# Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eMethods

### 1. Statistical methods

### 1.1 Endpoints

The primary endpoint was change between pre-PET and 90-day post-PET patient management in one or more of the following categories: AD drug therapy; other drug therapy; or counseling about safety and future planning. For each category, the algorithm defined change as starting, stopping or modifying (e.g. adjusting dose of an existing medication) that element of the treatment plan. Only the implemented elements of the post-PET management plan were used in the determination of whether change occurred. The primary hypothesis was that the composite change would be ≥ 30% in each of the MCI and dementia subgroups.

Additional endpoints reported in this article include: rates of change in diagnosis from AD to non-AD etiology and vice-versa (secondary endpoint), agreement between pre-PET suspected etiology and PET results (exploratory) and change between pre-PET and post-PET rates of referrals to therapeutic trials (exploratory). The article also includes a pre-specified multivariable analysis of factors associated with change in the primary management endpoint (exploratory).

Post-hoc analyses assessed: rates of change in individual components of the management endpoint in MCI and dementia subgroups, overall and stratified by scan results; changes in diagnosis stratified by PET results; changes between pre- and post-PET diagnostic confidence; changes between pre- and post-PET overall use of AD drugs and additional diagnostic tests (at the population level); changes between pre- and post-PET rates of amyloid positivity in patients referred to AD clinical trials.

### 1.2 Final analysis set

All patients registered for this aim of the study were considered for inclusion in the analysis. The final analysis set was defined as the set of all registered cases with the following exclusions (study flow chart, article Figure 1):

(a) Cases that were found not to meet eligibility criteria or had other major protocol violations, or were without pre-PET data were excluded from further analysis.

(b) Among the remaining cases, those who did not have a PET scan or did not complete a post-PET visit were also excluded.

(c) Among cases with a PET scan and with complete post-PET visit, cases with a post-PET visit conducted in less than 60 days or more than 120 days from the PET scan were not included in the analysis.

A comparison of baseline characteristics of the final analysis cohort compared to those of the full cohort of participants with pre-PET data is presented in eTable 1.

### 1.3 Sample size determination

The sample size for this aim of the study was chosen to provide 80% power for testing the primary hypothesis within the MCI and dementia subgroups assuming an alternative value of 32% for the overall rate of change in each arm. A minimum of 4,200 cases with complete data in each subgroup would be needed to achieve this power. A total sample size of 11,050 cases would ensure the minimum in each arm assuming a 40% / 60% ratio in dementia vs MCI cases and a 5% proportion of cases with missing or

incomplete information. The actual proportion of enrolled cases with missing or incomplete information was considerably higher.

### 1.4 Statistical analysis

For the primary endpoint we calculated binomial estimates of rates (proportions) of change with Wilson confidence intervals (CIs) for the overall composite and for each composite category. The primary null hypothesis (overall rate of change < 30%) was tested against the alternative hypothesis (overall rate of change ≥ 30%) separately for the MCI and dementia subgroups using a Wald test, at level 0.025 (one-sided). The choice of a one-sided p-value was made to reflect the one-sided testing performed. A Bonferroni correction was pre-specified in the protocol for testing the primary endpoint hypothesis for the MCI and Dementia subsets. Thus, these tests were conducted at level 0.025.

Binomial estimates with Wilson intervals were derived for rates of change in additional endpoints. Comparisons of correlated estimates of proportions, such as those obtained from pre- and post-test assessments on participants, were performed using McNemar's test. With the exception of the tests for the primary hypothesis, all other p-values reported in the article are two-sided.

In a pre-specified exploratory analysis, mixed-effects logistic regression was used to examine the relationship between amyloid PET results and the probability of change in overall management, while controlling for participant characteristics and accounting for clustering by practice. A mixed-effects logistic regression model was estimated using the GLIMMIX procedure from SAS. The model included a random

effect for site and fixed effects for age (in years), sex (male/female), education (dichotomized as college graduate or advanced degree vs other), pre-PET use of AD drugs (yes/no), primary etiologic diagnosis (AD vs other), level of impairment (MCI vs dementia), and amyloid PET test result (positive/negative). The analysis examined two- and three-way interactions between PET result, primary etiologic diagnosis, and level of impairment. The significance of fixed effect coefficients (including interactions) was assessed using t-tests. Models were also compared using Akaike's information criterion. The nine cases in the analysis set that had uninterpretable PET results were excluded.

