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# Alzheimer's Disease Neuroimaging Initiative 2 Clinical Core: Progress and plans

Paul S. Aisen[a,*], Ronald C. Petersen[b], Michael Donohue[c], Michael W. Weiner[d], for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Department of Neurosciences, University of California San Diego, San Diego, CA, USA*
[b]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[c]*Division of Biostatistics and Bioinformatics, Department of Family Medicine and Public Health, University of California San Diego, San Diego, CA, USA*
[d]*Departments of Radiology and Biomedical Imaging, Medicine, Psychiatry and Neurology, University of California San Francisco, San Fransisco, CA, USA*

**Abstract**

**Introduction:** This article reviews the current status of the Clinical Core of the Alzheimer's Disease Neuroimaging Initiative (ADNI), and summarizes planning for the next stage of the project.
**Methods:** Clinical Core activities and plans were synthesized based on discussions among the Core leaders and external advisors.
**Results:** The longitudinal data in ADNI-2 provide natural history data on a clinical trials population and continue to inform refinement and standardization of assessments, models of trajectories, and clinical trial methods that have been extended into sporadic preclinical Alzheimer's disease (AD).
**Discussion:** Plans for the next phase of the ADNI project include maintaining longitudinal follow-up of the normal and mild cognitive impairment cohorts, augmenting specific clinical cohorts, and incorporating novel computerized cognitive assessments and patient-reported outcomes. A major hypothesis is that AD represents a gradually progressive disease that can be identified precisely in its long presymptomatic phase, during which intervention with potentially disease-modifying agents may be most useful.


*Keywords:* Alzheimer's disease; Cognitive assessment; Amyloid

## 1. Introduction

Since its inception in 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has been advancing the standardized assessment of cognitive, clinical, and biomarker measures of the disease progression in cohorts of individuals who are clinically normal (CN) or have mild cognitive impairment (MCI) or mild dementia. The Clinical Core is being responsible for regulatory oversight, central recruitment efforts, site management, data capture, monitoring and tracking, supply management, safety monitoring, and clinical guidance of the project [1,2].

### 1.1. Operational activities of the ADNI Clinical Core

The current ADNI-2 grant period included plans to continue the longitudinal follow-up of subjects from the earlier ADNI phases, and recruitment of new participants into the normal cohort (n = 150), early MCI (EMCI, n = 100 to be added to 200 enrolled in the Alzheimer's Disease Neuroimaging Initiative Grand Opportunity (ADNI-GO) grant), late MCI (LMCI, n = 150), and mild dementia

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (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. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how to apply/ADNI Acknowledgement List.pdf.

*Corresponding author. Tel.: +1-858-246-1365; Fax: +1-858-246-0138.
E-mail address: paisen@ucsd.edu

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(n = 150). The EMCI group was differentiated from the LMCI group by virtue of degree of memory impairment. The EMCI participants were recruited with memory function approximately 1.0 standard deviation (SD) below expected education adjusted norms, whereas the LMCI participants were approximately 1.5 SD below expectation. In addition, during the course of ADNI-2, an additional cohort was added: individuals who are CN but with subjective memory concerns (SMC, n = 100); for entry into the SMC cohort, a score of 16 or greater on the first 12 questions of the Cognitive Change Index [3] was required. All enrollment targets were met or exceeded, with 780 new participants along with 391 individuals followed from ADNI-1 and ADNI-GO for a total of 1171 participants in ADNI-2.

Adverse events are captured in the Alzheimer's Disease Cooperative Study (ADCS) electronic data capture system, and reported on a quarterly basis to the ADCS Data and Safety Monitoring Board. To date there have been over 5000 adverse events, and over 400 serious adverse events occurring in ADNI-2 participants. The majority are unrelated

