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Neurobiology of Aging xx (2010) xxx

NEUROBIOLOGY OF AGING

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# Integrating ADNI results into Alzheimer's disease drug development programs[1]

Jeffrey L. Cummings

*Mary S. Easton Center for Alzheimer's Disease Research at UCLA, Departments of Neurology and Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States*

Received 27 January 2010; received in revised form 15 March 2010; accepted 21 March 2010

**Abstract**

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is providing critical new information on biomarkers in cognitively normal elderly, persons with mild cognitive impairment (MCI), and patients with mild Alzheimer's disease (AD). The data provide insights into the progression of the pathology of AD over time, assist in understanding which biomarkers might be most useful in clinical trials, and facilitate development of disease-modifying treatments. ADNI results are intended to support new AD treatment development; this report considers how ADNI information can be integrated in AD drug development programs. Cerebrospinal fluid (CSF) amyloid beta protein (A$\beta$) measures can be used in Phase I studies to detect any short term effects on A$\beta$ levels in the CSF. Phase II studies may benefit most from biomarker measures that can inform decisions about Phase III. CSF A$\beta$ levels, CSF total tau and phospo-tau measures, fluorodexoyglucose positron emission tomography (FDG PET), Pittsburgh Compound B (PIB) amyloid imaging, or magnetic resonance imaging (MRI) may be employed to select patients in enriched trials or as outcomes for specific disease-modifying interventions. Use of biomarkers may allow Phase II trials to be conducted more efficiently with smaller populations of patients or shorted treatment times. New drug applications (NDAs) may include biomarker outcomes of phase III trials. ADNI patients are highly educated and are nearly all of Caucasian ethnicity limiting the generalizability of the results to other populations commonly included in global clinical trials. ADNI has inspired or collaborates with biomarker investigations worldwide and together these studies will provide biomarker information that can reduce development times and costs, improve drug safety, optimize drug efficacy, and bring new treatments to patients with or at risk for AD.


## 1. Introduction

The Alzheimer's Disease Neuroimaging Initiative (ADNI) began in 2004 as a 5-year research project to study the rate of change of cognition, function, brain structure and function, and biomarkers in 200 elderly control subjects, 400 subjects with mild cognitive impairment (MCI), and 200 with Alzheimer's disease (AD). The success of the program has led to its renewal and extension. ADNI is a unique public-private partnership involving the National Institute on Aging (NIA), academic medical centers and trial sites, and pharmaceutical companies. The overarching goal of ADNI is to provide information and methods which will help lead to effective treatments and preventive interventions for AD (from the ADNI web site www.adni-info.org). The specific aims of ADNI are: (1) develop improved methods, which will lead to uniform standards for acquiring longitudinal, multisite magnetic resonance imaging (MRI) and positron emission tomography (PET) data on patients with AD, MCI, and elderly controls; (2) acquire a generally accessible data repository, which describes longitudinal changes in brain structure and metabolism and in parallel, acquire clinical, cognitive and biomarker data for validation of imaging surrogates; and (3) determine those methods, which provide maximum power to determine treatment effects in trials involving these patient groups (from the ADNI grant proposal application; M Weiner, Principal Investigator).

Corresponding author at: Mary S. Easton Center for Alzheimer's Disease Research, Suite 200, 10911 Weyburn Ave, Los Angeles, CA 90095-7226, United States. Tel.: +1 310 794 3665.

*E-mail address:* jcummings@mednet.ucla.edu (J. Cummings).

[1] Prepared for a special issue of *Neurobiology of Aging* on the Alzheimer's Disease Neuroimaging Initiative (ADNI).

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doi:10.1016/j.neurobiolaging.2010.03.016

To be made widely available to the world's population of AD patients, new treatments must meet efficacy, safety, and manufacturing standards specified by regulatory agencies such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA). Pharmaceutical companies are the enterprises with sufficient resources to discover, develop, and market agents that can address the world's unmet health needs. Biomarker development such as that undertaken by ADNI must be integrated into drug development plans of pharmaceutical companies if they are to serve the stated purpose of facilitating the development of new treatments for AD. In addition, biomarkers are themselves subject to regulatory standards if they are to be part of a new drug application (NDA) as supporting data for the biological effect of the agent or, eventually, as surrogate markers in place of clinical outcomes in prevention trials. This report addresses the role that ADNI data can play in a comprehensive drug development program. Issues hindering AD drug development that might be addressed within an ADNI-like framework also are described. Biomarker issues important in drug development and not addressed by ADNI are noted.