Multiple imputation was used to account for missing response data in the logistic regression analysis. Because the proportion of participants who did not have PET scans and thus had no PET result was substantial, we decided to not impute PET results and to perform the missing data analysis within the set of patients with completed scans (n=13,444, Figure 1). We imputed and analyzed 25 complete data sets using Rubin's methods for explicit, regression model based imputation and for combining the results from the imputed data sets.[1] The results of the imputation analysis were very similar to the results of the complete data analysis did not alter any of the conclusions (eTable 3).

A post-hoc Bonferroni correction was applied to the exploratory and post-hoc analyses in which we intended to report statistical significance. The comparisons covered by this correction comprise the tests for the ten coefficients of effects assessed in the logistic model (eight effects in Table 3, plus the 3-way interaction of amyloid PET result x primary pre-PET etiological diagnosis x level of impairment and the two-way interaction of primary pre-PET etiologic diagnosis with level of impairment) and the tests

for the four comparisons involved in the subset analysis of change in the use of AD drugs by PET result and impairment status. Thus significance would be declared if a p-value in these comparisons was below 0.05/14 = 0.0036.

Analyses presented in this article were performed using SAS/STAT version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

### 1.5. Interim analysis

There was no formal data monitoring committee and no provision for group sequential monitoring for efficacy in this single arm study. There was provision for a futility analysis to be conducted and reported to the Centers for Medicare & Medicaid Services (CMS). The analysis was designed with two interim looks, scheduled to be conducted when 1/3 and 2/3 of the post-PET information was available in each of the subsets. Because of the rapid accrual to the study, only the first interim analysis was feasible. The conditional power to reject the null hypothesis having obtained the first 1/3 of the data was computed using the subroutine Conditional Power of One Proportion Tests in the Pass15 software (PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.). The futility index was computed as 1-Conditional Power. The futility index estimated from this analysis was close to zero and accrual continued.

## eTable 1. Comparison of Final Analysis Cohort to All Participants With Pre-PET Data

| Characteristic | Level of Impairment | |
|---|---|---|
| | Participants with pre-PET data (n = 15,447) | Final analysis cohort (n = 11,409) |
| Age, median (IQR), years | 76 (71-81) | 75 (71-80) |
| Sex, No. (%) | | |
| Female | 8,017 (51.9) | 5,804 (50.9) |
| Male | 7,430 (48.1) | 5,605 (49.1) |
| Race[a], No. (%) | | |
| Black or African American | 612 (4.0) | 431 (3.8) |
| White or Caucasian | 13,343 (86.4) | 10,040 (88.0) |
| Other race[b] | 1,492 (9.7) | 938 (8.2) |
| Hispanic[c], No. (%) | 791 (5.1) | 453 (4.0) |
| Highest level of education, No. (%) | | |
| High school graduate (including equivalency) or less | 5,396 (34.9) | 3,741 (32.8) |
| Some college or associate degree | 3,690 (23.9) | 2,696 (23.6) |
| Bachelor's degree | 3,473 (22.5) | 2,704 (23.7) |
| Postgraduate degree | 2,888 (18.7) | 2,268 (19.9) |
| MMSE[d], median (IQR) | 26 (22-28) | 26 (22-28) |
| MoCA[e], median (IQR) | 21 (17-24) | 22 (17-24) |
| Leading suspected pre-PET etiology AD, No. (%) | 11,928 (77.2) | 8,770 (76.9) |
| Taking AD drugs at enrollment, No. (%) | 6,713 (43.5) | 5,055 (44.3) |
| Amyloid PET results[f], No. (%) | | |
| Positive | 8,112 (60.4) | 6,971 (61.1) |
| Negative | 5,312 (39.6) | 4,429 (38.9) |
| Level of impairment, No. (%) | | |
| MCI | 9,226 (59.7) | 6,905 (60.5) |
| Dementia | 6,221 (40.3) | 4,504 (39.5) |

Abbreviations: AD, Alzheimer disease; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment.

