA, global cortical atrophy; HCV, hippocampal volume; IQR, interquartile range; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; NWBV, normalized whole-brain volume.

[a] Data are presented as mean (SD) unless otherwise indicated.

[b] Educational level was determined according to the classification of Verhage.[32]

Table 2. Regression Coefficients of the Final Models[a]

| Variable | AD Dementia | | | Dementia | | |
|---|---|---|---|---|---|---|
| | Coefficient (SE) | *P* Value | Harrell C Statistic | Coefficient (SE) | *P* Value | Harrell C Statistic |
| Demographics | | | | | | |
| Age | 0.0319 (0.0092) | <.001 | | 0.0274 (0.0082) | .001 | |
| Sex | 0.4095 (0.1437) | .004 | 0.61 | 0.2349 (0.1302) | .07 | 0.59 |
| MMSE score | −0.1317 (0.0296) | <.001 | | −0.1221 (0.0267) | <.001 | |
| CSF | | | | | | |
| Aβ1-42 | −3.0362 (0.6010) | <.001 | | −1.5262 (0.4879) | .002 | |
| Tau | 3.7488 (0.4732) | <.001 | 0.75 | 2.1570 (0.3803) | <.001 | 0.67 |
| MMSE score | −0.1009 (0.0326) | .002 | | −1.0123 (0.0298) | .001 | |
| Aβ1-42 × tau | 10.0790 (2.1246) | <.001 | | 4.1556 (1.7927) | .02 | |
| MRI | | | | | | |
| HCV | −0.2102 (0.0883) | .02 | | −0.1835 (0.0789) | .02 | |
| NWBV | −0.0060 (0.0013) | <.001 | | −0.0056 (0.0012) | <.001 | |
| Age | −0.0032 (0.0130) | .80 | 0.67 | −0.0025 (0.0116) | .83 | 0.66 |
| MMSE score | −0.1492 (0.0351) | <.001 | | −0.1456 (0.0318) | <.001 | |
| NWBV × age | 0.0003 (0.0002) | .03 | | 0.0003 (0.0001) | .052 | |
| MRI and CSF | | | | | | |
| Aβ1-42 | −2.8353 (0.7180) | <.001 | | −0.8791 (0.5592) | .12 | |
| Tau | 3.8989 (0.5962) | <.001 | | 1.7655 (0.3943) | <.001 | |
| NWBV | −0.0059 (0.0013) | <.001 | | −0.0062 (0.0013) | <.001 | |
| MMSE score | −0.1082 (0.0376) | .004 | 0.78 | −0.1359 (0.0345) | <.001 | 0.70 |
| Aβ1-42 × tau | 10.4365 (2.8548) | <.001 | | NA | NA | |
| Aβ1-42 × age | NA | NA | | 0.1383 (0.0823) | .09 | |
| Age | NA | NA | | 0.0001 (0.0141) | .99 | |

Abbreviations: Aβ1-42, amyloid-β1-42; AD, Alzheimer disease; CSF, cerebrospinal fluid; HCV, hippocampal volume; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NA, not applicable; NWBV, normalized whole-brain volume.

[a] The CSF biomarkers (Aβ1-42 and tau) were log transformed. The interaction term was centered and standardized to allow inclusion in the model.

CI, 15%-36%; 1 year: 4% [95% CI, 3%-8%]) in older patients with an MMSE of 29 (Table 3). The corresponding C statistic of model performance was 0.67. The MRI model with visual rating scales is given in eTable 3 and eTable 4 in the Supplement and performs similarly.

Subsequently, we constructed a prognostic model with CSF biomarkers (containing Aβ1-42 and tau). Aβ1-42, tau, and MMSE score were related to AD dementia at follow-up, whereas the effect of age was excluded from the model (Table 2). Having abnormal tau values was a stronger determinant of AD dementia in patients with normal Aβ1-42 values (Aβ1-42 × tau: β = 10.4365, SE = 2.8548, $P < .001$). The CSF model showed that abnormal biomarkers (Aβ1-42 and tau) increased 3-year progression risk to 82% (95% CI, 73%-89%) from a 1-year risk of 26% (95% CI, 20%-33%) in patients with an MMSE score of 24 and to 64% (95% CI, 53%-74%) in patients with an MMSE score of 29 from a 1-year risk of 16% (95% CI, 11%-23%). By contrast, the models showed a strong negative predictive value of CSF biomarkers, with normal biomarkers (Aβ1-42 and tau) decreasing 3-year progression risk to 6% (95% CI, 3%-9%) from a 1-year risk of 1% (95% CI, 0.5%-2%) in patients with an MMSE score of 29 and to 9% (95% CI, 5%-17%) from a 1-year risk of 2% (95% CI, 1%-4%) in patients with a MMSE score of 24. The corresponding C statistic of model performance was 0.75.

Finally, we combined both MRI measures and CSF biomarkers in 1 model. In this model, the effect of HCV was not significant (Table 2). The interaction effect between Aβ1-42 and tau remained significant (Aβ1-42 × tau: β = 10.4364; SE = 2.8548; $P < .001$). The **Figure** shows isographs based on the combined model and the probability of progression within 1 and 3 years by Aβ1-42 and tau, stratified for NWBV. Three-year progression risk ranged from 4% (95% CI, 2%-7%) in patients with an MMSE score of 29 and normal biomarkers to 89% (95% CI, 79%-95%) in patients with an MMSE score of 24 and all abnormal biomarker results, and their corresponding 1-year progression risk ranged from 0.5% (95% CI, 0.2%-1%) to 26% (95% CI, 18%-36%) (**Table 4**). The corresponding C statistic of model performance was 0.77.

Subsequently, we repeated the analyses with dementia as the clinical end point, resulting in selection of the same variables for the demographic model (Harrell C = 0.59), MRI model (Harrell C = 0.67), and CSF model (Harrell C = 0.66) (eTable 5 in the Supplement). For the combined model, the interaction between tau and Aβ1-42 was not included in the final model via backward selection. The final model existed of tau, Aβ1-42, NWBV, age, MMSE score, and an interaction between Aβ1-42 and age (Harrell C = 0.70).

Internal validation confirmed prognostic discrimination in all 3 models (eTable 6 in the Supplement). External validation showed robustness of the models in the ADNI-2 (Harrell C = 0.63 in the demographic model, 0.64 in the MRI model, 0.76 in the CSF model, and 0.73 in the combined model) (eFigure 3 in the Supplement).

The models provide risk estimates for any given value of each biomarker, taking full advantage of their continuous nature. On request, we can provide a spreadsheet calculator, which is freely available for academic use. This calculator automatically calculates probabilities with accompanying CIs of AD dementia at 3- and 1-year follow-up. The model also appreciates the value of additional testing by comparing determinations of

Table 3. Probability of Progression to AD Dementia for Patients With Mild Cognitive Impairment: MRI and CSF Model[a]