## 2. Roles of biomarkers in drug development

Biomarkers can play comprehensive roles in drug development including characterizing the disease state and its progression, demonstrating the pharmacokinetic effects of the body on the drug (absorption, distribution, metabolism, excretion, toxicity, and blood-brain barrier penetration), proof of principle (POP) (for example, inhibition of cerebrospinal fluid [CSF] beta-site amyloid precursor protein cleavage enzyme [BACE]), dose selection, and efficacy (Fig. 1). These data then facilitate corporate decision-making such as prioritizing compounds, optimizing agents with promising but insufficient effects or untoward off-target effects, or terminating a development program (Day et al., 2009). The purpose of biomarkers is to improve drug safety, assist in drug candidate and dose choice, reduce development cycle times and costs, support the NDA, and improve the success rate of bringing compounds to market (Goodsaid et al., 2008). Biomarkers will become more useful as the relationships between treatment and biomarkers outcomes are understood; this information will assist in optimizing compounds, choosing among compounds, and developing agents with different mechanisms of action but affecting overlapping disease pathways (Cummings, 2009a).

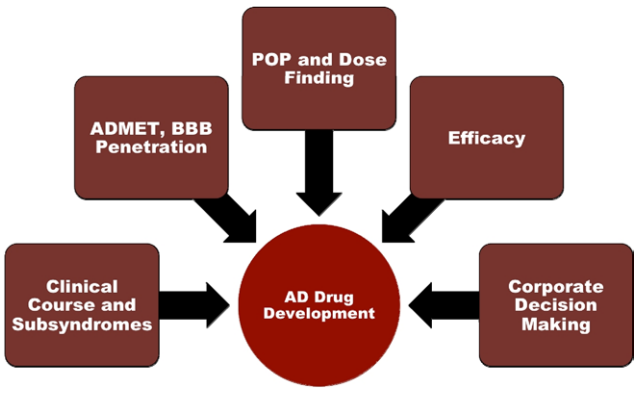


Fig. 1. Roles of biomarkers in AD drug development. ADMET = absorption, distribution, metabolism, excretion, toxicity; BBB = blood-brain barrier; POP = proof of principle.

Biomarker development begins in the preclinical studies where the response of the marker to intervention can be assessed in animal models and methods and standards can be advanced for use in human studies (Kawarabayashi et al., 2001; Lau et al., 2008; Maeda et al., 2007).

Biomarkers can assist in the development of both symptomatic agents and disease-modifying treatments for AD. Receptor occupancy studies, for example, can facilitate dose selection in the development of symptomatic agents. N-[C] methylpiperidin-4-yl acetate ([C]MP4A) PET demonstrates the inhibition of brain acetylcholinesterase (AChE) and informs the relationship between serum and brain AChE inhibition (Ota et al., 2009). This information is useful in considering how best to optimize the efficacy of AChE-inhibitors. The greatest promise of biomarkers involves their application in the development of disease-modifying drugs. ADNI biomarkers are specifically aimed at this aspect of AD drug development. The biomarkers chosen reflect measurable aspects of the AD disease process including amyloid beta protein (A$\beta$) metabolism (A$\beta$ in the CSF), tau protein metabolism (total tau and hyperphosphorylated tau [p-tau] in the CSF), A$\beta$ deposition (Pittsburgh Compound B [PIB] PET), synaptic function (fluorodeoxyglucose [FDG] PET), and neurodegeneration (MRI atrophy). They are designed to show the temporal course of these changes in patients with no disease, in patients with MCI (some of whom have early AD), an in subjects with mild AD dementia.

The predictive relationship between biomarker changes and clinical outcomes is critical to their successful utilization in AD drug development programs. This is not known for any AD-related biomarker. Preliminary correlations have been established (discussed below) for some clinical outcomes and some biomarkers; it is unknown if changes in a biomarker (such as reduced MRI ventricular enlargement with treatment) will correlate with reduced decline in cognition or function following treatment. There is no intervention in ADNI and the results of ADNI do not reveal relationships between treatment and biomarker changes. The ADNI dataset provides an important framework for selecting fit-for-purpose biomarkers most likely to predict clinical benefit.

Biomarkers will be incorporated into an NDA to support the candidate drug's mechanism of action, provide the basis for a claim for disease-modification, and differentiate the agent from symptomatic treatments or drugs with other

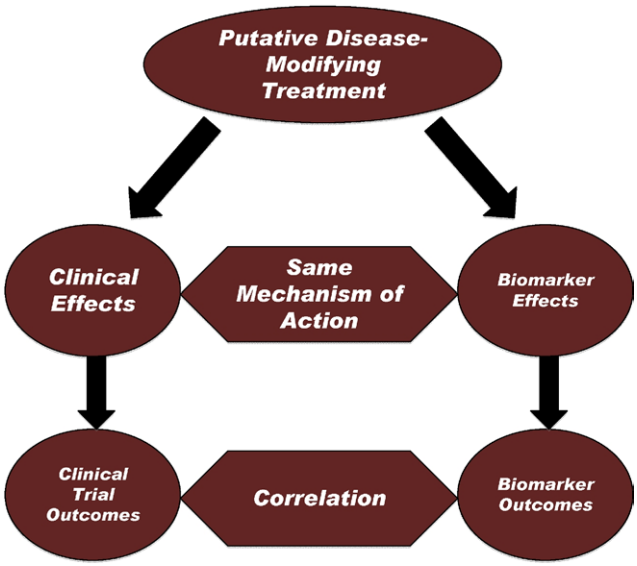


Fig. 2. Relationship of clinical outcomes and biomarkers in a clinical trial of an AD-modifying agent.