[a] Race as recorded by dementia specialist, study coordinator or practice administrator.
[b] American Indian, Asian, Native Hawaiian or Pacific Islander, unknown, or not reported

[c] Ethnicity as recorded by dementia specialist, study coordinator or practice administrator; grouped as Hispanic and Other (Not Hispanic, unknown, or not reported)

[d] MMSE range: 0 – 30, lower scores indicate worse global cognition.

[e] MoCA range: 0 – 30, lower scores indicate worse global cognition.

[f] Amyloid PET results: 9 cases with uninterpretable test results not included (6 in MCI and 3 in Dementia groups).

## eTable 2. PET Result Contribution to Post-PET Management Plan

| **Change in the overall management composite** | **All participants (n=11,409)** |
|---|---|
| No change in management, No. (%) | 4,391 (38.5) |
| Change in management, No. (%) | 7,018 (61.5) |
| PET result contributed significantly to post-PET management plan, No./Total (%) | 5,976/7,018 (85.2) |
| PET result did not contribute significantly to post-PET management plan, No./Total (%) | 1,042/7,018 (14.8) |

**eTable 3. Multiple Imputation Results for the Logistic Regression Model Shown in Table 3, Assessing Factors Associated With Change in the Composite Management Endpoint**

| Effect | OR (95% CI) | |
|---|---|---|
| | Complete-case analysis (n = 11,400)[a] | Multiple imputation analysis (n = 13,444)[b] |
| Intercept | 0.48 (0.28, 0.80) | 0.53 (0.32, 0.88) |
| Main effects | | |
| Age (10 years) | 1.09 (1.02, 1.17) | 1.01 (1.00, 1.01) |
| Gender (1=female, 0=male) | 1.04 (0.95, 1.13) | 1.05 (0.97, 1.14) |
| Education (1=college or advanced degree, 0=other) | 0.92 (0.84, 1.01) | 0.92 (0.84, 1.00) |
| Pre-PET AD drugs (1=yes, 0=no) | 0.93 (0.85, 1.02) | 0.93 (0.86, 1.02) |
| Amyloid PET result (1=positive, 0=negative) | 3.54 (2.96, 4.23) | 3.46 (2.91, 4.12) |
| Primary pre-PET etiological diagnosis (1=AD, 0=other) | 1.30 (1.12, 1.51) | 1.30 (1.12, 1.51) |
| Level of impairment (1=Dementia, 0=MCI) | 1.57 (1.36, 1.82) | 1.59 (1.37, 1.84) |
| Interactions | | |
| PET result × primary pre-PET etiological diagnosis AD | 0.60 (0.49, 0.73) | 0.61 (0.50, 0.74) |
| PET result × level of impairment | 0.54 (0.45, 0.64) | 0.54 (0.45, 0.64) |

Abbreviations: AD, Alzheimer disease; CI, confidence interval; MCI, mild cognitive impairment; OR, odds ratio.

[a] Complete-case analysis set did not include 9 cases with uninterpretable amyloid PET results.

[b] Imputation of missing data was performed within the set of participants who had completed the PET scan (Figure 1).