| Patient Group by MMSE Score | Probability, % (95% CI) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Demographics Only | MRI | | | | CSF | | | |
| | | −/− | +/− | −/+ | +/+ | −/− | +/− | −/+ | +/+ |
| **1-Year Follow-up** | | | | | | | | | |
| 60-Year-old men | | | | | | | | | |
| 29 | 6 (4-9) | 3 (2-5) | 5 (3-8) | 10 (6-16) | 14 (8-23) | 1 (0.5-2) | 8 (5-12) | 13 (8-21) | 16 (11-23) |
| 24 | 11 (9-15) | 7 (4-11) | 10 (6-16) | 20 (12-30) | 27 (17-41) | 2 (1-4) | 12 (8-18) | 21 (14-32) | 26 (20-33) |
| 60-Year-old women | | | | | | | | | |
| 29 | 9 (6-13) | 3 (2-5) | 5 (3-8) | 10 (6-16) | 14 (8-23) | 1 (0.5-2) | 8 (5-12) | 13 (8-21) | 16 (11-23) |
| 24 | 16 (12-21) | 7 (4-11) | 10 (6-16) | 20 (12-30) | 27 (17-41) | 2 (1-4) | 12 (8-18) | 21 (14-32) | 26 (20-33) |
| 73-Year-old men | | | | | | | | | |
| 29 | 9 (7-13) | 4 (3-8) | 6 (4-11) | 7 (4-11) | 9 (6-14) | 1 (0.5-2) | 8 (5-12) | 13 (8-21) | 16 (11-23) |
| 24 | 17 (13-23) | 9 (5-15) | 13 (8-20) | 14 (9-21) | 19 (14-27) | 2 (1-4) | 12 (8-18) | 21 (14-32) | 26 (20-33) |
| 75-Year-old women | | | | | | | | | |
| 29 | 14 (10-19) | 4 (3-8) | 6 (4-11) | 7 (4-11) | 9 (6-14) | 1 (0.5-2) | 8 (5-12) | 13 (8-21) | 16 (11-23) |
| 24 | 24 (18-32) | 9 (5-15) | 13 (8-20) | 14 (9-21) | 19 (14-27) | 2 (1-4) | 12 (8-18) | 21 (14-32) | 26 (20-33) |
| **3-Year Follow-up** | | | | | | | | | |
| 60-Year-old men | | | | | | | | | |
| 29 | 26 (19-34) | 18 (13-27) | 26 (18-38) | 47 (33-64) | 61 (43-79) | 6 (3-9) | 35 (25-48) | 56 (40-73) | 64 (53-74) |
| 24 | 44 (35-54) | 35 (25-49) | 47 (34-62) | 74 (58-88) | 86 (71-95) | 9 (5-17) | 51 (65-38) | 74 (57-88) | 82 (73-89) |
| 60-Year-old women | | | | | | | | | |
| 29 | 36 (27-45) | 18 (13-27) | 26 (18-38) | 47 (33-64) | 61 (43-79) | 6 (3-9) | 35 (25-48) | 56 (40-73) | 64 (53-74) |
| 24 | 58 (48-69) | 35 (25-49) | 47 (34-62) | 74 (58-88) | 86 (71-95) | 9 (5-17) | 51 (65-38) | 74 (57-88) | 82 (73-89) |
| 75-Year-old men | | | | | | | | | |
| 29 | 39 (31-47) | 24 (15-36) | 33 (22-47) | 35 (25-48) | 47 (37-58) | 6 (3-9) | 35 (25-48) | 56 (40-73) | 64 (53-74) |
| 24 | 61 (51-71) | 43 (29-61) | 56 (41-73) | 60 (45-75) | 73 (63-84) | 9 (5-17) | 51 (65-38) | 74 (57-88) | 82 (73-89) |
| 75-Year-old women | | | | | | | | | |
| 29 | 52 (43-63) | 24 (15-36) | 33 (22-47) | 35 (25-48) | 47 (37-58) | 6 (3-9) | 35 (25-48) | 56 (40-73) | 64 (53-74) |
| 24 | 76 (65-84) | 43 (29-61) | 56 (41-73) | 60 (45-75) | 73 (63-84) | 9 (5-17) | 51 (65-38) | 74 (57-88) | 82 (73-89) |

Abbreviations: Aβ1-42, amyloid-β1-42; AD, Alzheimer disease; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NWBV, normalized whole-brain volume.

[a] Biomarker values were selected as 80th percentile (normal [−]) and 20th percentile (abnormal [+]); for tau, the 20th percentile was selected as normal (−) and the 80th percentile as abnormal (+). This table is an example because the model can provide individualized risk estimates for any given value. For MRI, −/− indicates hippocampus and NWBV negative; +/−, hippocampus positive and NWBV negative; −/+, hippocampus negative and NWBV positive; and +/+, hippocampus and NWBV positive. For CSF, −/− indicates $A\beta_{1-42}$ and tau negative; +/−, $A\beta_{1-42}$ positive and tau negative; −/+, $A\beta_{1-42}$ negative and tau positive; and +/+, $A\beta_{1-42}$ and tau positive.

a priori risk (demographic model based on age, sex, and MMSE score only) to a posteriori determinations based on MRI and/or CSF biomarkers (eFigure 4 in the Supplement).

## Discussion

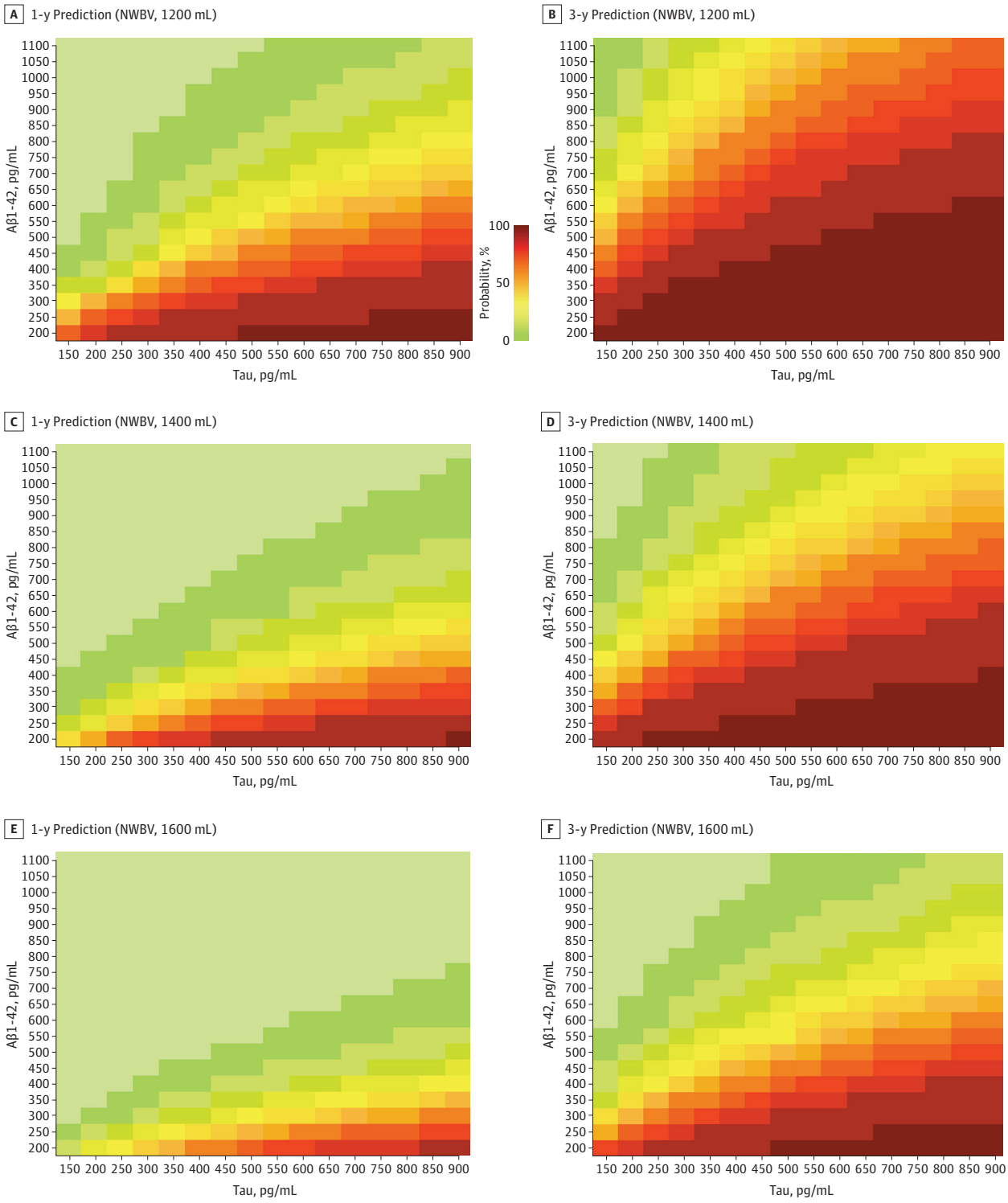
In the present study, we constructed prognostic models that provide a framework for a precision medicine approach by allowing personalized identification of clinical progression in patients with MCI using an equation based on patient characteristics and continuous biomarker values.

