Biomarker Positive and Negative Subjects in the ADNI Cohort: Clinical Characterization

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Abstract: Background: The Alzheimer’s Disease Neuroimaging Initiative (ADNI) was created to develop standards for brain imaging and biomarkers for diagnosis and treatment trials. Using the ADNI dataset, experts have found that low cerebrospinal fluid amyloid-β1-42 (CSF Aβ1-42) concentration and high total-tau/Aβ1-42 ratio are highly predictive of progression in amnestic mild cognitive impairment (aMCI), and recommended these biomarkers to support the diagnosis of prodromal Alzheimer’s disease and select patients for clinical trials. However, biomarker selection criteria may introduce systematic bias that undermines their utility.

Methods: We tested for systematic biases among individuals undergoing lumbar puncture in the ADNI dataset who fulfilled the following entry criteria: (1) aMCI with CSF Aβ1-42 ≤ 192 pG/mL, compared to aMCI with Aβ1-42 > 192 pG/mL, and (2) aMCI with total-tau/Aβ1-42 > 0.39, compared to aMCI with total-tau/Aβ1-42 ≤ 0.39, as well as comparisons between participants with aMCI with and without lumbar puncture.

Findings: Individuals with low CSF Aβ1-42 scored significantly poorer than individuals with high Aβ1-42 on several baseline measures of disease severity, including Logical Memory II (3.24 vs 4.73; p<0.001), Functional Activities Questionnaire (4.30 vs 2.37; p<0.001), and Alzheimer’s Disease Assessment Scale-cognitive (12.23 vs 10.09; p=0.002). Similar results were found using high total-tau/Aβ1-42. No differences were found for individuals with and without lumbar puncture except for marital status.

Interpretations: Individuals with high Aβ1-42 in the ADNI dataset appear to have more advanced disease than those with high Aβ1-42. Selection criteria based on ADNI, as well as design of future studies, must account for potential confounds between biomarker status and disease severity to ensure that the former, and not the latter, is the true determinant of predictive accuracy.

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Keywords: ADNI, Alzheimer’s disease, amyloid, biomarker, clinical trials, confounding, prediction.

INTRODUCTION

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a natural history, non-treatment, observational study formed to develop standards for brain imaging and biomarkers for diagnosis and treatment trials [1]. Using data from the ADNI, Shaw et al. [2] concluded that low cerebrospinal fluid (CSF) amyloid-β1-42 (Aβ1-42) concentrations or high total-tau protein to Aβ1-42 ratios in patients diagnosed with amnestic MCI (aMCI) predicted progression to AD with high sensitivity and specificity. They suggested that this biomarker could be used as clinical trials entry requirements to improve the efficiency and reduce the sample sizes of trials. Other investigators have made similar recommendations [3-6], and at least one pharmaceutical manufacturer has required similar biomarker criteria to support a prodromal AD diagnosis in a targeted design clinical trial [7].

Although the ADNI cohort has been characterized previously [6], separate descriptions based on biomarker selection criteria not available. We previously noted that individuals in ADNI with low levels of CSF Aβ1-42 scored significantly lower on screening measures of cognition and disease severity [8]. In this study, we followed up these observations by examining differences between biomarker-positive and biomarker-negative participants in the ADNI, and whether these differences represent systematic biases that could adversely affect recommendations for clinical trials using Aβ1-42 biomarkers as a selection criterion.
MATERIALS AND METHODS

Participants

Participants were drawn from the 405 individuals with a diagnosis of MCI at the baseline visit in the ADNI dataset. The MCI inclusion criteria, detailed elsewhere [6, 9], are identical to the amnestic MCI criteria used in previous clinical trials of cholinesterase inhibitors [10, 11], requiring a Clinical Dementia Rating (CDR) [12] score of 0.5 with the memory box scored at 0.5 or greater, and delayed recall from the Wechsler Memory Scale–Revised [13]. Logical Memory II (LM II) subscale of ≤ 8 for 16 years of education, ≤ 4 for 8–15 years, or ≤ 2 for 0–7 years. Patients had to be largely intact with regard to general cognition and functional performance, and could not qualify for a dementia diagnosis.