Table 1
Newly enrolled ADNI-GO and ADNI-2 subjects by baseline diagnosis

| | | CN | SMC | EMCI | LMCI | AD | Combined | |
|---|---|---|---|---|---|---|---|---|
| | N | (N = 184) | (N = 103) | (N = 301) | (N = 160) | (N = 145) | (N = 893) | *P*-value |
| Age (yrs) | 893 | 73.4 (6.3) | 72.2 (5.6) | 71.3 (7.4) | 72.2 (7.5) | 74.6 (8.1) | 72.5 (7.2) | <.001 |
| <60 | | 1 (1%) | 0 (0%) | 12 (4%) | 9 (5%) | 6 (4%) | 28 (3%) | <.001 |
| 60–69 | | 43 (23%) | 38 (37%) | 113 (38%) | 40 (25%) | 27 (19%) | 261 (29%) | |
| 70–79 | | 103 (56%) | 55 (53%) | 126 (42%) | 85 (53%) | 70 (48%) | 439 (49%) | |
| 80–89 | | 37 (20%) | 9 (9%) | 50 (17%) | 26 (16%) | 38 (26%) | 160 (18%) | |
| >90 | | 0 (0%) | 1 (1%) | 0 (0%) | 1 (1%) | 4 (3%) | 6 (1%) | |
| Sex: female | 893 | 94 (51%) | 61 (59%) | 132 (44%) | 74 (46%) | 59 (41%) | 420 (47%) | .027 |
| Education | 893 | 16.5 (2.5) | 16.7 (2.6) | 16.0 (2.7) | 16.5 (2.6) | 15.8 (2.7) | 16.3 (2.6) | .005 |
| Marital status | | | | | | | | |
| Married | 893 | 125 (68%) | 69 (67%) | 228 (76%) | 115 (72%) | 126 (87%) | 663 (74%) | <.001 |
| Widowed | | 25 (14%) | 13 (13%) | 21 (7%) | 21 (13%) | 13 (9%) | 93 (10%) | |
| Divorced | | 26 (14%) | 11 (11%) | 35 (12%) | 19 (12%) | 5 (3%) | 96 (11%) | |
| Never married | | 8 (4%) | 10 (10%) | 13 (4%) | 3 (2%) | 1 (1%) | 35 (4%) | |
| Unknown | | 0 (0%) | 0 (0%) | 4 (1%) | 2 (1%) | 0 (0%) | 6 (1%) | |
| Ethnicity | | | | | | | | |
| Unknown | 893 | 1 (1%) | 2 (2%) | 1 (0%) | 0 (0%) | 1 (1%) | 5 (1%) | .14 |
| Not Hisp/Latino | | 171 (93%) | 99 (96%) | 286 (95%) | 158 (99%) | 137 (94%) | 851 (95%) | |
| Hisp/Latino | | 12 (7%) | 2 (2%) | 14 (5%) | 2 (1%) | 7 (5%) | 37 (4%) | |
| Race | | | | | | | | |
| Asian | 893 | 5 (3%) | 0 (0%) | 4 (1%) | 1 (1%) | 5 (3%) | 15 (2%) | .24 |
| American Indian/Alaskan | | 1 (1%) | 0 (0%) | 1 (0%) | 0 (0%) | 0 (0%) | 2 (0%) | |
| Hawaiian/other PI | | 0 (0%) | 0 (0%) | 1 (0%) | 1 (1%) | 0 (0%) | 2 (0%) | |
| Black | | 14 (8%) | 3 (3%) | 7 (2%) | 6 (4%) | 6 (4%) | 36 (4%) | |
| White | | 162 (88%) | 97 (94%) | 279 (93%) | 151 (94%) | 132 (91%) | 821 (92%) | |
| More than one | | 2 (1%) | 3 (3%) | 6 (2%) | 1 (1%) | 2 (1%) | 14 (2%) | |
| Unknown | | 0 (0%) | 0 (0%) | 3 (1%) | 0 (0%) | 0 (0%) | 3 (0%) | |
| CDR-SB | | | | | | | | |
| 0 | 893 | 173 (94%) | 88 (85%) | 0 (0%) | 0 (0%) | 0 (0%) | 261 (29%) | <.001 |
| 0.5 | | 10 (5%) | 15 (15%) | 89 (30%) | 25 (16%) | 0 (0%) | 139 (16%) | |
| 1–1.5 | | 1 (1%) | 0 (0%) | 138 (46%) | 67 (42%) | 5 (3%) | 211 (24%) | |
| 2–2.5 | | 0 (0%) | 0 (0%) | 61 (20%) | 40 (25%) | 20 (14%) | 121 (14%) | |
| 3–3.5 | | 0 (0%) | 0 (0%) | 10 (3%) | 24 (15%) | 23 (16%) | 57 (6%) | |
| 4–4.5 | | 0 (0%) | 0 (0%) | 3 (1%) | 3 (2%) | 34 (23%) | 40 (4%) | |
| >4.5 | | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 63 (43%) | 64 (7%) | |
| CDR memory | | | | | | | | |
| 0 | 893 | 184 (100%) | 103 (100%) | 1 (0%) | 1 (1%) | 0 (0%) | 289 (32%) | <.001 |
| 0.5 | | 0 (0%) | 0 (0%) | 288 (96%) | 125 (78%) | 15 (10%) | 428 (48%) | |
| 1 | | 0 (0%) | 0 (0%) | 12 (4%) | 34 (21%) | 115 (79%) | 161 (18%) | |
| 2 | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 14 (10%) | 14 (2%) | |
| 3 | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 1 (0%) | |
| ADAS-cog 13 | 889 | 9.2 (4.5) | 8.9 (4.3) | 12.7 (5.4) | 18.7 (7.1) | 31.0 (8.4) | 15.5 (9.6) | <.001 |
| MMSE | 893 | 29.0 (1.3) | 29.0 (1.2) | 28.3 (1.6) | 27.6 (1.8) | 23.1 (2.1) | 27.6 (2.6) | <.001 |
| Participant ECog | 890 | 1.3 (0.3) | 1.6 (0.3) | 1.8 (0.5) | 1.8 (0.5) | 1.9 (0.6) | 1.7 (0.5) | <.001 |
| Study partner ECog | 887 | 1.2 (0.3) | 1.3 (0.3) | 1.6 (0.5) | 1.9 (0.7) | 2.7 (0.7) | 1.7 (0.7) | <.001 |