Clinicians show great variation in how they use and interpret biomarkers related to MCI. This variation is partly attributable to the imperfection of these markers. In addition, borderline (abnormal) or conflicting results are especially difficult to interpret. Furthermore, the meaning of biomarkers depends on the context as defined by the specific characteristics of a patient. Therefore, many clinicians are reluctant to disclose biomarker results to patients with MCI.

The clinical relevance of biomarker results in terms of their prognostic value for an individual is not clear. Although studies have repeatedly demonstrated the prognostic value of CSF and MRI biomarkers, these studies almost invariably showed prognostic value on group level (highly significant), precluding direct translation to the individual patient. The innovative aspect of our study is that our models allow neurologists to interpret individual patient data. We provide a calculator to translate hazard ratios to probabilities, which are easier to interpret from a clinical perspective. Finally, we provide CIs around each individually estimated probability. This process allows the clinician to appreciate the imperfectness of each biomarker and, for example, can help the identification of best- and worst-case scenarios. As such, we believe that our models can support clinicians in interpreting test results and provide them with a tool to determine AD dementia risk for an individual patient, thereby enabling them to start treatment or provide more accurate patient management. Of note, the models may have particular value in the case of normal biomarkers because the models revealed the negative predictive value of the MRI and CSF biomarkers.[33,34]

The model with both MRI and CSF measures provided the best prognostic value, which reveals the complementary value of both types of diagnostic tests and matches observations in earlier studies.[6,35,36] When evaluating individual modalities,

Figure. Probability Isographs for 1- and 3-Year Progression to Alzheimer Disease Dementia




Probability of conversion within 1 (A, C, E) and 3 (B, D, F) years based on amyloid-β1-42 (Aβ1-42) and tau stratified for normalized whole-brain volume (NWBV). Isographs are based on a mean hippocampal volume of 6.6 mL and a mean Mini-Mental State Examination score of 26.

CSF biomarkers, especially tau, performed better than MRI biomarkers, particularly in determining risk of AD dementia, which is in line with earlier findings.[9,29,35,37-39]

Several former studies[38,39] developed models to determine the risk of AD dementia among patients with MCI, revealing the utility of biomarkers. Those studies[38,39] often

Table 4. Probability of Conversion for Patients With Mild Cognitive Impairment: Combined Model[a]

| Biomarker Combination | | | | | | | |
|---|---|---|---|---|---|---|---|
| MRI Biomarkers | | CSF Biomarkers | | MMSE Score at 1-y Follow-up | | MMSE Score at 3-y Follow-up | |
| HCV | NWBV | Aβ1-42 | Tau | 29 | 24 | 29 | 24 |
| – | – | – | – | 0.5 (0.2-1.0) | 0.9 (0.3-2.0) | 4.0 (2.0-7.0) | 6.0 (2.0-13.0) |
| + | – | – | – | 0.5 (0.2-1.0) | 1.0 (0.3-2.0) | 4.0 (1.0-8.0) | 6.0 (3.0-14.0) |
| – | + | – | – | 1.0 (0.2-3.0) | 2.0 (1.0-4.0) | 6.0 (3.0-14.0) | 11.0 (5.0-24.0) |
| – | – | + | – | 3.0 (2.0-6.0) | 5.0 (3.0-10.0) | 20.0 (12.0-31.0) | 32.0 (20.0-48.0) |
| – | – | – | + | 7.0 (3.0-13.0) | 11.0 (6.0-21.0) | 39.0 (24.0-60.0) | 57.0 (36.0-80.0) |
| + | + | – | – | 1.0 (0-3.0) | 2.0 (1.0-4.0) | 7.0 (3.0-16.0) | 12.0 (5.0-26.0) |
| + | – | + | – | 4.0 (2.0-7.0) | 6.0 (3.0-11.0) | 22.0 (13.0-36.0) | 34.0 (22.0-52.0) |
| + | – | – | + | 7.0 (4.0-14.0) | 12.0 (7.0-22.0) | 42.0 (25.0-65.0) | 60.0 (40.0-82.0) |
| – | + | + | – | 6.0 (3.0-11.0) | 10.0 (5.0-17.0) | 36.0 (24.0-52.0) | 53.0 (36.0-72.0) |
| – | + | – | + | 13.0 (7.0-24.0) | 22.0 (12.0-38.0) | 64.0 (43.0-84.0) | 83.0 (61.0-96.0) |
| – | – | + | + | 8.0 (5.0-14.0) | 13.0 (8.0-20.0) | 43.0 (31.0-58.0) | 61.0 (46.0-77.0) |
| + | + | + | – | 6.0 (4.0-12.0) | 11.0 (6.0-18.0) | 38.0 (25.0-55.0) | 56.0 (40.0-74.0) |
| + | + | – | + | 15.0 (8.0-26.0) | 23.0 (14.0-39.0) | 68.0 (47.0-87.0) | 85.0 (67.0-96.0) |
| + | – | + | + | 9.0 (5.0-14.0) | 14.0 (9.0-21.0) | 46.0 (32.0-63.0) | 65.0 (50.0-79.0) |
| – | + | + | + | 15.0 (9.0-24.0) | 24.0 (15.0-36.0) | 69.0 (54.0-83.0) | 86.0 (72.0-95.0) |
| + | + | + | + | 16.0 (14.0-35.0) | 26.0 (18.0-36.0) | 72.0 (58.0-84.0) | 89.0 (79.0-95.0) |

Abbreviations: Aβ1-42, amyloid-β1-42; CSF, cerebrospinal fluid; HCV, hippocampal volume; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NWBV, normalized whole-brain volume.

[a] Biomarker values were selected as 80th percentile (normal [–]) and 20th percentile (abnormal [+]); for tau, the 20th percentile was selected as normal (–) and the 80th percentile as abnormal (+). This table is an example because the model can provide individualized risk estimates for any given value.

explored an optimal set of variables of progression from MCI to AD dementia, not taking into account the risk differences related to specific patient characteristics available without further diagnostic workup. We deliberately determined interactions between biomarkers and patient characteristics to secure optimal interpretation of biomarker results for AD dementia risk in individual patients. In agreement with an earlier study,[40] we found that MRI markers, particularly low NWBV, were more accurate in determining AD dementia risk in younger compared with older patients. This finding may be explained by the fact that at an older age, brain atrophy occurs in general and is not always related to underlying neurodegenerative disease. Several studies[41,42] found that CSF AD biomarker performance also varies as a function of age because amyloid pathologic findings increase with age. In our study, we found no such age effect when determining the risk of AD dementia. By contrast, when examining the risk of any type of dementia, the prognostic value of amyloid was stronger in younger patients. This finding might fit with the notion that with increasing age, dementia is more often attributable to multiple pathologic findings and less often attributable to AD.

We used volumetric MRI measurements, which tend to be better determinants of AD dementia in patients with MCI than a qualitative rating or the assessment MRIs.[43] To account for changes in measurements attributable to scanner differences, we included field strength as an additional determinant in the models. Of note, this factor did not improve the prognostic performance, a finding that shows the robustness of our models for scanner differences. Volumetric measures are not yet applicable in daily practice. However, software tools are in development to enable quantitative analysis of MRI in daily practice.[44-46] Because qualitative rating is used more frequently by clinicians, we also constructed prognostic models for medial temporal lobe atrophy and global cortical atrophy visual rating with broadly similar performance. These models can be found in the eAppendix in the Supplement.