Measures

The primary measures were the main clinical ratings in the ADNI, which reflected clinical trials outcomes. The Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-cog) [14] evaluates memory, reasoning, orientation, praxis, language, and word finding difficulty, and is scored from 0 to 70 errors. The CDR [12] is used to rate impairment (from 0 = not impaired to 3 = severely impaired) in each of 6 categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care; and are summed into the CDR sum of the boxes score (CDR-sb) as a severity measure from 0 to 18. The Mini-Mental State Examination (MMSE) [15] is used to evaluate orientation, registration, attention, concentration, recall, language, and visual construction. Scores are the number of correct items and range from 0 to 30. The Functional Activities Questionnaire (FAQ) [16] relies on an interview with a study partner to rate a participant’s ability to perform 10 complex activities of daily living (e.g., manage finances, shop, prepare a meal, travel). Each activity is rated on 3 levels (0 = does without difficulty, 1 = needs frequent advice or assistance, and 2 = someone has taken over the activity); scores range from 0 to 20. The delayed Logical Memory (LM II) subtest of the Weschler Memory Scale–Revised (WMS-R) [13] measures the ability to recall information from an orally-presented story. Scores range from 0 to 25 items recalled. The Rey Auditory Verbal Learning Test (AVLT) [17] measures immediate recall, delayed recall, susceptibility to interference, and recognition memory using word lists of nouns. There are 5 immediate memory trials, 1 delayed memory trial, and a recognition test each scored from 0 to 15 items recalled. Clinical assessments were done at 6-month intervals over the first 2 years.

Selection Criteria

The total MCI sample was initially divided into groups based on whether participants underwent lumbar puncture (LP). The group that underwent LP was further subdivided using two biomarker criteria: (1) CSF Aβ1-42 ≤ 192 pg/mL and (2) t-tau/Aβ1-42 > 0.39. The latter two criteria were specifically recommended previously [2]. In the context of amnestic MCI, these criteria would fulfill newly proposed research criteria for prodromal AD [3, 18] and for MCI due to AD [19], and are consistent with criteria for a commercial prodromal AD clinical trial [7].

Biomarker Assays

Details of the biomarker collection for ADNI are described elsewhere [2]. Briefly, LP was performed in the morning after an overnight fast. CSF was collected and transferred into polypropylene tubes, followed by freezing on dry ice within 1 hour after collection, and shipped overnight to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center on dry ice. Aliquots (0.5ml) were prepared from these samples after thawing (1 hour) at room temperature and gentle mixing. The aliquots were stored in bar code labeled polypropylene vials at -80°C.

Aβ1-42 and t-tau were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use–only reagents) immunoassay kit–based reagents. The Innogenetics kit reagents utilize monoclonal antibodies specific for Aβ1-42 (4D7A3), t-tau (AT120), and p-tau181p (AT270), coupled to unique sets of color-coded beads and analyte-specific detector antibodies (HT7, 3D6). Previous studies have shown the specificity of the antibodies, with no detectable cross-reactivity to synthetic Aβ and tau peptides that did not contain the epitope of interest; and assay linearity over pairs of CSF samples, containing low and high concentrations of the analytes, mixed in different proportions. Full details of this combination of immunoassay reagents and analytical platform are provided elsewhere [20, 21].

For the ADNI dataset, calibration curves were produced for each biomarker using aqueous buffered solutions that contained the combination of biomarkers at concentrations ranging from 56 to 1,948pg/ml for recombinant tau, 27 to 1,574pg/ml for synthetic Aβ1-42 peptide, and 8 to 230pg/ml for a p-tau181p synthetic peptide, which encompass the normal range for Aβ1-42 and t-tau in the population. Inter-laboratory comparisons among the ADNI centers demonstrated a coefficient of variation of 10-20% [22].

