# Potential Applications of Artificial Intelligence in Clinical Trials for Alzheimer's Disease

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**Abstract**

Clinical trials for Alzheimer's disease (AD) face multiple challenges, such as the high screen failure rate and even allocation of heterogeneous participants. Artificial intelligence (AI), which has become a potent tool of modern science with the expansion in the volume, variety, and velocity of biological data, offers promising potential to address these issues in AD clinical trials. In this review, we introduce the current status of AD clinical trials and topic of machine learning. Then, a comprehensive review is focused on the potential applications of AI in the steps of AD clinical trials, including the prediction of AD biomarkers and differential diagnosis of AD in the prescreen during eligibility assessment and the likelihood stratification of patients who will progress to AD dementia and fast cognitive decline group from the slow decline group in randomization. Finally, this review provides challenges, developments and the future outlook on the integration of AI into AD clinical trials.

**Keywords:** Alzheimer's disease, artificial intelligence, clinical trials, eligibility assessment, randomization

## 1. Introduction

Recent advances in understanding the neurobiology of Alzheimer's Disease (AD) revealed that the initiation of disease processes leading to symptomatic and functional neurodegeneration preceded the onset of dementia by 15-20 years [1,2]. AD is pathologically characterized by the aggregation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau proteins in the form of neurofibrillary tangles (NFTs). The amyloid cascade hypothesis explains that Aβ triggers the following procession, such as the development of NFTs, cortical atrophy, cognitive impairments, and loss of activities of daily living [3,4]. These AD biomarkers appear in the predementia stage, which includes normal cognition (NC) and mild cognitive impairment (MCI). Thus, previous clinical trials have focused on the development of Aβ targeting diagnostic and therapeutic methods. There are also growing clinical trials targeting tau and NFTs, as tau pathology is more closely correlated with cognitive decline than Aβ [5].

Despite the stagnancy in AD clinical trials for the past 18 years ever since memantine was launched in 2003, a recent clinical trial of Biogen's aducanumab has demonstrated a statistically significant reduction in amyloid beta plaques [6,7]. The US Food and Drug Administration has approved aducanumab for AD treatment using the Accelerated Approval pathway, and this is expected to serve as an impetus for global AD clinical trial efforts. AD clinical trials involve two notable steps: eligibility assessment and randomization. During eligibility assessment, recruited participants are screened for either enrollment or exclusion, and, during randomization, selected participants are allocated into intervention and control groups. However, there are several challenges present in these steps. Principally, AD clinical trials have a high screen failure rate, which could be attributed to the stringent screening criteria of AD trials such as Aβ PET positivity. Secondary and tertiary prevention trials for AD have average screen failure rates of 88% and 44%, respectively, which, given the expensive and time-consuming nature

of screening procedures, would suggest the need for considerable work to recruit even one eligible subject [8]. Furthermore, given the heterogeneity in prognosis of NC or MCI with AD biomarkers, it is important to stratify the risk of participants and allocate them evenly into intervention and control groups for a reliable observation of the intervention [9,10].

Artificial Intelligence (AI) refers to "the ability of a digital machine or computer to accomplish tasks that traditionally required human intelligence." [11] A convergence of advanced machine learning (ML) algorithms, data proliferation, tremendous increases in computing power, and memory storage has propelled AI from hype to reality. ML algorithms could enhance the ability to detect hidden structures or underlying patterns of the data to improve the performance over time and learn how to make a prediction rather than explicit instruction. In this Review, we aim to explore the applications of AI for a specific domain in clinical trials for AD in the steps of eligibility assessment and randomization. Finally, the development of explainable AI techniques for the identification of genetic pathways and multiscale interactome for drug candidates and testing performance to rigorous external validations cohorts with greater diversity would be substantially beneficial in AD clinical trials.