## Limitations

A potential limitation of this study is the mean (SD) follow-up period of 2.4 (1.0) years, which was short and varied among patients. Therefore, we did not have sufficient power to determine a 5-year outcome. In addition, we cannot completely rule out circularity in diagnostic reasoning because information from MRI and CSF biomarkers was available for the clinician at follow-up. To reduce the effect of this risk of circularity, we included any type of dementia as an additional clinical end point. The syndrome diagnosis of dementia is not influenced by knowledge of biomarkers because this diagnosis is a reflection of clinical functioning only. Furthermore, the outcome of any type of dementia may be considered to have more clinical relevance than that of AD dementia as long as there are no disease-modifying therapies available. The models for both outcomes were largely comparable, although the prognostic performance of the models for any type of dementia was slightly lower. This outcome was expected because we primarily evaluated AD biomarkers. An alternative approach would be the use of continuous outcome measures, such as the MMSE or Clinical Dementia Rating Scale–Sum of Boxes, which are not accounted for in the current study because we deliberately attempted to identify a clinical, dichotomous outcome measure.

Another potential limitation is the drift of Aβ1-42 levels over time, which might confound results and reduce statistical power.[47-49] We did not include biomarker drift in our

models because the models are intended for use in future patients, and we cannot identify how drift will develop in coming years. Furthermore, the effect of drift on overall prognostic performance is probably low. Finally, both CSF concentrations and volumetric MRI measurements vary considerably across different methods. The generalizability of the models is restricted to the use of identical methods. We validated our models in ADNI-2 using a *z* score approach, and we demonstrated that the prognostic models performed well despite differences in samples and methods.

## Conclusions

The prognostic models described in our study could be easily implemented in daily practice, contributing to personalized diagnostic care and harmonization of clinical practice. In this article, we present a framework for a precision medicine approach. Worldwide translation of these models remains challenging and requires particular attention to generalizability across samples and measurement methods. Furthermore, models will further improve when longer-term follow-up becomes available. Nonetheless, our models show how biomarker research can be translated into clinical practice in a tractable manner.

Our models may aid the clinician in interpreting biomarker values and providing individually tailored prognostic information, and the models also allow the appreciation of the incremental value of additional testing. After further validation, we intend these models to serve as input for a web-based tool (application) to support clinicians in integrating biomarkers in their daily diagnostic practice.

ARTICLE INFORMATION

**Accepted for Publication:** July 24, 2017.

**Published Online:** October 16, 2017. doi:10.1001/jamaneurol.2017.2712

**Author Affiliations:** Department of Neurology and Alzheimer Center, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands (van Maurik, Zwan, Tijms, Bouwman, Scheltens, van der Flier); Department of Epidemiology and Biostatistics, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands (van Maurik, Berkhof, van der Flier); Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands (Teunissen); Department of Radiology and Nuclear Medicine, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands (Wattjes, Barkhof); Institutes of Neurology and Healthcare Engineering, University College London, London, England (Barkhof).

**Author Contributions:** Ms van Maurik and Dr van der Flier had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* van Maurik, Teunissen, Scheltens, van der Flier.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* van Maurik, Teunissen, Scheltens, Wattjes, Berkhof.
*Critical revision of the manuscript for important intellectual content:* Zwan, Tijms, Bouwman, Teunissen, Scheltens, Wattjes, Barkhof, Berkhof, van der Flier.
*Statistical analysis:* van Maurik, Berkhof.
*Obtained funding:* Scheltens, van der Flier.
*Administrative, technical, or material support:* van Maurik, Zwan, Scheltens, Wattjes, Barkhof, van der Flier.
*Study supervision:* Bouwman, Scheltens, Wattjes, Berkhof, van der Flier.

**Conflict of Interest Disclosures:** Dr Scheltens reported receiving grant support (for the institution) from GE Healthcare, Danone Research, Piramal, and Merck and, in the past 2 years, receiving consultancy/speaker fees (paid to the institution) from Lilly, GE Healthcare, Novartis, Sanofi, Nutricia, Probiodrug, Biogen, Roche, Avraham, and EIP Pharma. Dr Barkhof reported serving as a consultant for Biogen-Idec, Janssen Alzheimer Immunotherapy, Bayer Schering, Merck Serono, Roche, Novartis, Genzume, and Sanofi; receiving sponsorship from European Horizon 2020, Netherlands Organisation for Scientific Research, National Institute for Health Research–University College London Hospitals Biomedical Research Centre, Scottish Multiple Sclerosis Register, Teva, Novartis, and Toshiba; and serving on the editorial boards of Radiology, Brain, Neuroradiology, MSJ, and Neurology.
Dr van der Flier reported performing contract research and serving as an invited speaker for Boehringer Ingelheim and working on research programs funded by ZonMW, Netherlands Organisation for Scientific Research, European 7th Framework Programme, Alzheimer Nederland, Cardiovasculair Onderzoek Nederland, stichting Dioraphte, Gieskes-Strijbis fonds, Boehringer Ingelheim, Piramal Neuroimaging, Roche BV, Janssen Stellar, and Combinostics (all funding is paid to her institution). No other disclosures were reported.

**Funding/Support:** Data collection and sharing for this project were funded by grant U01 AG024904 from the National Institutes of Health and W81XWH-12-2-0012 from the US Department of Defense to the ADNI. The ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and contributions from the following: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica Inc, Biogen, Bristol-Myers Squibb, CereSpir Inc, Cogstate, Eisai Inc, Elan Pharmaceuticals Inc, Eli Lilly and Company, Euroimmun, F. Hoffmann–La Roche Ltd and its affiliated company Genentech, Fujirebio, GE Healthcare, IXICO Ltd, Janssen Alzheimer Immunotherapy Research & Development LLC, Johnson & Johnson Pharmaceutical Research & Development LLC, Lumosity, Lundbeck, Merck & Co, Meso Scale Diagnostics LLC, NeuroRx Research, Neurotrack Technologies, Novartis, Pfizer, Piramal Imaging, Servier, Takeda, and Transition Therapeutics. The Canadian Institutes of Health Research has been providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. The ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Research of the VU University Medical Center Alzheimer Center is part of the neurodegeneration research program of Amsterdam Neuroscience. The VU University Medical Center Alzheimer Center is supported by Alzheimer Nederland and Stichting VU University Medical Center funds. This study is funded by ZonMW-Memorabel (Alzheimer's Biomarkers in Daily Practice [ABIDE]; project 733050201), a project in the context of the Dutch Deltaplan Dementie.

**Role of the Funder/Sponsor:** The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Group Information:** The ADNI group consists of the following individuals. ADNI Grant Opportunities and II: Part A: Leadership and Infrastructure: Michael W. Weiner, MD, University of California, San Francisco (principal investigator); Paul Aisen, MD, University of Southern California, Los Angeles (ADCS principal investigator and director of Coordinating Center Clinical Core); Executive Committee: Michael W. Weiner, MD, University of California, San Francisco; Paul Aisen, MD, University of Southern California, Los Angeles; Ronald Petersen, MD, PhD, Mayo Clinic, Rochester; Clifford R. Jack Jr, MD, Mayo Clinic, Rochester; William Jagust, MD, University of California, Berkeley; John Q. Trojanowski, MD, PhD, University of Pennsylvania; Arthur W. Toga, PhD, University of South California, Los Angeles; Laurel Beckett, PhD, University of California, Davis; Robert C. Green, MD, MPH, Brigham and Women's Hospital/Harvard Medical School; Andrew J. Saykin, PsyD, Indiana University; John Morris, MD, Washington University in St Louis; Leslie M. Shaw, University of Pennsylvania; ADNI External Advisory Board: Zaven Khachaturian, PhD, Prevent Alzheimer's Disease 2020 (chair); Greg Sorensen, MD, Siemens; Maria Carrillo, PhD, Alzheimer's Association; Lew Kuller, MD, University of Pittsburgh; Marc Raichle, MD, Washington University in St Louis; Steven Paul, MD, Cornell University; Peter Davies, MD, Albert Einstein College of Medicine of Yeshiva University; Howard Fillit, MD, AD Drug Discovery Foundation; Franz Hefti, PhD, Acumen Pharmaceuticals; David Holtzman, MD, Washington University in St Louis; M. Marcel Mesulam, MD, Northwestern University; William Potter, MD, National Institute of Mental