Statistical Analysis

Baseline characteristics were summarized for each of the groups and biomarker subgroups, using mean and standard deviation (SD) for continuous variables and proportion or percent for categorical variables. Comparisons between groups were made using a nonparametric Kruskal-Wallis test for continuous variables and χ² or Fisher’s exact tests for categorical variables. A Hochberg procedure [23] was used to correct for multiple comparisons. All hypothesis tests were 2-sided with α=0.05.

All analyses were performed using SAS version 9.2 [24] and R version 2.10.1 [25]. Data were downloaded from the ADNI website (http://www.loni.ucla.edu/twiki/bin/view/ADNI/ADNIClinicalFAQ) on November 9, 2010.

RESULTS

Patient Characteristics

A total of 397 individuals had a diagnosis of aMCI (with 95% due to AD) and LM II scores falling below education-adjusted cutoffs. Of these, 198 underwent lumbar puncture and had Aβ1-42 data available, while 199 did not. Results of comparisons between the groups are shown in Table 1.
Slightly more married individuals underwent lumbar puncture; otherwise, there were no significant differences on demographics, ApoE4 allele frequency, or outcome measures.

Of the individuals with Aβ1-42 data, 147 (74.2%) fell below the cutoff of 192 pG/mL and 51 (25.8%) did not. No significant differences were found on any demographic measures (Table 1). The low Aβ1-42 group, however, had a higher proportion of individuals with 1 or 2 copies of the ApoE4 allele (64%) than the group with high Aβ1-42 (24%). Larger percentages of the low Aβ1-42 group had poorer scores on the cognitive measures and clinical outcome scales than individuals in the high Aβ1-42 group, even for those outcomes that were not statistically significant (Fig. 1). Notably, individuals with low Aβ1-42 had poorer scores on the LM II, AVLT delayed recall, FAQ, and ADAS-cog than those with high Aβ1-42, remaining significant at p < 0.05 after correction for multiple testing.

Similarly, there were 136 (69.7%) individuals with t-tau/Aβ1-42 > 0.39 and 59 (30.3%) individuals less than this value. Results of comparisons between these two groups agreed with the comparisons using Aβ1-42 alone (Table 1). This is not surprising as there is considerable overlap between the two biomarkers; only 14 of 147 individuals with low Aβ1-42 had low t-tau/Aβ1-42 and only 5 of 51 individuals with high Aβ1-42 had high t-tau/Aβ1-42.

**Functional Impairment**

Of the total sample, 227 (57%) had an FAQ score >= 2, indicating mild impairment in 2 or more areas of daily function or moderate impairment in 1 or more areas. There were 149 (37.7%) of the total sample individuals with a score of 2 or greater in at least 1 area of daily function, indicating moderate or greater impairment. There were no significant differences in the proportion of individuals with and without LP having an FAQ score >= 2. The proportion with functional impairment differed between individuals with low Aβ1-42 (63%) and high Aβ1-42 (41%) (p<0.001 and p<0.015).

**DISCUSSION**

ADNI was designed to inform future clinical investigations and trials and establish standards for biomarkers in both diagnosis and treatment [2,4,6,9]. Thus, it is critical to know if any systematic bias exists in the overall cohort, or in any subgroups on which diagnostic and/or treatment guidelines would be based. Longitudinal studies [26-29], including ADNI [2,30], have demonstrated that CSF Aβ1-42 and t-tau concentrations are significant predictors of clinical progression in MCI patients; and subgroups defined by CSF biomarkers might be utilized in clinical trials to increase the probability of detecting a significant treatment effect [2,26-30]. However, for designing targeted clinical trials, it is important to identify and validate biomarkers that are not only predictive of disease progression but also of treatment response [5,31]. Our analyses demonstrate that individuals in the ADNI dataset with low CSF Aβ1-42 biomarker score significantly more poorly on several cognitive and functional measures, including delayed recall and functional activities (LM II, RAVLT, ADAS-cog, and FAQ), in addition to being more likely to progress to a diagnosis of dementia over a 2-year period. Statistical trends toward poorer performance were also noted on other measures (CDRsb and MMSE).