## eTable 4. Changes in Diagnostic Testing and Referrals

| | Pre-PET: recommended | | Post-PET: implemented | |
|---|---|---|---|---|
| **Additional Actions** | **N** | **% (95% CI)** | **N** | **% (95% CI)** |
| **Neuropsychological testing referral** | 2,379 | 20.9 (20.1, 21.6) | 1,136 | 10.0 (9.4, 10.5) |
| **Any imaging** | 1,971 | 17.3 (16.6, 18.0) | 1,020 | 8.9 (8.4, 9.5) |
| CT/CTA with/without contrast | 180 | 1.6 (1.4, 1.8) | 323 | 2.8 (2.5, 3.2) |
| MRI/MRA with/without contrast | 584 | 5.1 (4.7, 5.5) | 674 | 5.9 (5.5, 6.4) |
| Brain FDG-PET | 1,279 | 11.2 (10.6, 11.8) | 184 | 1.6 (1.4, 1.9) |
| [$^{123}$I]Ioflupane SPECT | 176 | 1.5 (1.3, 1.8) | 85 | 0.7 (0.6, 0.9) |
| Cerebral perfusion SPECT | 74 | 0.6 (0.5, 0.8) | 8 | 0.1 (0.0, 0.1) |
| Other imaging | 38 | 0.3 (0.2, 0.5) | 40 | 0.4 (0.3, 0.5) |
| **Genetic tests** | 478 | 4.2 (3.8, 4.6) | 173 | 1.5 (1.3, 1.8) |
| ApoE genotyping | 443 | 3.9 (3.5, 4.3) | 159 | 1.4 (1.2, 1.6) |
| Autosomal dominant mutations for AD | 39 | 0.3 (0.3, 0.5) | 6 | 0.1 (0.0, 0.1) |
| Autosomal dominant mutations for other conditions | 26 | 0.2 (0.2, 0.3) | 11 | 0.1 (0.1, 0.2) |
| **CSF tests** | 1,230 | 10.8 (10.2, 11.4) | 101 | 0.9 (0.7, 1.1) |
| AD CSF biomarkers | 1,197 | 10.5 (9.9, 11.1) | 77 | 0.7 (0.5, 0.8) |
| Other CSF studies | 185 | 1.6 (1.4, 1.9) | 45 | 0.4 (0.3, 0.5) |
| **Serologic tests** | 198 | 1.7 (1.5, 2.0) | 135 | 1.2 (1.0, 1.4) |
| **EEG** | 850 | 7.5 (7.0, 7.9) | 656 | 5.7 (5.3, 6.2) |
| **Polysomnography** | 377 | 3.3 (3.0, 3.6) | 239 | 2.1 (1.8, 2.4) |
| **Other tests** | 44 | 0.4 (0.3, 0.5) | 57 | 0.5 (0.4, 0.6) |
| **Other specialist referrals (e.g. psychiatrist, sleep medicine)** | 698 | 6.1 (5.7, 6.6) | 669 | 5.9 (5.4, 6.3) |
| **Surgical intervention (e.g. shunting for hydrocephalus)** | 43 | 0.4 (0.3, 0.5) | 25 | 0.2 (0.1, 0.3) |
| **Substance abuse treatment/support programs** | 58 | 0.5 (0.4, 0.7) | 31 | 0.3 (0.2, 0.4) |
| **Physical, occupational or speech therapy rehabilitation** | 411 | 3.6 (3.3, 4.0) | 372 | 3.3 (3.0, 3.6) |
| **Cognitive rehabilitation** | 677 | 5.9 (5.5, 6.4) | 463 | 4.1 (3.7, 4.4) |
| **Clinical trial referrals** | 2,023 | 17.7 (17.0, 18.4) | 1,503 | 13.2 (12.6, 13.8) |
| Drug therapy or other therapeutic trial for AD | 1,966 | 17.2 (16.6, 17.9) | 1,401 | 12.3 (11.7, 12.9) |
| Drug therapy or other therapeutic trial for non-AD disorder | 166 | 1.5 (1.3, 1.7) | 169 | 1.5 (1.3, 1.7) |

Abbreviations: AD, Alzheimer disease; ApoE, apolipoprotein E; CI, confidence interval; CTA, CT angiogram; EEG, electroencephalogram; FDG, [$^{18}$F]fludeoxyglucose; MRA, MR angiogram.

## eTable 5. Combinations of Changes on Components of the Composite Management Endpoint

| Domain | All participants (n=11,409) | Participants with MCI (n=6,905) | Participants with dementia (n=4,504) |
|---|---|---|---|
| | No. (%) | No. (%) | No. (%) |
| AD drugs only | 2,566 (22.5) | 1,499 (21.7) | 1,067 (23.7) |
| AD drugs and non-AD drugs | 964 (8.4) | 530 (7.7) | 434 (9.6) |
| AD drugs and counseling | 933 (8.2) | 580 (8.4) | 353 (7.8) |
| Non-AD drugs only | 873 (7.7) | 449 (6.5) | 424 (9.4) |
| Counseling only | 793 (7.0) | 498 (7.2) | 295 (6.5) |
| AD drugs, non-AD drugs, and counseling | 573 (5.0) | 405 (5.9) | 168 (3.7) |
| Non-AD drugs and counseling | 316 (2.8) | 198 (2.9) | 118 (2.6) |

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

Non-AD drugs include drugs that impact cognition, mood or behavior and drugs used to treat other neurological conditions or address dementia risk factors.