Health; Peter Snyder, PhD, Brown University; ADNI 2 Private Partner Scientific Board: Adam Schwartz, MD, Eli Lilly (chair); Data and Publications Committee: Robert C. Green, MD, MPH, Brigham and Women's Hospital/Harvard Medical School (chair); Resource Allocation Review Committee: Tom Montine, MD, PhD, University of Washington (chair); Clinical Core Leaders: Ronald Petersen, MD, PhD, Mayo Clinic, Rochester (core principal investigator); Paul Aisen, MD, University of Southern California, Los Angeles; Clinical Informatics and Operations: Ronald G. Thomas, PhD, Michael Donohue, PhD, Sarah Walter, MSc, Devon Gessert, Tamie Sather, MA, Gus Jiminez, MBS, Archana B. Balasubramanian, PhD, Jennifer Mason, MPH, Iris Sim, University of California, San Diego; Biostatistics Core Leaders and Key Personnel: Laurel Beckett, PhD (core principal investigator), Danielle Harvey, PhD, Michael Donohue, PhD, University of California, San Diego; Magnetic Resonance Imaging Core Leaders and Key Personnel: Clifford R. Jack Jr, MD (core principal investigator), Matthew Bernstein, PhD, Mayo Clinic, Rochester; Nick Fox, MD, University of London, Paul Thompson, PhD, University of California, Los Angeles School of Medicine; Norbert Schuff, PhD, University of California, San Francisco; Charles DeCarli, MD, University of California, Davis; Bret Borowski, RT, Jeff Gunter, PhD, Matt Senjem, MS, Prashanthi Vemuri, PhD, David Jones, MD, Kejal Kantarci, Chad Ward, Mayo Clinic, Rochester; Positron Emission Tomography Core Leaders and Key Personnel: William Jagust, MD, University of California, Berkeley (core principal investigator); Robert A. Koeppe, PhD, University of Michigan; Norm Foster, MD, University of Utah; Eric M. Reiman, MD, Banner Alzheimer's Institute; Kewei Chen, PhD, Banner Alzheimer's Institute; Chet Mathis, MD, University of Pittsburgh; Susan Landau, PhD, University of California, Berkeley; Neuropathology Core Leaders: John C. Morris, MD, Nigel J. Cairns, PhD, FRCPath, Erin Franklin, MS, CCRP, Lisa Taylor-Reinwald, BA, HTL (ASCP, past investigator), Washington University in St Louis; Biomarkers Core Leaders and Key Personnel: Leslie M. Shaw, PhD, John Q. Trojanowski, MD, PhD, Virginia Lee, PhD, MBA, Magdalena Korecka, PhD, Michal Figurski, PhD, University of Pennsylvania School of Medicine; Informatics Core Leaders and Key Personnel: Arthur W. Toga, PhD (core principal investigator), Karen Crawford, Scott Neu, PhD, University of California, San Francisco; Genetics Core Leaders and Key Personnel: Andrew J. Saykin, PsyD, Tatiana M. Foroud, PhD, Indiana University; Steven Potkin, MD, University of California, Irvine; Li Shen, PhD, Kelley Faber, MS, CCRC, Sungeun Kim, PhD, Kwangsik Nho, PhD, Indiana University; Initial Concept Planning & Development: Michael W. Weiner, MD, University of California, San Francisco; Lean Thal, MD, University of California, San Diego; Zaven Khachaturian, PhD, Prevent Alzheimer's Disease 2020; Early Project Proposal Development: Leon Thal, MD, University of California, San Diego; Neil Buckholtz, National Institute on Aging, Michael W. Weiner, MD, University of California, San Francisco; Peter J. Snyder, PhD, Brown University; William Potter, MD, National Institute of Mental Health; Steven Paul, MD, Cornell University; Marilyn Albert, PhD, Johns Hopkins University; Richard Frank, MD, PhD, Richard Frank Consulting; Zaven Khachaturian, PhD, Prevent Alzheimer's Disease 2020; John Hsiao, MD, National Institute on Aging. Part B: Investigators by Site: Oregon Health & Science University: Jeffrey Kaye, MD, Joseph Quinn, MD, Lisa Silbert, MD, Betty Lind, BS, Raina Carter, BA (past investigator), Sara Dolen, BS (past investigator); University of Southern California, Los Angeles: Lon S. Schneider, MD, Sonia Pawluczyk, MD, Mauricio Becerra, BS, Liberty Teodoro, RN, Bryan M. Spann, DO, PhD (past investigator); University of California, San Diego: James Brewer, MD, PhD, Helen Vanderswag, RN, Adam Fleisher, MD (past investigator); University of Michigan: Judith L. Heidebrink, MD, MS, Joanne L. Lord, LPN, BA, CCRC (past investigator), Mayo Clinic, Rochester: Ronald Petersen, MD, PhD, Sara S. Mason, RN, Colleen S. Albers, RN, David Knopman, MD, Kris Johnson, RN (past investigator); Baylor College of Medicine: Rachelle S. Doody, MD, PhD, Javier Villanueva-Meyer, MD, Valory Pavlik, PhD, Victoria Shibley, MS, Munir Chowdhury, MBBS, MS (past investigator), Susan Rountree, MD (past investigator), Mimi Dang, MD (past investigator); Columbia University Medical Center: Yaakov Stern, PhD, Lawrence S. Honig, MD, PhD, Karen L. Bell, MD; Washington University in St Louis: Beau Ances, MD, John C. Morris, MD, Maria Carroll, RN, MSN, Mary L. Creech, RN, MSW, Erin Franklin, MS, CCRP, Mark A. Mintun, MD (past investigator), Stacy Schneider, APRN, BC, GNP (past investigator), Angela Oliver, RN, BSN, MSG (past investigator); University of Alabama, Birmingham: Daniel Marson, JD, PhD, David Geldmacher, MD, Marissa Natelson Love, MD, Randall Griffith, PhD, ABPP (past investigator), David Clark, MD (past investigator), John Brockington, MD (past investigator); Erik Roberson, MD (past investigator); Mount Sinai School of Medicine: Hillel Grossman, MD, Effie Mitsis, PhD; Rush University Medical Center: Raj C. Shah, MD, Leyla deToledo-Morrell, PhD (past investigator); Wien Center: Ranjan Duara, MD, Maria T. Greig-Custo, MD, Warren Barker, MA, MS; Johns Hopkins University: Marilyn Albert, PhD, Chiadi Onyike, MD, Daniel D'Agostino II, BS, Stephanie Kielb, BS (past investigator); New York University: Martin Sadowski, MD, PhD, Mohammed O. Sheikh, MD, Anaztasia Ulysse, Mrunalini Gaikwad; Duke University Medical Center: P. Murali Doraiswamy, MBBS, FRCP, Jeffrey R. Petrella, MD, Salvador Borges-Neto, MD, Terence Z. Wong, MD (past investigator), Edward Coleman (past investigator); University of Pennsylvania: Steven E. Arnold, MD, Jason H. Karlawish, MD, David A. Wolk, MD, Christopher M. Clark, MD; University of Kentucky: Charles D. Smith, MD, Greg Jicha, MD, Peter Hardy, PhD, Partha Sinha, PhD, Elizabeth Oates, MD, Gary Conrad, MD; University of Pittsburgh: Oscar L. Lopez, MD, MaryAnn Oakley, MA, Donna M. Simpson, CRNP, MPH; University of Rochester Medical Center: Anton P. Porsteinsson, MD, Bonnie S. Goldstein, MS, NP, Kim Martin, RN, Kelly M. Makino, BS (past investigator), M. Saleem Ismail, MD (past investigator), Connie Brand, RN (past investigator); University of California, Irvine: Steven G. Potkin, MD, Adrian Preda, MD, Dana Nguyen, PhD; University of Texas Southwestern Medical School: Kyle Womack, MD, Dana Mathews, MD, PhD, Mary Quiceno, MD; Emory University: Allan I. Levey, MD, PhD, James J. Lah, MD, PhD, Janet S. Cellar, DNP, PMHCNS-BC; University of Kansas Medical Center: Jeffrey M. Burns, MD, Russell H. Swerdlow, MD, William M. Brooks, PhD; University of California, Los Angeles: Liana Apostolova, MD, Kathleen Tingus, PhD, Ellen Woo, PhD, Daniel H.S. Silverman, MD, PhD, Po H. Lu, PsyD (past investigator), George Bartzokis, MD (past investigator); Mayo Clinic, Jacksonville: Neill R Graff-Radford, MBBCH, FRCP (London), Francine Parfitt, MSH, CCRC, Kim Poki-Walker, BA, Indiana University: Martin R. Farlow, MD, Ann Marie Hake, MD, Brandy R. Matthews, MD (past investigator), Jared R. Brosch, MD, Scott Herring, RN, CCRC, Yale University School of Medicine: Christopher H. van Dyck, MD, Richard E. Carson, PhD, Martha G. MacAvoy, PhD, Pradeep Varma, MD, McGill University, Montreal-Jewish General Hospital: Howard Chertkow, MD, Howard Bergman, MD, Chris Hosein, MEd, Sunnybrook Health Sciences, Ontario: Sandra Black, MD, FRCPC, Bojana Stefanovic, PhD Curtis Caldwell, PhD, UBC Clinic for AD and Related Disorders: Ging-Yuek Robin Hsiung, MD, MHSc, FRCPC, Benita Mudge, BS, Vesna Sossi, PhD, Howard Feldman, MD, FRCPC (past investigator), Michele Assaly, MA (past investigator); Cognitive Neurology–St Joseph's, Ontario: Elizabeth Finger, MD, Stephen Pasternack, MD, PhD, Irina Rachisky, MD, Dick Trost, PhD (past investigator), Andrew Kertesz, MD (past investigator); Cleveland Clinic Lou Ruvo Center for Brain Health: Charles Bernick, MD, MPH, Donna Munic, PhD, Northwestern University: Marek-Marsel Mesulam, MD, Emily Rogalski, PhD, Kristine Lipowski, MA, Sandra Weintraub, PhD, Borna Bonakdarpour, MD, Diana Kerwin, MD (past investigator), Chuang-Kuo Wu, MD, PhD (past investigator), Nancy Johnson, PhD (past investigator); Premiere Research Institute (Palm Beach Neurology): Carl Sadowsky, MD, Teresa Villena, MD; Georgetown University Medical Center: Raymond Scott Turner, MD, PhD, Kathleen Johnson, NP, Brigid Reynolds, NP; Brigham and Women's Hospital: Reisa A. Sperling, MD, Keith A. Johnson, MD, Gad Marshall, MD, Stanford University: Jerome Yesavage, MD, Joy L. Taylor, PhD, Barton Lane, MD, Allyson Rosen, PhD (past investigator), Jared Tinklenberg, MD (past investigator), Banner Sun Health Research Institute: Marwan N. Sabbagh, MD, Christine M. Belden, PsyD, Sandra A. Jacobson, MD, Sherye A. Sirrel, CCRC, Boston University: Neil Kowall, MD, Ronald Killiany, PhD, Andrew E. Budson, MD, Alexander Norbash, MD (past investigator), Patricia Lynn Johnson, BA (past investigator); Howard University: Thomas O. Obisesan, MD, MPH, Saba Wolday, MSc, Joanne Allard, PhD, Case Western Reserve University: Alan Lerner, MD, Paula Ogrocki, PhD, Curtis Tatsuoka, PhD, Parianne Fatica, BA, CCRC; University of California, Davis, Sacramento: Evan Fletcher, PhD, Pauline Maillard, PhD, John Olichney, MD, Charles DeCarli, MD (past investigator), Owen Carmichael, PhD (past investigator); Neurological Care of CNY: Smita Kittur, MD (past investigator); Parkwood Hospital: Michael Borrie, MB, ChB, T.-Y. Lee, PhD, Rob Bartha, PhD, University of Wisconsin: Sterling Johnson, PhD, Sanjay Asthana, MD, Cynthia M. Carlsson, MD, MS, University of California, Irvine-BIC: Steven G. Potkin, MD, Adrian Preda, MD, Dana Nguyen, PhD, Banner Alzheimer's Institute: Pierre Tariot, MD, Anna Burke, MD, Ann Marie Milliken, NMD, Nadira Trncic, MD, PhD, CCRC (past investigator), Adam Fleisher, MD (past investigator), Stephanie Reeder, BA (past investigator); Dent Neurologic Institute: Vernice Bates, MD, Horacio Capote, MD, Michelle Rainka, PharmD, CCRP; Ohio State University: Douglas W. Scharre, MD, Maria Kataki, MD, PhD, Brendan Kelley, MD; Albany Medical College: Earl A. Zimmerman, MD, Dzintra Celmins, MD, Alice D. Brown, FNP; Hartford Hospital, Olin