## 2. Eligibility assessment

Clinical trials for AD have been performed through disease-modifying therapies (DMTs) or symptomatic treatments. DMTs aim to detect AD at the predementia stage and halt its progression. As clinical trials involving DMTs target AD biomarkers such as Aβ and tau, these trials screen the recruited population to enroll the biomarker-guided diagnosed participants. Meanwhile, clinical trials involving symptomatic treatments utilize palliative interventions such as donepezil and memantine in clinically diagnosed participants to alleviate the negative symptomatic effects of established AD. Therefore, AI applications in clinical trials involving

DMTs and symptomatic treatments require prescreening algorithms for the prediction of AD biomarkers and differential diagnosis; the recruited population would be clustered into high and low likelihood groups, with the former undergoing screening procedures for validation and the latter being excluded from the clinical trials (figure 1).

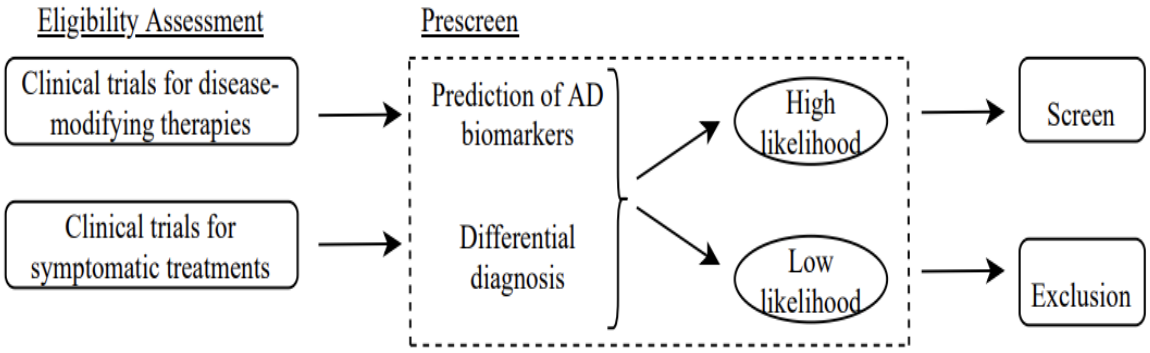


**Figure 1.** Diagram of eligibility assessment in AD clinical trials. AI-applications in eligibility assessment would prescreen the recruited population to identify high likelihood and low likelihood groups. For clinical trials involving disease-modifying therapies, algorithms would predict AD biomarkers such as amyloid and tau, while they would differentiate ADD from other forms of dementia for clinical trials involving symptomatic treatments. The high likelihood group would be selected for further

## 2.1 AI for prediction of AD biomarkers

Clinical trials for DMTs require algorithms to predict AD biomarkers in NC or MCI participants. Current screening procedures to identify AD biomarkers consist of the use of amyloid and tau positron emission tomography (PET). However, they are associated with high costs, lack of accessibility, and patient's hesitation due to the fear of radiation exposure. To reduce screen failure, machine learning algorithms can be applied in the prescreening step to select a subset of individuals who are likely to be amyloid or tau positive, in which case those certain individuals would be screened for validation.

A gradient boosting method (GBM), a tree-based ensemble approach that generates accurate classifiers using a linear combination of base classifiers iteratively adjusted by their

weight, can assist in the biomarker-guided diagnosis of prodromal AD patients with amnestic mild cognitive impairment (aMCI) [12]. Upon training the GBM algorithm with a model that consisted of age, education, gender, diabetes, hypertension, apolipoprotein E gene (*APOE*) status, neuropsychological test scores, and MRI features such as hippocampal volume and cortical thickness as variables, the algorithm demonstrated highly accurate predictive performance on the validation and test sets: a Brier score (mean square error of estimator of a procedure for estimating an unobserved quantity) of 0.138 and the area under the receiver operating characteristic curve (AUROC), derived by integrating the receiver operating characteristic (ROC) curve, of 0.893 with the 95% confidence interval of 0.858-0.896 [13]. Furthermore, variable importance could be calculated using the mean decreased accuracy (MDA), which is derived from the discrepancy of the error when the variable split the subset space; the GBM algorithm suggested that *APOE* status, interaction of cortical thickness of the temporal lobe and hippocampal volume, and scores in the delayed recall tasks of Seoul Verbal Learning Test (SVLT) and Rey Complex Figure Test (RCFT) and the immediate recall task of RCFT were highly important features. Additionally, a radiomics approach can be taken to predict amyloid positivity in MCI patients by extracting specific radiomics features from structural MR images (including T1, T2 FLAIR) and undertaking feature selection and prediction using a LASSO (least absolute shrinkage and selection operator [14].