mechanisms. The terminology that will be allowed by the FDA for these findings is unknown. Biomarker findings included in the labeling of the product inform prescribers, patients, caregivers, and pharmaceutical purchasing organizations of the effects of the drug. In the product label for glatiramer actetate (Copaxone™), a treatment for multiple sclerosis, for example, differing MRI rate in drug and placebo arm for the number of enhancing white matter lesions are shown (Cummings, 2009b). Similarly, ADNI-type biomarkers could be included in product labeling to provide information on rate of MRI atrophy, A$\beta$ accumulation with PIB imaging, or changes in CSF A$\beta$ or tau measures.

To support a claim that biomarker effects and clinical effects are mediated by similar underlying pathways the 2 must be correlated (Fig. 2). Such a correlation does not prove a mechanistic relationship, but is necessary (although not sufficient) for the concept (Katz, 2004). Studying the relationships between biomarkers and clinical measures in the ADNI database is imperative as a means to understanding these potential correlations.

## 3. ADNI biomarkers in clinical trials

Following drug discovery, preclinical studies of pharmacokinetics and pharmacodynamics, lead optimization, and development of formulations acceptable for human consumption, candidate agents enter the steps of drug development (Prang, 2006; Rockwood and Gauthier, 2006) (Fig. 3). Phase I studies comprise first-in-human exposures beginning with single ascending doses and progressing to multiple ascending doses in small cohorts of subjects (6–10 per dose group). Subjects in these studies are typically normal healthy volunteers. An exception involves the development of immunotherapy where vaccinations and antibody infusions are given to patients with AD even in Phase I studies. Phase IIa studies seek proof-of-concept (POC) in studies with clinical outcomes and POP in studies with biomarker outcomes. These studies typically include 50–200 individuals per study arm of the intended treatment population (e.g., mild-to-moderate AD, MCI, etc). Phase IIb studies identify the dose or doses to be advanced to Phase III. Phase IIa and IIb may be combined in a multiple dose POC or POP study. Phase III studies include 200–600 patients per arm with the target disorder. Phase III studies of disease-modifying agents typically last 18 months. Clinical measures such as the Alzheimer's Disease Assessment Scale, cognitive portion (ADAS-cog), Clinical Dementia Rating (CDR), or the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS ADL) scale are the primary outcomes of Phase III studies. The clinical measures may be supported by biomarkers in the NDA.

### 3.1. Phase I

Biomarkers studied in ADNI can be used on all phases of drug development. Phase I studies are short in duration and use small sample sizes; they are not likely to show drug-placebo differences on structural neuroimaging measures. A$\beta$ can be measured in CSF of normal persons and these

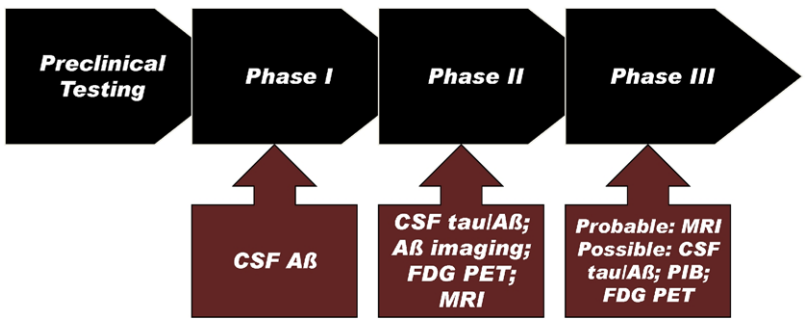


Fig. 3. AD drug development. Black arrows show the phases of drug development; the brick-colored arrows show the ADNI biomarkers that could be used in that stage. Aß = amyloid beta protein; CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography.

measures may provide insight into the mechanistic impact of agents on A$\beta$ metabolism (Galasko et al., 2007; Siemers et al., 2007). They are appropriate for Phase I studies.

### 3.2. Phase II

Biomarkers may facilitate Phase II studies substantially. Sponsors are faced with the conundrum of doing long, large Phase II studies to achieve POC or to do smaller shorter trials depending on biomarkers not proven to predict clinical success (Cummings, 2008). The former strategy has less risk but increases cost and expends valuable patent life of the compound; the latter approach is less expensive and faster but has greater risk for experiencing a negative outcome in Phase III. Phase III trials are much more expensive than Phase II trials (Prang, 2006) and decisions can be de-risked by generating as much information at possible in Phase II regarding whether to advance the compound. Biomarkers are attractive in this setting because they promise to show drug effects with fewer patients exposed for shorter periods than required to demonstrate drug-placebo differences on clinical measures.