## eTable 6. Changes in Management by Scan Result

| Domain | All participants | | Participants with MCI | | Participants with dementia | |
|---|---|---|---|---|---|---|
| | Aβ PET+ | Aβ PET- | Aβ PET+ | Aβ PET- | Aβ PET+ | Aβ PET- |
| | % (Fraction) | % (Fraction) | % (Fraction) | % (Fraction) | % (Fraction) | % (Fraction) |
| **Overall** | 67.2 (4,686/6,971) | 52.6 (2,329/4,429) | 69.0 (2,635/3,817) | 49.4 (1,521/3,082) | 65.0 (2,051/3,154) | 60.0 (808/1,347) |
| **AD drugs** | 49.4 (3,443/6,971) | 35.9 (1,590/4,429) | 52.8 (2,017/3,817) | 32.3 (994/3,082) | 45.2 (1,426/3,154) | 44.2 (596/1,347) |
| **Non-AD drugs** | 25.1 (1,747/6,971) | 22.1 (978/4,429) | 24.2 (923/3,817) | 21.3 (658/3,082) | 26.1 (824/3,154) | 23.8 (320/1,347) |
| **Counseling** | 24.3 (1,697/6,971) | 20.7 (917/4,429) | 26.9 (1,028/3,817) | 21.2 (652/3,082) | 21.2 (669/3,154) | 19.7 (265/1,347) |

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer disease; Aβ, amyloid-beta.

This analysis does not include 9 participants with uninterpretable amyloid PET results.

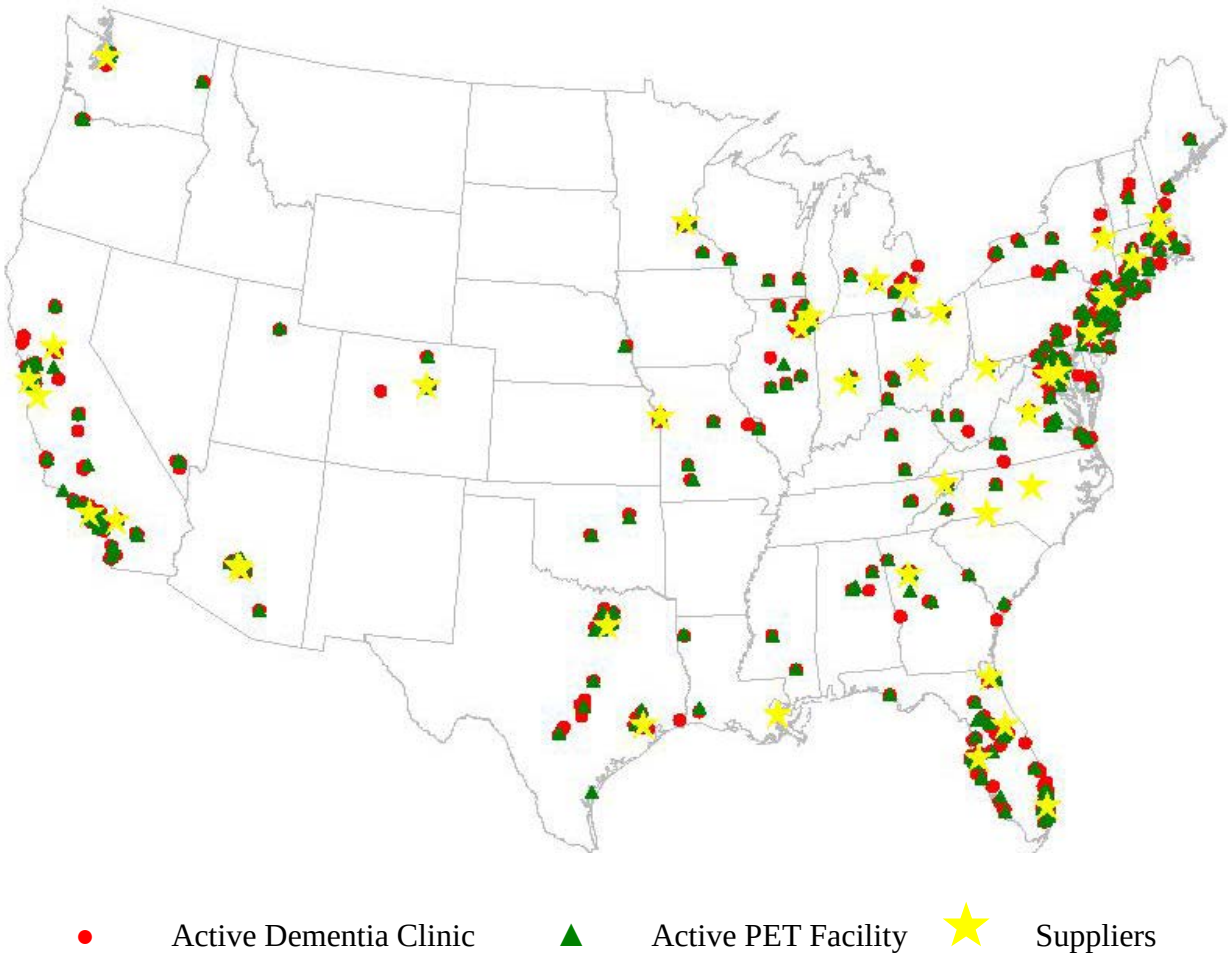
**eTable 7. Pre-PET and Post-PET Alzheimer Disease Drug Use by Level of Impairment and Amyloid PET Result**