While most diagnostic efforts focus on amyloid positivity, there are ML algorithms to diagnose abnormal tau accumulation in prodromal AD patients, which can, perhaps, serve as a highly predictive instrument for predicting cognitive decline. One study used GBM and random forest (RF) to predict tau accumulation [15]. RF is an ensemble ML algorithm that constructs a multitude of decision trees to output the class that is the mode of the classes or the mean prediction. Both GBM and RF algorithms incorporating demographics,

neuropsychological results, *APOE4* genotype, *SUVR of FDG PET*, and cortical thickness showed a good predictive performance for predicting tau burden in the Aβ + MCI populations (GBM: AUC of 0.815, 95% CI 0.804-0.830; RF: AUC of 0.82, 95% CI 0.808-0.839). The relative feature importance of GBM and RF models was similar: the most important features identified were the cortical thickness of parietal and occipital lobes and the neurophysiological test results related to memory domains. This was consistent with a study that suggested a strong relationship between increased tau pathology and reduced cortical thickness with worse performance on neuropsychological tests pronounced in bilateral temporoparietal regions [16].

### 2.2 AI for differential diagnosis

Clinical trials for symptomatic treatment require algorithms to perform differential diagnosis of participants with AD dementia from other forms of degenerative dementia. Clinical features were historically employed for differential diagnosis of various neurodegenerative diseases, yet the similarities in the clinical presentation of diseases led to unsatisfactory differential diagnosis. Commonly mistaken forms of dementia, especially in the early onset of dementia, are AD and frontotemporal dementia (FTD) due to their clinical similarities such as the progressive alterations in behavior (behavior variant FTD, bvFTD) and language ability (primary progressive aphasia, PPA; subdivided into non-fluent variant PPA, nfvPPA, and semantic variant PPA, svPPA). In fact, traditional diagnostic criteria such as the NINCDS-ADRDA criteria had 93% sensitivity of distinguishing AD subjects from FTD patients, but 23% specificity for FTD recognition, since most FTD patients had also fulfilled the criteria for AD [17].

An individual subject classifier can be built by establishing hierarchical diagnostic categories created through an ML-based classification method using surface-based cortical thickness data. MR image preprocessing and cortical thickness can be achieved by applying the

FreeSurfer software for an automated surface modeling and measurement of each subject's cortical thickness. To enhance the accuracy of the classifier, the Laplace Beltrami operator (LBO) could be performed to transform cortical thickness data from the geometrical domain into frequency space, after which original data would be represented in the form of oscillations of alternating thin and thick cortex across the cortical space [18]. The hierarchical classifier is constructed using the principal component analysis (PCA) for the dimension reduction and linear discriminant analysis (LDA) for the classification of unlabeled subjects into the following different classes: step 1, NC and Dementia (AD and FTD); step 2, AD and FTD; step 3, bvFTD and PPA; step 4, svPPA and nfvPPA. The classifier demonstrated a remarkable accuracy in differential diagnosis (step 1: 86.1%, step 2: 90.8%, step 3: 86.9%, and step 4: 92.1%) [19]. Discriminative regions in the cortical space for the differential diagnosis were derived by visualizing the weight vector of the classifier, and the 10-fold cross-validation was performed to evaluate the classification performance.