Neuropsychiatry Research Center: Godfrey D. Pearlson, MD, Karen Blank, MD, Karen Anderson, RN; Dartmouth-Hitchcock Medical Center: Laura A. Flashman, PhD, Marc Seltzer, MD, Mary L. Hynes, RN, MPH, Robert B. Santulli, MD (past investigator); Wake Forest University Health Sciences: Kaycee M. Sink, MD, MAS, Leslie Gordineer, Jeff D. Williamson, MD, MHS (past investigator), Pradeep Garg, PhD (past investigator), Franklin Watkins, MD (past investigator), Rhode Island Hospital: Brian R. Ott, MD, Geoffrey Tremont, PhD, Lori A. Daiello, PharmD, ScM; Butler Hospital: Stephen Salloway, MD, MS, Paul Malloy, PhD, Stephen Correia, PhD, University of California, San Francisco: Howard J. Rosen, MD, Bruce L. Miller, MD, David Perry, MD, Medical University South Carolina: Jacobo Mintzer, MD, MBA, Kenneth Spicer, MD, PhD, David Bachman, MD, St. Joseph's Health Care: Elizabeth Finger, MD, Stephen Pasternak, MD, Irina Rachinsky, MD, John Rogers, MD, Andrew Kertesz, MD (past investigator), Dick Drost, MD (past investigator), Nathan Kline Institute: Nunzio Pomara, MD, Raymundo Hernando, MD, Antero Sarrael, MD, University of Iowa College of Medicine; Susan K. Schultz, MD, Karen Ekstam Smith, RN, Hristina Koleva, MD, Ki Won Nam, MD, Hyungsub Shim, MD (past investigator), Cornell University, Norman Relkin, MD, PhD, Gloria Chiang, MD, Michael Lin, MD, Lisa Ravdin, PhD, University of South Florida Health Byrd Alzheimer's Institute: Amanda Smith, MD, Balebail Ashok Raj, MD, Kristin Fargher, MD (past investigator). US Department of Defense ADNI Part A: Leadership and Infrastructure Principal Investigator: Michael W. Weiner, MD, University of California, San Francisco, ADCS Principal Investigator and Director of Coordinating Center Clinical Core: Paul Aisen, MD, University of Southern California; Executive Committee: Michael Weiner, MD, University of California, San Francisco; Paul Aisen, MD, University of Southern California; Ronald Petersen, MD, PhD, Mayo Clinic, Rochester, Robert C. Green, MD, MPH, Brigham and Women's Hospital/Harvard Medical School, Danielle Harvey, PhD, University of California, Davis, Clifford R. Jack Jr, MD, Mayo Clinic, Rochester, William Jagust, MD, University of California, Berkeley, John C. Morris, MD, Washington University in St Louis; Andrew J. Saykin, PsyD, Indiana University, Leslie M. Shaw, PhD, Perelman School of Medicine, University of Pennsylvania, Arthur W. Toga, PhD, University of California, Davis, John Q. Trojanowski, MD, PhD, Perelman School of Medicine, University of Pennsylvania Psychological Evaluation/PTSD Core Thomas Neylan, MD, University of California, San Francisco; Traumatic Brain Injury/TBI Core: Jordan Grafman, PhD, Rehabilitation Institute of Chicago, Feinberg School of Medicine; Northwestern University Data and Publication Committee (DPC): Robert C. Green, MD, MPH, BWH/HMS (chair); Resource Allocation Review Committee: Tom Montine, MD, PhD, University of Washington (chair); Clinical Core Leaders: Michael Weiner, MD (core principal investigator), Ronald Petersen, MD, PhD (core principal investigator), Mayo Clinic, Rochester; Paul Aisen, MD, University of Southern California; Clinical Informatics and Operations: Ronald G. Thomas, PhD, Michael Donohue, PhD, Devon Gessert, Tamie Sather, MA, Melissa Davis, Rosemary Morrison, MPH, Gus Jiminez, MBS, University of California, San Diego; Thomas Neylan, MD, Jacqueline Hayes, Shannon Finley, University of California, San Francisco; Biostatistics Core Leaders and Key Personnel: Danielle Harvey, PhD (core principal investigator), Michael Donohue, PhD, University of California, San Diego; Magnetic Resonance Imaging Core Leaders and Key Personnel: Clifford R. Jack Jr, MD (core principal investigator), Matthew Bernstein, PhD, Bret Borowski, RT, Jeff Gunter, PhD, Matt Senjem, MS, Kejal Kantarci, Chad Ward, Mayo Clinic, Rochester; PET Core Leaders and Key Personnel: William Jagust, MD, University of California, Berkeley (core principal investigator), Robert A. Koeppe, PhD, University of Michigan, Norm Foster, MD, University of Utah, Eric M. Reiman, MD, and Kewei Chen, PhD, Banner Alzheimer's Institute; Susan Landau, PhD, University of California, Berkeley; Neuropathology Core Leaders: John C. Morris, MD, Nigel J. Cairns, PhD, FRCPath, Erin Householder, MS, Washington University in St Louis; Biomarkers Core Leaders and Key Personnel: Leslie M. Shaw, PhD, John Q. Trojanowski, MD, PhD, Virginia Lee, PhD, MBA, Magdalena Korecka, PhD, Michal Figurski, PhD, Perelman School of Medicine, University of Pennsylvania; Informatics Core Leaders and Key Personnel: Arthur W. Toga, PhD (core principal investigator), Karen Crawford, Scott Neu, PhD, University of Southern California; Genetics Core Leaders and Key Personnel: Andrew J. Saykin, PsyD, Tatiana M. Foroud, PhD, Indiana University, Steven Potkin, MD, University of California, Irvine, Li Shen, PhD, Kelley Faber, MS, CCRC, Sungeun Kim, PhD, Kwangsik Nho, PhD, Indiana University; Initial Concept Planning & Development: Michael W. Weiner, MD, University of California, San Francisco; Karl Friedl, US Department of Defense (retired). Part B: Investigators by Site University of Southern California: Lon S. Schneider, MD, MS, Sonia Pawluczyk, MD, Mauricio Becerra, University of California, San Diego: James Brewer, MD, PhD, Helen Vanderswag, RN, Columbia University Medical Center: Yaakov Stern, PhD, Lawrence S. Honig, MD, PhD, Karen L. Bell, MD, Rush University Medical Center: Debra Fleischman, PhD, Konstantinos Arfanakis, PhD, Raj C. Shah, MD; Wien Center: Ranjan Duara, MD (principal investigator), Daniel Varon, MD (coprincipal investigator); Maria T. Greig; HP Coordinator, Duke University Medical Center: P. Murali Doraiswamy, MBBS, Jeffrey R. Petrella, MD, Olga James, MD; University of Rochester Medical Center: Anton P. Porsteinsson, MD (director), Bonnie Goldstein, MS, NP (coordinator), Kimberly S. Martin, RN; University of California, Irvine: Steven G. Potkin, MD, Adrian Preda, MD, Dana Nguyen, PhD; Medical University of South Carolina: Jacobo Mintzer, MD, MBA, Dino Massoglia, MD, PhD, Olga Brawman-Mintzer, MD, Carl Sadowsky, MD, Walter Martinez, MD, Teresa Villena, MD, University of California, San Francisco: William Jagust, MD, Susan Landau, PhD, Howard Rosen, MD, David Perry; Georgetown University Medical Center: Raymond Scott Turner, MD, PhD, Kelly Behan Brigid Reynolds, NP; Brigham and Women's Hospital: Reisa A. Sperling, MD, Keith A. Johnson, MD, Gad Marshall, MD; Banner Sun Health Research Institute: Marwan N. Sabbagh, MD, Sandra A. Jacobson, MD, Sherye A. Sirrel, MS, CCRC; Howard University: Thomas O. Obisesan, MD, MPH, Saba Wolday, MSc, Joanne Allard, PhD; University of Wisconsin: Sterling C. Johnson, PhD, J. Jay Fruehling, MA, Sandra Harding, MS; University of Washington: Elaine R. Peskind, MD, Eric C. Petrie, MD, MS, Gail Li, MD, PhD; Stanford University: Jerome A. Yesavage, MD, Joy L. Taylor, PhD, Ansgar J. Furst, PhD, Steven Chao, MD; Cornell University: Norman Relkin, MD, PhD, Gloria Chiang, MD; Premiere Research Institute (Palm Beach Neurology): Lisa Ravdin, PhD.