| | | Post-PET AD drug use | | |
|---|---|---|---|---|
| | | Taking AD drugs | Not taking AD drugs | Total |
| Amyloid PET result | Pre-PET AD drug use | No. (%) | No. (%) | No. (%) |
| **MCI** | | | | |
| Positive | Taking AD drugs | 1,494 (96.8) | 49 (3.2) | 1,543 (40.4) (95% CI 38.9, 42.0) |
| | Not taking AD drugs | 1,615 (71.0) | 659 (29.0) | 2,274 (59.6) |
| | Total | 3,109 (81.5) (95% CI 80.2-82.7) | 708 (18.5) | 3,817 (100.0) |
| Negative | Taking AD drugs | 510 (60.8) | 329 (39.2) | 839 (27.2) (95% CI 25.7, 28.8) |
| | Not taking AD drugs | 220 (9.8) | 2,023 (90.2) | 2,243 (72.8) |
| | Total | 730 (23.7) (95% CI 22.2-25.2) | 2,352 (76.3) | 3,082 (100.0) |
| **Dementia** | | | | |
| Positive | Taking AD drugs | 1,951 (97.9) | 41 (2.1) | 1,992 (63.2) (95% CI 61.5, 64.8) |
| | Not taking AD drugs | 927 (79.8) | 235 (20.2) | 1,162 (36.8) |
| | Total | 2,878 (91.2) (95% CI 90.2-92.2) | 276 (8.8) | 3,154 (100.0) |
| Negative | Taking AD drugs | 455 (67.2) | 222 (32.8) | 677 (50.3) (95% CI 47.6, 52.9) |
| | Not taking AD drugs | 131 (19.6) | 539 (80.4) | 670 (49.7) |
| | Total | 586 (43.5) (95% CI 40.9-46.2) | 761 (56.5) | 1,347 (100.0) |

Abbreviations: AD, Alzheimer disease; MCI, minor cognitive impairment.