**3. Randomization**

Drugs targeting Aβ have been developed and actively applied in clinical trials in ADD, but most have resulted in failure. Consequently, many recent clinical trials have shifted their focus on the non-demented Aβ+ population as a target group. MCI, particularly the amnestic form, has been of interest, since it is regarded as a transitional state between normal aging and ADD. However, amnestic MCI (aMCI) patients are heterogenous; some remain stable or even revert to normal cognition [20]. Furthermore, patients can be further classified into "fast decliner" and "slow decliner" based on the trajectory of their cognitive decline [21]. Randomization is an important step to stratify the risk and allocate different participants evenly into intervention and control groups, which reduces the bias in the treatment assignment (figure 2).

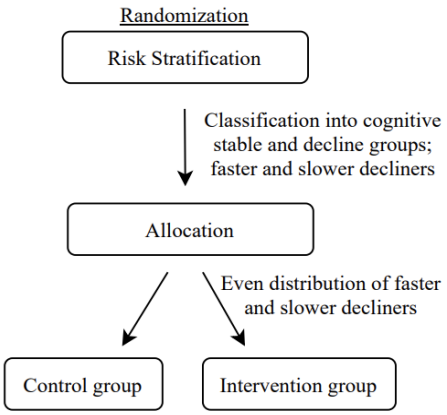


**Figure 2.** Diagram of randomization in AD clinical trials. AI-applications in randomization carries out risk stratification on the Aβ+ MCI patients into cognitive stable and decline groups, with the latter further classified into faster and slower decliners. The faster and slower decliners are evenly allocated into control and intervention groups to minimize the bias in the treatment assignment.

Upon classifying aMCI subjects into subgroups by the modality (verbal memory dysfunction, visual memory dysfunction, and both), severity of memory dysfunction, and multiplicity of the involved cognitive domain, a nomogram for risk stratification was created using a multivariable logistic regression model [22]. The variables incorporated were age, sex, years of education, BMI, three neuropsychological features (modality, severity, and multiplicity), and *APOE4* status. Using the absolute beta values, a point value was assigned to each variable, and the summed total point value for each predictor was allocated to an overall risk score through the linear predictor method (rms package in R). The nomogram predictive performance could be quantified with discrimination and calibration: to quantify discrimination, a concordance index (C-index), the area under the ROC curve, can be used, while a graphical assessment with calibration curve showing the relationship between the actual observed and predicted probabilities could be used for calibration. The multivariable logistic regression in the study had the C-statistic of 0.80, and the bias-corrected calibration plot was close to the ideal predicted values, affirming the predictive power of these multimodal biomarkers. The model delineated that age (OR (odds ratio) 1.1, 95% CI 1.05-1.16) and APOE4 (OR 4.71, 95% CI 2.12-10.49) were significant predictors for the conversion of MCI to ADD; moreover, patients with verbal-aMCI (OR 2.50, 95% CI 0.77-8.10) and both verbal-aMCI and visual-aMCI (OR 6.21, 95% CI 2.15-7.90) had a higher dementia risk compared to the verbal-aMCI group [23].

An uneven allocation of fast and slow decliners into intervention and control groups could have a profound impact on AD clinical trials. For example, if faster decliners are mostly selected for the intervention group and slow decliners are mostly selected for the control group, the reported treatment effect would likely be underestimated and statistically insignificant because of the bias in the treatment assignment. Therefore, risk stratification of the cognitive decline group into fast and slow decliners is vital for a reliable observation of the intervention impact. A recent study, using the Aβ+ MCI patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, employed a multivariable regression analysis (rms package in R 3.4.3), using the following biomarkers as potential predictors: age, MCI stage (early and late), *APOE4*, CSF Aβ, t-tau and p-tau, FDG SUVR, AV45 SUVR, and corrected hippocampal volume (HV) [24]. Findings suggested that advanced MCI stage (LMCI), higher CSF t-tau or p-tau, lower HV, hypometabolism in AD signature regions (lower FDG SUVR), and the presence of *APOE4* genotype were significantly predictive of fast decliners group status, with the predictive performance of 90% on validation with the testing dataset. Furthermore, an SAS procedure for estimating group-based trajectory models could be conducted using the Proc Traj software to cluster individuals with the same cognitive progression trajectory into fast and slow decliners, with cortical thickness and baseline demographics and neuropsychological features as variables [25].