Abbreviations: CN, clinically normal; SMC, subjective memory concerns; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; ADAS-cog 13, 13 item version of the cognitive subscale of the Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination; GO, Grand Opportunity; PI, Prevention Instruments study, CDR-SB, Clinical Dementia Rating scale sum-of-boxes.

NOTE. Count (%) or mean (standard deviation). *P*-values are from F-tests and Pearson chi-square tests.

to study participation. The most common adverse events that have been considered to be related to the study are headaches occurring in about 4% of participants after lumbar puncture.

Baseline data for the ADNI-2 cohorts are shown in Table 1. Baseline assessments are displayed graphically in Fig. 1.

In general, the groups of participants progressed in an expected fashion. Cognitive progression by cohort is shown in Fig. 2. The CN group progressed to MCI at a rate of approximately 3.6% per year, whereas the EMCI developed dementia at a rate of 2.3% and LMCI participants went on to dementia at a rate of 17.5% per year.

The discontinuation rates of subjects in the various clinical groups has been reasonably low, at 6% to 10% per year. The continued participation of the subjects has been a testimonial to their dedication to the project.

### *1.2. Academic aims of the Clinical Core*

Apart from its operational mission, the Clinical Core pursues academic goals: using ADNI data to study the course of the disease and to advance clinical trial methodology. These goals include the optimization of outcome measures, evaluation of statistical analysis approaches, development of new trial designs, refinement of models of disease trajectories and staging, and clinical features of AD.

Work on outcome measures ranges from standard cognitive assessments to novel instruments. An important study of cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) items clarified the impact of the delayed recall component at specific stages of disease [4]. New instruments were described for use as end points in preclinical phase studies [5,6]. Also using ADNI data, the added efficiency of continuous outcomes as opposed to categorical endpoints in prodromal AD trials was quantified [7] and mixed models were compared with slope-based analyses [8]. A novel approach to generating long-term trajectories from relatively short-interval ADNI data was used to test hypotheses proposed in the Jack models [9](see also Biostatistics Core article in this issue).