Since the ADNI inclusion criteria required specific cutoff values for these latter two measures to qualify for a diagnosis of MCI [6,9], it is likely that the restricted range of values kept the differences from becoming statistically significant. Similar results were obtained using low t-tau/Aβ1-42 ratio as a biomarker.

The findings indicate that a positive Aβ1-42 biomarker within the ADNI dataset identifies more advanced aMCI or prodromal AD [3]. Decline in CSF Aβ1-42 is an early event in the pathophysiology of AD, and levels may plateau prior to clinical symptoms of MCI [4]. This would make Aβ1-42 an appropriate marker for diagnosis but not for determining severity. In contrast, neuropsychological tests of memory, such as the LM II and RAVLT, continue to show decline until the late stages of AD. The change in tests of memory is correlated with progression of hippocampal atrophy in healthy controls and AD on magnetic resonance imaging (MRI), which is thought to represent the core pathological change in AD [32]. Episodic memory deficits are also correlated with increased amyloid deposition in the temporolateral neocortex measured by positron emission tomography using Pittsburgh Compound B (PiB-PET) in healthy elderly subjects [33]. These deficits have also been linked to increased deposition of amyloid in the hippocampus, although the effect appears to be mediated by hippocampal atrophy [34]. Thus baseline neuropsychological testing appears to be the more pragmatic predictor of disease progression, and an appropriate marker of disease severity [29,35-38]. At a minimum, for predicting outcomes in the ADNI dataset, analyses between biomarker groups should adjust for the differences in severity (as reflected in differences in neuropsychological test scores) so that any significant differences between biomarker groups are not due to baseline differences in severity.

This finding has much broader implications for clinical trials, however, as experts have suggested that more advanced disease may be more resistant to treatment due to the greater degree of neurodegeneration [31]. If this hypothesis is true, then subjects with a positive Aβ1-42 biomarker in the ADNI dataset may be individuals who are both more impaired and less, rather than more, responsive to therapeutic interventions. Such a selection bias cannot be corrected statistically, so that recommendations based solely on ADNI data for the use of biomarkers as inclusion criteria in therapeutic trials may actually run counter to current recommendations that inclusion criteria target participants in the earliest prodromal stages of AD. Moreover, future studies to evaluate biomarker criteria should incorporate appropriate designs to account for the potential confound between biomarker status and disease severity and ensure that the former, not the latter, is the factor determining predictive accuracy in treatment response.

In addition, studies of targeted designs or designs based on biomarkers have noted that effective biomarkers for clinical trials should have a prevalence of less than 50% of the population, and identify excluded or biomarker negative groups in which the treatment is substantially less effective compared to the biomarker positive groups [39]. Both of these criteria seem missed using the CSF biomarker results.
Table 1. Comparison of Baseline Characteristics Among Biomarker Groups. P-values in bold remain significant after adjustment for multiple testing.