## 4. Challenges and Future Directions

AI systems with large-scale data have facilitated the development of disease prediction that can potentially reduce the screen failure rate of clinical trials [26]. Furthermore, the identification of suitable participants in trial recruitment contributes to reducing associated expenses and accelerates drug developments [27]. However, it is important to acknowledge several challenges in clinical trials.

Advanced AI models derived from high-quality databases often demonstrated favorable performance; additional information from explainable and transparent AI technology might further understanding of biomedical data and improve their applications in clinical trials. A common form of a visible machine learning algorithm such as a graphical neural network might provide structural connections between different medical entities (e.g., diseases, drugs, and proteins). For example, GNNexplainer identifies a small set of important variables and genetic pathways that contribute to human disease [28]. Identification of disease mechanisms through the multiscale interactome has facilitated efficacious and safe therapeutic development. In addition, earlier access to the drug candidates could help improve the time and expenditure of prescreening process in clinical trials. Thus, developing an explainable and transparent AI system would substantially benefit both the speed and efficiency of clinical trials and drug discovery.

Another challenge is the limited generalizability that arises from the lack of external validations, which reduces the confidence in the predictive power of AI algorithms. External and internal validations are crucial for the development of a reliable algorithm. Internal validation methods such as bootstrap and cross-validation quantify the algorithm optimism and provide information about the degree of overfitting, whereas external validation uses

independently derived data to ensure generalizability. Review studies, however, have demonstrated that a substantial number of studies did not perform any validation or performed either external or internal validation [29]. Internal validation methods could be limited by a small sample size. A minimum of 300 subjects is generally recommended for internal validation, but categorical data in AD clinical trials, such as brain imaging measurements, could be limited due to the associated costs and time [30]. For external validation, over-reliance on one cohort population and unavailability of similar but different cohort populations remain a challenge. These shortcomings limit the clinical relevance of AI despite its promising computational results.

Further studies need to focus on improving the efficiency and effectiveness of AI techniques for AD clinical trials. Firstly, AI technologies, such as visible neural networks, could incorporate the inner workings of AI models into complex and hierarchical biological systems [31,32]. AI models can be enriched with biological knowledge, which includes multilevel interactions composed of sequences, protein complexes, cells, tissues, organs, and organisms. Compared to the current deep learning schemes to model entire system at once, this approach models how various AD-related entities interact with each other at different levels to develop the multiscale interactome for AD drug candidates. Moreover, these models could leverage genetic and genomic data to identify genetic determinants of AD to guide therapies with individual's genomic profiles, which allows for precision medicine and personalized treatment. Secondly, rigorous external validations in other populations with greater diversity is necessary to assess generalizability and reproducibility. Finally, given that the ML efficiency increases as the quantity and quality of data increases, the integration of genomics, proteomics, and other omics data in the AD clinical research could help investigate molecular pathways of AD, with potential implications for novel diagnostic biomarkers and precision medicine [33].

## 5. Conclusion

Clinical trials for AD face challenges of high screen failure and even allocation of the heterogeneous subject population. Many recent works have investigated the potential applications of AI to address these challenges in clinical trials, particularly in the steps of eligibility assessment and randomization. The prediction of AD biomarkers and differential diagnosis of AD from other causes of dementia, such as FTD, in the prescreening process could drastically reduce the high screen failure rate. Also, the ML-based stratification of the subject population into cognitive stable group, faster decliners, and slow decliners can guide the even allocation of the heterogeneous subject population into intervention and control groups. AI algorithms have not been integrated into AD clinical trials due to the lack of explainability and poor external and internal validations. However, the integration of biological knowledge to develop the multiscale interactome and rigorous external validations for generalizability and reproducibility could result in novel diagnostic biomarkers and precision medicine.

## Author Contributions

**Younghoon Seo:** Writing – original draft, Writing – review & editing. **Hyemin Jang:** Writing – review & editing. **Hyejoo Lee:** Writing – review & editing, Conceptualization.

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## Conflicts of Interest

The authors declare no conflict of interest.

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