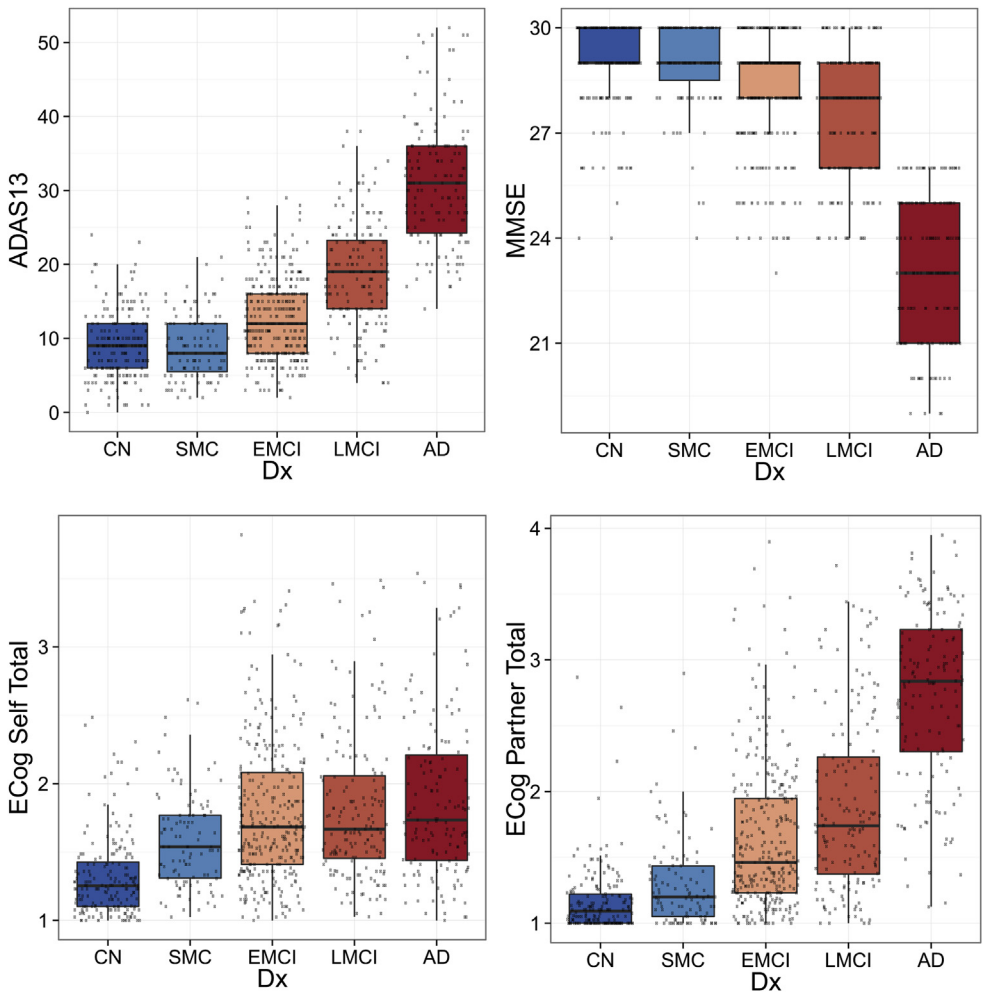


Fig. 1. Baseline assessments by diagnosis. Abbreviations: CN, clinically normal; SMC, subjective memory concerns; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, mild Alzheimer's disease dementia; ADAS13, 13 item version of the cognitive subscale of the Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination; ECog, measurement of everyday cognition.