**Additional Contributions:** Data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. We thank the ABIDE study group, Amsterdam, the Netherlands. Department of Neurology and Alzheimer Center, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands: Wiesje M. van der Flier, PhD, Philip Scheltens, MD, PhD, Femke H. Bouwman, MD, PhD, Marissa D. Zwan, PhD, Ingrid S. van Maurik, MSc, Arno de Wilde, MD, Wiesje Pelkmans, MSc, Colin Groot, MSc, Ellen Dicks, MSc, and Els Dekkers; Department of Radiology and Nuclear Medicine, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands: Bart N. M. van Berckel, MD, PhD, Frederik Barkhof, MD, PhD, and Mike P. Wattjes, MD, PhD; Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands: Charlotte E. Teunissen, PhD, and Eline A. Willemse, MSc; Department of Medical Psychology, University of Amsterdam, Academic Medical Center, Amsterdam, the Netherlands: Ellen M. Smets, PhD, Marleen Kunneman, PhD, and Sanne Schepers, MSc; BV Cyclotron, Amsterdam, the Netherlands: E. van Lier, MSc; Spaarne Gasthuis, Haarlem, the Netherlands: Niki M. Schoonenboom, MD, PhD; Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, the Netherlands: Geert Jan Biessels, MD, PhD, and Jurre H. Verwer, MSc; Department of Geriatrics, University Medical Center Utrecht, Utrecht, the Netherlands: Dieneke H. Koek, MD, PhD; Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, the Netherlands, Utrecht, the Netherlands: Monique G. Hobbelink, MD; Vilans, Center of Expertise in Long-Term Care: Mirella M. Minkman, PhD, Cynthia S. Hofman, PhD, and Ruth Pel, MSc; Espria, Meppel, the Netherlands: Esther Kuiper, MSc; Piramal Imaging GmbH, Berlin, Germany: Andrew Stephens, MD, PhD; Roche Diagnostics International Ltd, Rotrkreuz, Switzerland: Richard Bartra-Utermann, MD; and the members of the ABIDE memory clinic panel: Niki M. Schoonenboom, MD, PhD (Spaarne Gasthuis, Haarlem, the Netherlands); Barbera van Harten, MD, PhD, Niek Verwey, MD, PhD, and Peter van Walderveen, MD (Medisch Centrum Leeuwarden, Leeuwarden. the Netherlands); Ester Korf, MD, PhD (Admiraal de Ruyter Ziekenhuis, Vlissingen, the Netherlands); Gerwin Roks, MD, PhD (Sint Elisabeth Ziekenhuis, Tilburg, the Netherlands); Bertjan Kerklaan, MD, PhD (Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands); Leo Boelaarts, MD (Medisch Centrum Alkmaar, Alkmaar, the Netherlands); Annelies. W. E. Weverling, MD (Diaconessenhuis, Leiden, the Netherlands); Rob J. van Marum, MD, PhD (Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands); Jules J. Claus, MD, PhD (Tergooi Ziekenhuis, Hilversum, the Netherlands); and Koos Keizer, MD, PhD (Catherina Ziekenhuis, Eindhoven, the Netherlands).