<table>
<thead>
<tr>
<th></th>
<th>With Lumbar puncture</th>
<th>Without lumbar puncture</th>
<th>P Value</th>
<th>Aβ1-42 &gt; 192nG/mL</th>
<th>Aβ1-42 ≤ 192 nG/mL</th>
<th>P Value</th>
<th>Aβ42/tau &lt; 0.39</th>
<th>Aβ42/tau ≥ 0.39</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>198</td>
<td>199</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean, SD</td>
<td>74.5 (7.51)</td>
<td>7.51 (7.41)</td>
<td>0.383</td>
<td>74.5 (8.71)</td>
<td>74.5 (7.08)</td>
<td>0.841</td>
<td>74.4 (7.67)</td>
<td>74.5 (7.46)</td>
<td>0.958</td>
</tr>
<tr>
<td>Gender, male %</td>
<td>67%</td>
<td>62%</td>
<td>0.365</td>
<td>73%</td>
<td>65%</td>
<td>0.301</td>
<td>76%</td>
<td>62%</td>
<td>0.389</td>
</tr>
<tr>
<td>Race, Caucasian %</td>
<td>95%</td>
<td>91%</td>
<td>0.107</td>
<td>92%</td>
<td>97%</td>
<td>0.189</td>
<td>93%</td>
<td>96%</td>
<td>0.240</td>
</tr>
<tr>
<td>Marital status, married %</td>
<td>84%</td>
<td>76%</td>
<td>0.035</td>
<td>84%</td>
<td>84%</td>
<td>0.995</td>
<td>90%</td>
<td>82%</td>
<td>0.828</td>
</tr>
<tr>
<td>Education, college %</td>
<td>65%</td>
<td>63%</td>
<td>0.704</td>
<td>71%</td>
<td>63%</td>
<td>0.303</td>
<td>71%</td>
<td>62%</td>
<td>0.905</td>
</tr>
<tr>
<td>APOE e4 genotype %</td>
<td>54%</td>
<td>53%</td>
<td>0.957</td>
<td>24%</td>
<td>64%</td>
<td>0.009</td>
<td>25%</td>
<td>66%</td>
<td>0.010</td>
</tr>
<tr>
<td>LM delay, screening, mean (SD)</td>
<td>3.63 (2.63)</td>
<td>3.98 (2.70)</td>
<td>0.199</td>
<td>4.73 (2.47)</td>
<td>3.24 (2.58)</td>
<td>&lt;0.001</td>
<td>4.81 (2.52)</td>
<td>3.11 (2.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AVLT delay, baseline, mean (SD)</td>
<td>3.10 (3.53)</td>
<td>2.56 (3.01)</td>
<td>0.138</td>
<td>3.73 (3.16)</td>
<td>2.15 (2.86)</td>
<td>&lt;0.001</td>
<td>3.59 (3.23)</td>
<td>2.05 (2.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE, screening, mean (SD)</td>
<td>26.9 (1.79)</td>
<td>27.1 (1.76)</td>
<td>0.227</td>
<td>27.31 (1.76)</td>
<td>26.79 (1.79)</td>
<td>0.065</td>
<td>27.08 (1.72)</td>
<td>26.83 (1.82)</td>
<td>0.340</td>
</tr>
<tr>
<td>FAQ, baseline, mean (SD)</td>
<td>3.80 (4.43)</td>
<td>3.88 (4.52)</td>
<td>0.925</td>
<td>2.37 (4.25)</td>
<td>4.30 (4.39)</td>
<td>&lt;0.001</td>
<td>2.81 (4.49)</td>
<td>4.25 (4.37)</td>
<td>0.002</td>
</tr>
<tr>
<td>CDR-sb, screening, mean (SD)</td>
<td>1.56 (0.88)</td>
<td>1.65 (0.89)</td>
<td>0.218</td>
<td>1.30 (0.72)</td>
<td>1.64 (0.92)</td>
<td>0.019</td>
<td>1.41 (0.86)</td>
<td>1.63 (0.89)</td>
<td>0.074</td>
</tr>
<tr>
<td>ADAS-cog, baseline, mean (SD)</td>
<td>11.68 (4.59)</td>
<td>11.33 (4.26)</td>
<td>0.534</td>
<td>10.09 (4.37)</td>
<td>12.23 (4.55)</td>
<td>0.002</td>
<td>9.96 (3.88)</td>
<td>12.39 (4.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia, 6 mo., %</td>
<td>5%</td>
<td>6%</td>
<td>0.633</td>
<td>2%</td>
<td>6%</td>
<td>0.597</td>
<td>4%</td>
<td>6%</td>
<td>0.597</td>
</tr>
<tr>
<td>Dementia, 12 mo., %</td>
<td>21%</td>
<td>15%</td>
<td>0.182</td>
<td>10%</td>
<td>24%</td>
<td>0.004</td>
<td>7%</td>
<td>27%</td>
<td>0.004</td>
</tr>
<tr>
<td>Dementia, 18 mo., %</td>
<td>28%</td>
<td>27%</td>
<td>0.867</td>
<td>12%</td>
<td>33%</td>
<td>&lt;0.001</td>
<td>10%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia, 24 mo., %</td>
<td>36%</td>
<td>39%</td>
<td>0.631</td>
<td>11%</td>
<td>45%</td>
<td>&lt;0.001</td>
<td>11%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

in ADNI [8]. Further, the high sensitivity of ApoE in identifying those with low Aβ1-42 also calls into question the cost of the potentially high refusal rates for accepting a lumbar puncture, if, for example, less invasive ApoE genotyping can be substituted with similar accuracy.