Biomarkers with a high degree of diagnostic specificity can be used to enrich a trial population of MCI or putative AD patients with individuals very likely to harbor the AD process. ADNI studies have shown that a CSF profile of low A$\beta$42 and elevated total-tau and p-tau characterizes AD; the p-tau/A$\beta$42 ratio has a sensitivity of 91.1%, specificity of 71.2%, accuracy of 81.5%, positive predictive value of 77.3%, and negative predictive value of 88.1% (Shaw et al., 2009). Similarly, a positive PIB scan identifies the presence of fibrillar amyloid plaques and demonstrates the presence of plaques in nearly all AD, 60% of MCI, and 20%–30% of cognitively normal elderly (Jack et al., 2009). FDG PET shows reduced metabolism in the posterior cingulate, precuneus, parietotemporal regions, and frontal cortex of patients with AD (Langbaum et al., 2009), and some patients with MCI. The ADNI sample demonstrates that medial temporal atrophy on MRI in patients with MCI predicts those MCI patients who will progress to AD dementia (Evoy et al., 2009; Misra et al., 2009; Querbes et al., 2009). Any of these biomarkers can be used to identify patients with the predementia form of MCI or to eliminate non-AD patients from AD dementia studies.

Data from ADNI studies have been used to determine sample sizes for clinical trials required to show a 20% or 25% reduction in disease progression (Table 1). Biomarkers (MRI, FDG PET) provide a numerical advantage over clinical measures in demonstrating a disease-modifying effect.

Caution must be exercised in extrapolating these calculations directly to clinical trials. The ADNI calculations are based on studying the rate or amount of change occurring in a structure in a given time (e.g., hippocampal change in 12 months) and calculating how many patients would be required to show a drug-placebo difference if the drug had a

Table 1
Sample size calculations based on ADNI data for patients with AD

| Technique and reference | Structure or test | *n* required to show 25% disease slowing | *n* required to show 20% disease slowing |
|---|---|---|---|
| TBM (Hua et al., 2009) | Temporal lobe | 48 (80% power); 64 (90% power) | |
| | ADAS-cog | 619 (80% power); 828 (90% power) | |
| | CDR-SB | 408 (80% power); 546 (90% power) | |
| MRI (Holland et al., 2009) | Entorhinal cortex | 52–83 (confidence interval for 80% power) | |
| | Inferior temporal cortex | 92–153 | |
| | Hippocampus | 91–158 | |
| | Whole brain | 139–271 | |
| | Ventricles | 168–371 | |
| | ADAS-cog | 192–457 | |
| | CDR-SB | 165–365 | |
| MRI (Schuff, 2009) | MRI hippocampal volume (2 scans, 0–6 m) | 462 (90% power) | |
| | 2 scans (0–12 m) | 252 | |
| | 3 scans (0–6–12 m) | 255 | |
| | 3 scans + ApoE-4 | 196 | |
| | ADAS-cog (0–6 m) | 745 | |
| | ADAS-cog (0–12 m) | 814 | |
| | ADAS-cog (0–6–12) | 569 | |
| FDG PET (Landau et al., 2009) | FDG-ROIs (scans at 0–12 m) | 180 | |
| | ADAS-cog | 300 | |
| MRI (Nestor, 2008) | Ventricular volume (all AD); 6 mo | | 342 |
| | Ventricular volume (AD without ApoE-4); 6 mo | | 468 |
| | Ventricular volume (AD without ApoE-4); 6 mo | | 257 |
| | ADAS-cog (all AD); 6 mo | | 1607 |
| | ADAS-cog (AD without ApoE-4); 6 mo | | 2100 |
| | ADAS-cog (AD with ApoE-4); 6 mo | | 1370 |

Key: AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease Assessment Scale cognitive portion; ADNI, Alzheimer's Disease Neuroimaging Initiative; Apo-E, apolipoprotein E; CDR-SB, Clinical Dementia Rating-Sum of the Boxes; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; ROIs, regions of interest; TBM, tensor based morphometry.

20% or 25% effect. An agent, however, that decreased A$\beta$ production by 25% might not have a 25% effect on MRI volumetrics because these are measures of neurodegeneration and the relationships between A$\beta$ production and neurodegeneration are unknown. Power calculations for trials should allow for these uncertainties.

Biomarkers will be more useful in trials if they correlate with clinical outcomes. ADNI biomarkers data have been investigated from this perspective. In AD, rates of left and right hippocampal atrophy correlated with baseline CDR sum of the boxes (CDR-SB), (left 0.173, $p < 0.01$; right, 0.181, $p < 0.01$) and change in CDR-SB ($-0.174$, $p < 0.01$; 0.171, $p < 0.01$) (Morra et al., 2009). Temporal lobe atrophy assessed with tensor based morphometry (TBM) correlated with CDR-SB in AD and MCI and with the immediate and delayed recall scores of the logical memory tests of the Wechsler Memory Scale-Revised (Hua et al., 2008a). MRI demonstrates a correlation between ventricular enlargement and CDR-SB (Jack et al., 2009) and between ventricular enlargement and ADAS-cog scores (Evans et al., 2010). TBM measures of ventricular expansion also correlated with CDR-SB ($p = 0.002$) (Hua et al., 2008b). Structural Abnormality Index (STAND) scores reflecting the degree of AD-like anatomic features on MRI correlated with CDR-SB in MCI and AD (Vemuri et al., 2009). Mini Mental State examination (MMSE) scores and ADAS-cog scores correlated with FDG-PET but not with PIB or CSF A$\beta$42 measures (Jagust et al., 2009; Landau et al., 2009). These observations suggest that hippocampal atrophy changes measurably over time; ventricular enlargement may have the most robust correlations with commonly used clinical trial measures such as CDR-SB.