## REFERENCES


1. Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *Lancet*. 2016;388(10043):505-517.
2. Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol*. 2009;8(7):619-627.
3. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment 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(3):270-279.
4. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron*. 2013;80(6):1347-1358.
5. Bouwman FH, Schoonenboom SN, van der Flier WM, et al. CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. *Neurobiol Aging*. 2007;28(7):1070-1074.
6. Davatzikos C, Bhatt P, Shaw LM, Batmanghelich KN, Trojanowski JQ. Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification. *Neurobiol Aging*. 2011;32(12):2322-2327.
7. van Harten AC, Visser PJ, Pijnenburg YA, et al. Cerebrospinal fluid Aβ42 is the best predictor of clinical progression in patients with subjective complaints. *Alzheimers Dement*. 2013;9(5):481-487.
8. Richard E, Schmand BA, Eikelenboom P, Van Gool WA; Alzheimer's Disease Neuroimaging Initiative. MRI and cerebrospinal fluid biomarkers for predicting progression to Alzheimer's disease in patients with mild cognitive impairment: a diagnostic accuracy study. *BMJ Open*. 2013;3(6):e002541.
9. Duits FH, Prins ND, Lemstra AW, et al. Diagnostic impact of CSF biomarkers for Alzheimer's disease in a tertiary memory clinic. *Alzheimers Dement*. 2015;11(5):523-532.
10. Kester MI, Boelaarts L, Bouwman FH, et al. Diagnostic impact of CSF biomarkers in a local hospital memory clinic. *Dement Geriatr Cogn Disord*. 2010;29(6):491-497.
11. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308.
12. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. 2007;6(8):734-746.
13. Frisoni GB, Perani D, Bastianello S, et al. Biomarkers for the diagnosis of Alzheimer's disease in clinical practice: an Italian intersocietal roadmap. *Neurobiol Aging*. 2017;52:119-131.
14. de Wilde A, van Maurik IS, Kunneman M, et al. Alzheimer's Biomarkers in Daily Practice (ABIDE) project: rationale and design. *Alzheimers Dement (Amst)*. 2017;6:143-151.
15. van der Flier WM, Pijnenburg YA, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *J Alzheimers Dis*. 2014;41(1):313-327.
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.
17. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250-260.
18. McKeith IG, Dickson DW, Lowe J, et al; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863-1872.
19. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51(6):1546-1554.
20. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(pt 9):2456-2477.
21. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014.
22. Wattjes MP, Henneman WJ, van der Flier WM, et al. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64-detector row CT. *Radiology*. 2009;253(1):174-183.
23. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J Neurol*. 1995;242(9):557-560.
24. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. *Eur Neurol*. 1996;36(5):268-272.
25. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. 2011;56(3):907-922.
26. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage*. 2002;17(1):479-489.
27. Mulder C, Verwey NA, van der Flier WM, et al. Amyloid-β(1-42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. *Clin Chem*. 2010;56(2):248-253.
28. Teunissen CE, Petzold A, Bennett JL, et al. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. *Neurology*. 2009;73(22):1914-1922.
29. Duits FH, Teunissen CE, Bouwman FH, et al. The cerebrospinal fluid "Alzheimer profile": easily said, but what does it mean? *Alzheimers Dement*. 2014;10(6):713-723.e2.
30. Newson RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *Stata J*. 2010;10(3):339-358.
31. Cefalu M. Pointwise confidence intervals for the covariate-adjusted survivor function in the Cox model. *Stata J*. 2011;11(1):64-81.
32. Verhage F. *Intelligence and Age: Research Among the Dutch Aged 12 to 77* [in Dutch]. Assen, the Netherlands: van Gorcum; 1964.
33. Dubois B, Hampel H, Feldman HH, et al; Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12(3):292-323.
34. Karlawish J. Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease. *Neurology*. 2011;77(15):1487-1493.
35. Vos S, van Rossum I, Burns L, et al. Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI. *Neurobiol Aging*. 2012;33(10):2272-2281.
36. Walhovd KB, Fjell AM, Brewer J, et al; Alzheimer's Disease Neuroimaging Initiative. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. *AJNR Am J Neuroradiol*. 2010;31(2):347-354.
37. Dickerson BC, Wolk DA; Alzheimer's Disease Neuroimaging Initiative. Biomarker-based prediction of progression in MCI: comparison of AD signature and hippocampal volume with spinal fluid amyloid-β and tau. *Front Aging Neurosci*. 2013;5:55.
38. Ewers M, Walsh C, Trojanowski JQ, et al; North American Alzheimer's Disease Neuroimaging Initiative (ADNI). Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiol Aging*. 2012;33(7):1203-1214.
39. Shaffer JL, Petrella JR, Sheldon FC, et al; Alzheimer's Disease Neuroimaging Initiative. Predicting cognitive decline in subjects at risk for Alzheimer disease by using combined cerebrospinal fluid, MR imaging, and PET biomarkers. *Radiology*. 2013;266(2):583-591.
40. Schuff N, Woerner N, Boreta L, et al; Alzheimer's Disease Neuroimaging Initiative. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*. 2009;132(pt 4):1067-1077.
41. Jansen WJ, Ossenkoppele R, Knol DL, et al; Amyloid Biomarker Study Group. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313(19):1924-1938.
42. Mattsson N, Rosén E, Hansson O, et al. Age and diagnostic performance of Alzheimer disease CSF biomarkers. *Neurology*. 2012;78(7):468-476.
43. Clerx L, van Rossum IA, Burns L, et al. Measurements of medial temporal lobe atrophy for prediction of Alzheimer's disease in subjects with mild cognitive impairment. *Neurobiol Aging*. 2013;34(8):2003-2013.
44. Antila K, Lötjönen J, Thurfjell L, et al. The PredictAD project: development of novel biomarkers and analysis software for early diagnosis of the Alzheimer's disease. *Interface Focus*. 2013;3(2):20120072.
45. Hall A, Muñoz-Ruiz M, Mattila J, et al; Alzheimer Disease Neuroimaging Initiative; AddNeuroMed consortium; DESCRIPA and Kuopio L-MCI. Generalizability of the disease state index prediction model for identifying patients progressing from mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis*. 2015;44(1):79-92.
46. Bron EE, Smits M, van der Flier WM, et al; Alzheimer's Disease Neuroimaging Initiative. Standardized evaluation of algorithms for computer-aided diagnosis of dementia based on structural MRI: the CADDementia challenge. *Neuroimage*. 2015;111:562-579.
47. Bertens D, Tijms BM, Scheltens P, Teunissen CE, Visser PJ. Unbiased estimates of cerebrospinal fluid β-amyloid 1-42 cutoffs in a large memory clinic population. *Alzheimers Res Ther*. 2017;9(1):8.
48. Schindler SE, Sutphen CL, Teunissen C, et al. Upward drift in cerebrospinal fluid amyloid β 42 assay values for more than 10 years [published online July 12, 2017]. *Alzheimers Dement*. doi:10.1016/j.jalz.2017.06.2264
49. Willemse EAJ, van Uffelen KWJ, van der Flier WM, Teunissen CE. Effect of long-term storage in biobanks on cerebrospinal fluid biomarker Aβ1-42, T-tau, and P-tau values. *Alzheimers Dement (Amst)*. 2017;8:45-50.