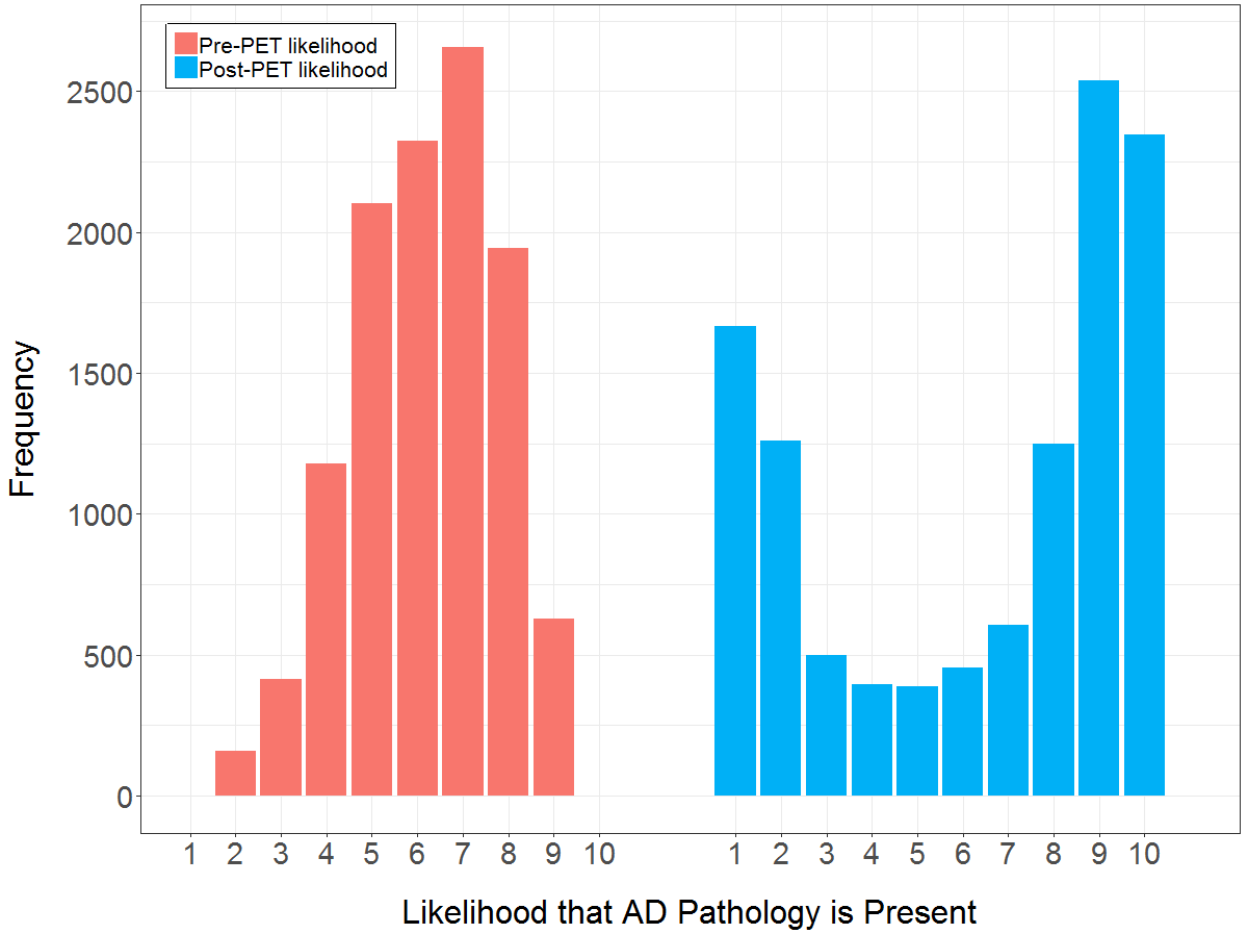
This analysis does not include 9 participants with uninterpretable amyloid PET results.

**eFigure 1. Location of Dementia Clinics, PET Facilities, and Radiopharmaceutical Suppliers for the IDEAS Study**




Most participating dementia clinics were solo (40.3%) or group (38.2%) practices, while 10.9% were university-based. 83.1% of participating dementia specialists were board certified in neurology, 13.8% in psychiatry and 9.4% in geriatric medicine (total >100% because of specialists with multiple board certifications).

**eFigure 2. Changes in Diagnostic Confidence of Underlying Alzheimer Disease Pathology**




Abbreviations: AD, Alzheimer disease. Results combined from participants with MCI and dementia.

## eReferences

1. Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.