Correlations in the natural history of the disease do not necessarily predict linked change in response to therapy and measures that show little relationship to diagnosis or cognition might respond to therapeutic interventions. Serum A$\beta$42, for example, does not distinguish AD from normal elderly but declined in patients treated with the gamma-secretase inhibitor LY-450139 (Fleisher et al., 2008) suggesting that it might function as an outcome measure reflective of reduced A$\beta$42 production.

Measures that are closely related to the mechanism of action of the drug are most likely to show a treatment effect. CSF A$\beta$ measures have promise as outcomes of secretase inhibitors (Hussain et al., 2007); CSF total tau and p-tau are most reflective of treatment mechanisms targeting neurofibrillary tangle formation (Tapiola et al., 2009); FDG PET most closely reflects synaptic activity (Langbaum et al., 2009); PIB measures fibrillary amyloid deposition (Ikonomovic et al., 2008); and MRI measures neurodegeneration with loss of neurons and brain substance (Bobinski et al., 2000). When choosing among biomarkers, fit-for-purpose decisions will include sensitivity, specificity, relationship to mechanism of action of the agent, and purpose of the biomarker in the trial (e.g., identify the optimal patients, validate the mechanism of action, demonstrate effects on a widely available tool such as MRI, etc).

### 3.3. Phase III

Phase III trials require clinical outcomes for the NDA and the sample sizes cannot be reduced using biomarkers. Moreover, larger samples are needed to provide the necessary exposures to detect safety or tolerability issues associated with the trial agent. Biomarkers, however, are required to support a disease-modifying type claim unless randomized start or randomized withdrawal trial designs are utilized to demonstrate disease modification (Katz, 2004). Biomarkers will be included as part of a disease-modifying NDA in most cases.

Enrichment strategies such as those discussed above may be used in Phase III trials to insure the presence of the AD process in the trial population. If enrichment is used in trials submitted as part of the NDA, the labeling will reflect this decision. The indication language will specify the use of the agent in the enriched population. Thus, the indication might be for patients with a high CSF p-tau/A$\beta$42 ratio, positive PIB imaging, or medial temporal atrophy, depending on the biomarker chosen for enrichment.

MRI is the biomarker of choice for either enrichment or as an outcome marker in Phase III trials. ADNI has demonstrated the feasibility of multicenter collection of magnetic resonance images and ADNI investigators have developed the technology for phantom-based calibration, automatic image quality assessment, and automated segmentation of subregions such as the hippocampus (Chupin et al., 2009; Clarkson et al., 2009; Mortamet et al., 2009). MRI technology is widely available, making it possible to obtain scans on all cooperative trial subjects and avoiding issues that may confound analyses when nested subgroups of subjects are assessed with biomarkers and attempts made to generalize the findings.

### 3.4. Primary prevention trials

Prevention trials are aimed at developing medications that can be administered to cognitively normal individuals to forestall or prevent the occurrence of AD (Andrieu et al., 2009). No FDA-approved preventive therapies for AD are available currently. Although AD is a common disorder, it is rare in any limited group of elderly persons followed for a relatively short period. Demonstrating a drug-placebo difference in a clinical trial depends on having enough patients who decline cognitively or progress to a defined state (MCI or AD) in the placebo group to observe a treatment benefit in the active therapy group. With regard to AD, any aged group will be comprised of 3 subpopulations: (1) persons who will never get AD; (2) persons who have risk factors and may eventually develop AD; and (3) persons who have AD established in the brain but are still cognitively normal (Cummings et al., 2007). Epidemiologic factors can construct populations of those in the second group;

biomarkers are most useful for identifying those in the third. To the extent possible those in the first group should not be exposed to possibly harmful medications. PIB imaging and CSF A$\beta$ measures identify patients who are cognitively normal and who have evidence of AD pathology in the brain (Jack et al., 2009; Shaw et al., 2009).

Outcome measures for prevention trials could include clinical decline, development of MCI or AD, or progression on a biomarker. If a biomarker is proposed as a primary outcome, it must serve as a surrogate for clinical measures and known to predict clinical outcomes. Surrogate validation requires that the biomarker predict the clinical outcome across several trials and across several classes of relevant agents (Cummings, 2009a). Drugs can be approved by the FDA on the basis of effects on an unvalidated surrogate if the biomarker is relatively likely to predict clinical outcomes, the predicted effect is considered very important (delaying cognitive decline), and there are few or no other treatment options (Katz, 2004). If a drug is approved on the basis of an unvalidated surrogate, the sponsor may be required to conduct postapproval studies to demonstrate the link between the biomarker and the clinical benefit. Several ADNI biomarkers could serve as outcomes in prevention trials including MRI atrophy, CSF t-tau or p-tau, p-tau/A$\beta$42 ratio, PIB imaging or FDG PET. None are validated surrogates but might qualify as unvalidated surrogates or could serve as key secondary outcomes in trials using clinical measures as primary outcomes.