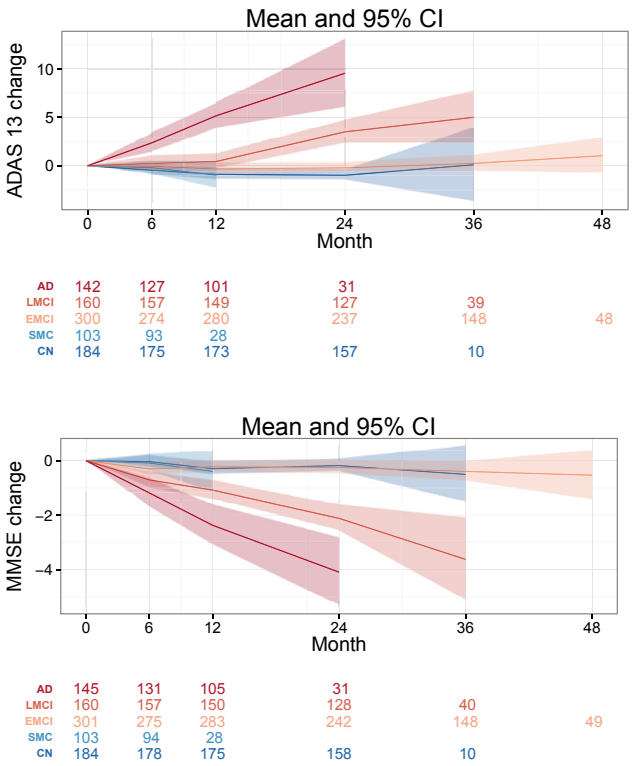


Fig. 2. Mean change (observed scores) by baseline diagnosis. Shaded areas represent 95% confidence intervals. The number of observations for each cohort at each time point is shown below the graphs. Abbreviations: CN, clinically normal; SMC, subjective memory concerns; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, mild Alzheimer's disease dementia; ADAS13, 13 item version of the cognitive subscale of the Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination.

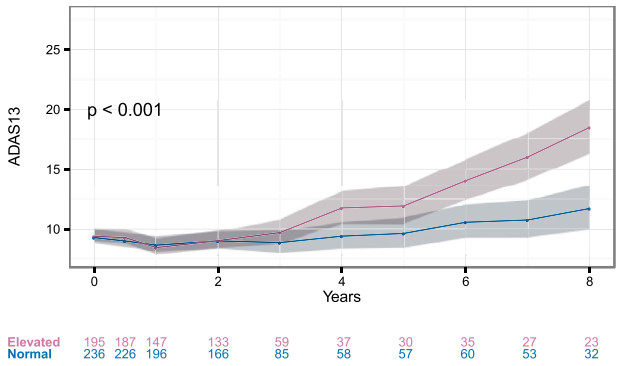


Fig. 3. Long-term ADAS13 trajectories of CN or SMC with and without elevated amyloid. Trajectories are modeled using a categorical time mixed model of repeated measures with covariates for apolipoprotein E (*APOE*) ε4, age, gender, education, and ventricular volume at baseline. All these covariate effects were significant at .05 level except *APOE* ε4. Age, gender, and education were highly significant ($P < .001$). Trajectories are similar when we only control for age. Abbreviations: ADAS13, 13 item version of the cognitive subscale of the Alzheimer's Disease Assessment Scale; CN, clinically normal; SMC, subjective memory concerns.

The clinical and biomarker characterization and outcome of MCI has continued [10]. Participants in ADNI diagnosed with late MCI were followed longitudinally and classified by their biomarker profiles. Their frequency of biomarkers and outcomes were compared with a group of community participants from the Mayo Clinic Study of Aging. The participants were classified on their amyloid status and features of neurodegeneration such as hippocampal atrophy or fludeoxyglucose positron emission tomography (FDG-PET) hypometabolism. A group of participants designated as MCI SNAP (suspected non-Alzheimer's disease pathology) was described because they had no evidence of amyloid on imaging but had features of neurodegeneration. These participants progressed to dementia at rates similar to those with the presence of amyloid and neurodegeneration. These findings will be pursued in ADNI 3 (see later) with the advent of tau imaging to further characterize neurodegeneration.

Among individuals with MCI, those with subsyndromal symptoms of depression show faster rates of conversion to dementia and significantly greater levels of disability compared with MCI participants without symptoms of depression [11]. These results suggest that even very mild depressive symptoms in older adults may be accompanied by neurodegenerative brain changes, which impact cognitive decline and functional status. Additionally, biochemical biomarkers of depressive symptoms in older adults may be useful in investigations of pathophysiological mechanisms of depression in aging and neurodegenerative dementias and as targets of novel treatment approaches [12]. Based on such observations, a new study (Depression-ADNI) has been launched with National Institute on Aging funding to characterize biomarker trajectories associated with depressive symptoms in older individuals.