Finally, our analyses showed that a significant proportion (58%) of the ADNI cohort with a diagnosis of aMCI had a FAQ score ≥ 2, i.e., mildly impaired on two activities or moderately impaired on one. A substantial proportion (37.7%) had an FAQ score ≥ 2 on at least 1 subscale, indicating moderate impairment in at least one area. This degree of impairment indicates that many of the individuals would not meet the criterion of "normal activities of daily living" required for a diagnosis of aMCI [40], and, instead, would meet criteria for dementia and having mild AD. Furthermore, the proportion of individuals with FAQ scores ≥ 2 was higher (63%) in the group with low Aβ1-42 compared to those with high Aβ1-42, again emphasizing that the former group has more advanced disease than the latter group.
Our analyses did not find any significant differences on demographics, ApoE status, or outcome measures between individuals in the ADNI dataset who did undergo LP and those who did not with the exception that slightly more married individuals than unmarried had the procedure (84% versus 76%). This is encouraging for past and future studies of biomarkers using the ADNI dataset, as there does not appear to be selection bias based on the voluntary nature of the LP for participants.

Our results are obviously limited to the ADNI dataset and the systematic differences observed here may not apply to other studies. However, given the widespread use of the ADNI dataset for many analyses that could be used in determining clinical trial design, the limitations and implications of the ADNI dataset have significant consequences. Overall, this study indicates that biomarker inclusion criteria for treatment studies based on the ADNI dataset may be complicated by systematic differences in severity between biomarker positive and negative groups, such that participants less responsive to therapy are actually being selected. Appropriate consideration of these differences is necessary in the interpretation of results from the ADNI dataset and in the design of future studies incorporating biomarker selection criteria.

CONFLICT OF INTEREST

Dr. Kennedy is funded by NIH grants R01AG037561 (L. Schneider, PI) and T32HL072757 (D. Allison, PI).

Dr. Schneider is funded by NIH grant R01AG037561. He also reports being an editor on the Cochrane Collaboration Dementia and Cognitive Improvement Group, which oversees systematic reviews of drugs for cognitive impairment and dementia; receiving a grant from the Alzheimer’s Association for a registry for dementia and cognitive impairment trials; receiving grant or research support from Baxter, Elan Pharmaceuticals, Johnson & Johnson, Eli Lilly, Myriad, Novartis, and Pfizer; and having served as a consultant for or receiving consulting fees from Abbott Laboratories, AC Immune, Allergan, Alon, Alzheimer Drug Discovery Foundation, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Exonhit, Forest, GlaxoSmithKline, Institute Ipsen, Johnson & Johnson, Lundbeck, Myriad, Medavante, Medivation, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, Servier, Toyama, and Transition Therapeutics.

Dr. Cutter is funded by NIH grant R01AG037561. He also reports having served on data and safety monitoring committees for AntiSense, Sanofi-Aventis, Bayhill, BioMS, Daichi-Sankyo, Eli Lilly, GlaxoSmithKline, Genmab, Medivation, Ono, PTC Therapeutics, Vivirus, NHLBI, NINDS, and the NMSS; and having served as a consultant to or receiving consulting fees from Alexion, Accentia, Bayer, BarofoLD, Biogen-Idec, CibaVision, Enzo, Eisai, Genentech, Millennium, Novartis, Consortium of Multiple Sclerosis Centers, Peptimmune, Klein-Buendel Incorporated, Incyte, Somnus, Teva, Visioneer Technologies.

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sis, or interpretation of data; in writing the report; or in decision to submit for publication.

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The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

REFERENCES