## 4. ADNI clinical sample: implications for clinical trials

### 4.1. Demographic features

Table 2 summarizes several important clinical features of the ADNI sample (Petersen et al., 2010). Notably, the sample is very well educated with educational levels of 14.7–16 years indicating that most subjects had completed several years of college. Patients with higher education levels tend to have later onset of AD and faster progression after onset (Musicco et al., 2009). This high level of education may complicate extrapolating some results to other trials, particularly international trials which tend to include more persons with low educational levels. Similarly, most trials have more women than men (Schneider and Sano, 2009), while the ADNI cohort has the reverse (% female ranging from 35.4 to 48). This might affect the generalization of some aspects of ADNI.

Table 2
Demographic features of the ADNI sample (Petersen et al., 2010)

| Characteristic | Cognitively normal controls | MCI | AD |
|---|---|---|---|
| *n* | 229 | 398 | 192 |
| Age, years (mean ± SD) | 75.8 ± 5.0 | 74.7 ± 7.4 | 75.3 ± 7.5 |
| Education (mean ± SD) | 16 ± 2.9 | 15.7 ± 3.0 | 14.7 ± 3.1 |
| % Female | 48 | 35.4 | 47.4 |
| ApoE-e4 carrier | 26.6 | 53.3 | 66.1 |
| White | 90.8 | 90.5 | 92.2 |

Key: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ApoE-e4, apolipoprotein epsilon 4; MCI, mild cognitive impairment.

### 4.2. Clinical trials groups

ADNI includes 3 groups: cognitively normal controls, patients with MCI, and patients with mild AD. The inclusion and exclusion features for the groups are given in Table 3. Data from 11 recently completed and 12 ongoing 18-month AD trials were recently reviewed by Schneider and Sano (Schneider and Sano, 2009). They reviewed the MMSE range, mean age, % female, and educational level of completed trials and the MMSE range of the ongoing trials. Two of the 23 trials reviewed had MMSE ranges that mimicked those of the ADNI protocol (2 completed tarenflurbil trials). All the other trials included patients with mild-to-moderate AD. The ADNI cohort provides data on more mild AD patients and anticipates the likely inclusion of more mild patients in clinical trials. Extrapolating biomarker data from ADNI to typical protocols including mild-to-moderate AD (typically an MMSE range of 16–26) is difficult; patients with more severe disease tend to progress more rapidly and may have different biomarker-clinical relationships (Ito et al., 2010).

The cognitively normal group of ADNI showed almost no change in a 12-month period (Petersen et al., 2010). Observed changes were MMSE 0.0 ± 1.4, ADAS-cog −0.5 ± 3, and CDR-SB 0.1 ± 0.3. This indicates that an enrichment strategy will be necessary for prevention trials to have enough decline in the placebo group that a treatment-related benefit can be observed. The biomarker features of such an enriched group will require study to inform future trials. Enrichment alternatives include identifying persons with normal cognition and medial temporal atrophy, positive amyloid imaging, low CSF A$\beta$, declining cognition on sequential assessment, older age, family history of dementia or AD, predisposing genotype (e.g., ApoE-4 carriers), or demographic risk factors (e.g., low education level, small head size, history of midlife hypertension, history of hypercholesterolemia) (Cummings et al., 2007).

### 4.3. MCI

MCI is a syndrome of variable etiology and outcome. Persons with MCI may recover normal cognition, remain in the MCI state, progress to AD type dementia, or progress to a non-AD dementia (Matthews et al., 2008). Most but not all studies report that the prevalence of predementia AD is higher among patients with amnestic type of MCI (Yaffe et al., 2006), but approximately 30% of patients presenting with amnestic MCI have non-AD pathology as the primary diagnosis at autopsy (Jicha et al., 2006). New therapies for AD are focused on aspects of AD molecular biology and the AD substrate is required for their proposed mechanism of action. Biomarkers are an optimal means for identifying