Among the highest impact efforts from the ADNI Clinical Core investigators has been the development of the first trial design for studies conducted in the preclinical, asymptomatic stage of sporadic AD [13]; the design was based in part on the observation in ADNI that the presence of elevated brain amyloid in CN individuals distinguished those that will decline cognitively from those that will remain stable (Fig. 3). This design has now been implemented in the A4 (antiamyloid treatment in Asymptomatic Alzheimer's) trial that is under way, and will be the basis for another pivotal trial to be launched later this year. In the A4 trial, CN individuals aged 65 or older are screened with an amyloid PET scan; those who have elevated brain amyloid qualify for randomization into a 3-year randomized placebo-controlled trial of antiamyloid immunotherapy, with a cognitive measure [5] as the primary outcome. If this trial successfully demonstrates that antiamyloid treatment slows cognitive decline in the individuals, it may lead to regulatory approval of the first therapeutic for the secondary prevention of the clinical manifestations of AD. In essence, the analysis of ADNI clinical, cognitive, and biomarker data was vital in facilitating a new phase in drug development for AD.

### 1.3. Future aims of the Clinical Core

In the application for the next phase of ADNI, ADNI-3, the Clinical Core will continue to be responsible for the operational management of the project: data management, tracking and quality control, recruitment and retention of participants, and regulatory oversight and financial management. Clinical Core investigators will continue work on the characterization of the cross-sectional features and longitudinal trajectories of cognitively normal older individuals and MCI, study of the relationships among clinical/demographic, cognitive, genetic, biochemical, and neuroimaging features of AD from the preclinical through dementia stages, and the assessment of genetic, biomarker, and clinical predictors of decline. Refinement of clinical trial designs, including secondary prevention, slowing of progression in symptomatic disease, and cognitive/behavioral management, will continue to be a primary focus.

Toward these aims, the ADNI-3 phase would maintain the longitudinal follow-up of the current ADNI-2 predementia cohorts (normals with and without subjective memory concerns, and EMCI and LMCI). We estimate that approximately 700 ADNI-2 subjects will remain in ADNI-3. Additional recruitment will allow the enrollment of new participants, to an approximate total number of 900 participants at the CN (Clinical Dementia Rating scale [CDR] = 0, aged 65 and years, with or without memory concerns), MCI (CDR = 0.5, Mini-Mental State Examination [MMSE] 24–30, logical memory scores at least 1.0–1.5 SDs below education-adjusted norms), and mild AD dementia stages (CDR 0.5–1, MMSE 20–26).

Most of the cognitive and clinical assessments of ADNI-2 will continue. In addition, there will be a particular focus on computerized cognitive assessment (now being piloted in ADNI-2), and patient-reported outcomes. The computerized instrument, CogState is being introduced in a pilot study in ADNI-2 and will likely be included in ADNI-3. CogState involves four tests largely assessing psychomotor speed and working memory using a playing card format. The participants perform simple reaction time, choice reaction time, and two working memory tasks in approximately 15 minutes. These tasks have been shown to be sensitive to change over time while minimizing any practice effects. If successful, these tasks will be given to participants in ADNI-3 to track their performance over time. Eventually these tasks can be performed by the participants in their homes and the data will be transmitted to the Clinical Core of ADNI.

The Clinical Core will continue its efforts to advance AD therapeutic trial design. Continued characterization of early phase disease will be a focus, including the confirmation of the hypothesis that brain amyloid deposition in CN older individuals identifies a population that will progress to the symptomatic stages of AD. The inclusion of patient-reported outcomes and web-based computerized assessments will add potential outcomes for preclinical trials. Web-based cognitive assessment may also provide a means for selection of candidates for early stage trials, perhaps including primary prevention studies.

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## RESEARCH IN CONTEXT

1. Systematic review: The content of this report is based on discussions among the Alzheimer's Disease Neuroimaging Disease (ADNI) Clinical Core leaders and review of the relevant scientific literature.
2. Interpretation: The Clinical Core continues to provide operational support to ADNI, and has elucidated clinical and biomarker features of the disease course facilitating major advances in trial design.
3. Future directions: Continued longitudinal follow-up of existing participants, recruitment of new cohorts, and additional novel cognitive and clinical assessments will support further advances to our understanding of the disease course and optimal therapeutic interventions.

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