Table 3
Characteristics of the patient groups included in the ADNI protocol

| Trial feature | Normal controls | MCI | Mild AD |
|---|---|---|---|
| *n* | 200 | 400 | 200 |
| MMSE score | 24–30 | 24–30 | 20–26 |
| CDR | 0; memory box score must be 0 | 0.5; memory box score must be at least 0.5 | 0.5 or 1 |
| Memory complaint | | Memory complaint by subject or study partner that is verified by a study partner | Memory complaint by subject or study partner that is verified by a study partner |
| Memory function | Normal memory function documented by scoring at specific cutoffs on the logical memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-revised (the maximum score is 25): (a) more than or equal to 9 for 16 or more years of education; (b) more than or equal to 5 for 8–15 years of education; (c) more than or equal to 3 for 0–7 years of education | Abnormal memory function documented by scoring below the education adjusted cutoff on the logical memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-revised (the maximum score is 25): (a) less than or equal to 8 for 16 or more years of education; (b) less than or equal to 4 for 8–15 years of education; (c) less than or equal to 2 for 0–7 years of education | Same as MCI |
| General cognition | Cognitively normal, based on an absence of significant impairment in cognitive functions or activities of daily living | General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease cannot be made by the site physician at the time of the screening visit | NINCDS/ADRDA criteria for probable AD |
| Modified Hachinski Ischemia Scale score | $\leq 4$ | $\leq 4$ | $\leq 4$ |
| Geriatric Depression Scale score | $< 6$ | $< 6$ | $< 6$ |
| Education | Completed 6 grades of education (or had a good work history sufficient to exclude mental retardation) | Completed 6 grades of education (or had a good work history sufficient to exclude mental retardation) | Completed 6 grades of education (or had a good work history sufficient to exclude mental retardation) |

Key: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; NINCDS/ADRDA, National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association.

MCI patients whose cognitive decline reflects the presence of underlying AD. ADNI biomarkers that identify which patients with MCI have very early AD are most useful to drug development efforts. Cortical thickness mapping (Querbes et al., 2009) and regional atrophy measures (Evoy et al., 2009) predict progression from MCI to AD type dementia and could be used to enrich MCI trial populations with MCI of the AD type. Likewise, FDG PET, PIB imaging and CSF A$\beta$ and tau measures can identify MCI patients with early AD.

The combination of a clinical syndrome of amnesic MCI and a biomarker indicative of AD fulfills the main criteria for the definition of AD proffered by Dubois et al. (2007). This definition of AD embraces both the predementia and dementia phases of the illness and provides a means of defining a trial population of AD patients who are in the most mild stage of the disease before the occurrence of dementia.

The clinical definition of MCI also bears on the likelihood of evolution to AD dementia (Matthews et al., 2008). The definition of MCI used to define the ADNI cohort differs from the definition of MCI developed by Petersen et al. (1999; 2001). Table 4 summarizes the differences between the 2 definitional approaches to MCI. The definition employed in the ADNI MCI population is more defined operationally with MMSE score ranges and thresholds for neuropsychological assessments. Patients with more than mild depression or more than minimal vascular symptoms are excluded. These differences will affect the composition of the trial population and the ADNI biomarker findings will apply most readily to MCI populations using the same MCI definition. Minor differences in MCI definitions have substantial effects in clinical trials as evidenced by the markedly different percentages of apolipoprotein e4 carriers across MCI trials (Jelic et al., 2006). Results must be extrapolated from trial to trial with caution; and ADNI results also must be generalized with careful consideration of the sample selection criteria.

## 5. Qualification of biomarkers

Biomarkers must go through a qualification process before inclusion in regulatory-quality clinical trials. The FDA has specified the qualification process (Goodsaid and Frueh, 2007) and the steps of the process are shown in Fig. 4. Investigation of biomarkers for AD by ADNI provides a platform on which to build the qualification process and establish that a specific biomarker is fit-for-purpose for a specific trial and could be included in an NDA.

## 6. Comment

ADNI has led to remarkable progress in understanding biomarkers in AD and MCI. The course of biomarker change over time is being mapped, the relationship among biomarkers is being defined, and the associations between biomarkers and clinical changes are being demonstrated. Biomarkers are positioned to play a larger role in drug development based on ADNI data. Phase II studies may be shortened, Phase III studies may include biomarkers as part of a disease-modifying NDA, and biomarkers may play key roles in primary prevention trials. Biomarkers will help de-risk Phase III decisions, reduce drug development times and costs, improve safety, and speed the development of urgently needed new treatments.

Review of the ADNI studies reveal several unmet needs in the realm of biomarker development. Most critical are

Table 4
MCI as defined by ADNI and as defined by Petersen et al. (1999; 2001)

| Clinical feature | Petersen MCI | ADNI MCI |
|---|---|---|
| MMSE score | Not specified | 24–30 |
| CDR | Not specified | 0.5; memory box score must be at least 0.5 |
| Memory complaint | Memory complaint documented by the patient and collateral source | Memory complaint by subject or study partner that is verified by a study partner |
| Memory function | Memory impaired for age and education | Abnormal memory function documented by scoring below the education adjusted cutoff on the logical memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-revised (the maximum score is 25): (a) less than or equal to 8 for 16 or more years of education; (b) less than or equal to 4 for 8–15 years of education; (c) less than or equal to 2 for 0–7 years of education |
| General cognition | Relatively normal; does not meet DSM-IV criteria for dementia | General cognition and functional performance sufficiently preserved such that a diagnosis of AD cannot be made by the site physician at the time of the screening visit |
| Modified Hachinski Ischemia Scale score | Not specified | $\leq 4$ |
| Geriatric Depression Scale score | Not specified | $< 6$ |
| Education | Not specified | Completed 6 grades of education (or had a good work history sufficient to exclude mental retardation) |

Key: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (American Psychiatric Association, 1994); MCI, mild cognitive impairment; MMSE, Mini Mental State Examination.

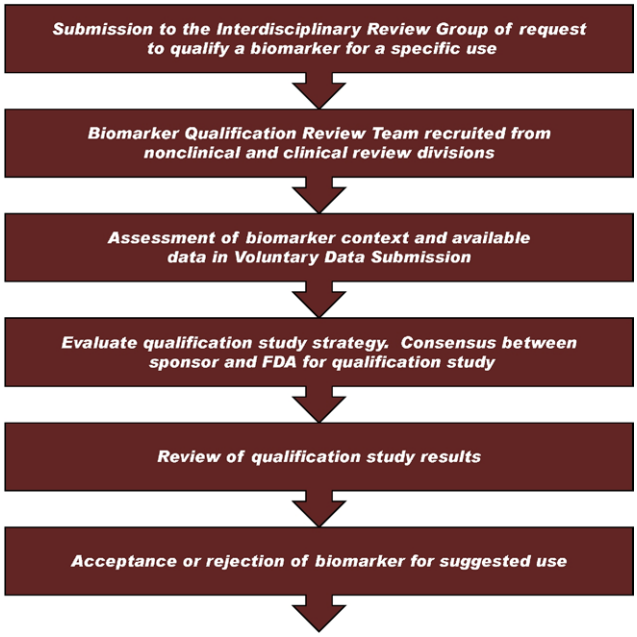


Fig. 4. Steps in the process of biomarker qualification as specified by the FDA (Goodsaid and Freuh, 2007).

more data on the link between clinical and biomarkers changes in response to treatment. Only a few studies including both outcomes have been reported (Fox et al., 2005; Gilman et al., 2005; Lannfelt et al., 2008; Salloway et al., 2009), and only the repeated use of biomarkers in studies of drugs affecting AD pathways will eventually inform the use of these measures as predictors of clinical benefit (Cummings, 2009a). ADNI is a noninterventional natural history observational study and cannot contribute to this aspect of biomarker development.

Another unmet need in biomarker development pertains to measures of target engagement or drug activity. ADNI biomarkers characterize the natural history of AD. Drug development has been accelerated by combining a target engagement biomarker with natural history outcomes (Wagner, 2008). For example, in the development of statins, cholesterol-lowering can be measured directly as an immediate drug effect and linked to patient outcomes such as death, myocardial infarction, or stroke. Pharmaceutical development in AD would be facilitated by development of drug activity biomarkers that directly measure the effect of the candidate treatment on the target pathways (e.g., A$\beta$ production, inflammation, oxidation) and including such measures together with natural history biomarkers and clinical outcomes in clinical trials. Biomarkers of the drug effect should be sought and characterized during the preclinical phase of drug development and extended into the clinical phases of the development program (Choi et al., 2009; Dubois et al., 2010; Higuchi et al., 2010).

The populations studied by ADNI anticipate the need to treat patients early in the course of AD and include patients with predementia syndromes and mild dementia. Most AD drugs are tested in patients with mild-to-moderate AD with MMSE scores in the 16–26 range. ADNI data apply only to the more mild end of this range of severity. Biomarker data are needed on patients with more severe disease to assist drug development in this broader AD population.

Clinical trials are increasingly global enterprises. While the USA conducts more clinical trials than any other single country, collectively more trials are conducted outside the USA than in the USA (Glickman et al., 2009). Ex-US populations are often more poorly educated and less likely to be Caucasian than the ADNI cohort. The very high educational level of ADNI participants and the low rate of inclusion of nonwhite subjects limit the generalizability of the clinical and biomarker findings. The global biomarker interest inspired in part by ADNI will assist in characterizing persons with a broader range of educational levels and ethnic backgrounds. Among these worldwide studies are the European ADNI (Buerger et al., 2009; Frisoni et al., 2008); the AddNeuroMed study (Lovestone et al., 2009); the Australian Imaging, Biomarkers, and Lifestyle (AIBL) Study of Aging (Ellis et al., 2009); the Swedish Brain Power Initiative; and similar studies in Japan, Korea, and China (Miller, 2009).

Together with data from international collaborators, ADNI biomarker data provide information that is increasingly critical to the successful development of new treatments for AD, new therapies to slow the progression of MCI to AD dementia, and agents to prevent cognitive decline in the elderly. Ultimately, ADNI and related biomarkers promise to reduce drug development times, increase success rates, reduce costs, de-risk trials using clinical outcomes, and hasten the development of new treatments for AD.

## Disclosure statement

Dr Cummings has no disclosures specific to the contents of this article.

## Acknowledgements

Dr Cummings is supported by the Sidell-Kagan Foundation, the Jim Easton Gift, a California Alzheimer's Disease Center grant and an National Institute on Aging (NIA) Alzheimer's Disease Research Center grant (P50 AG16570).

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