Disease Simulation in Drug Development
External Validation Confirms Benefit in Decision Making

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Introduction

Disease simulations offer a potential mechanism for extending the findings of clinical trials over longer time span and to broader populations than those considered in the clinical trials themselves. A flexible and transparent disease simulator is a cost-effective means of assessing the value of new target compounds, identifying key drivers, conducting "what if" analyses, and aiding in decision making at stage-gate reviews during early drug development.

For a disease simulator to be reliable, however, it is necessary to understand the model's predictive performance across different clinical settings, populations, and subgroups of interest. The robustness and generalizability of a developed model should be verified in one or more external validation studies by comparing the simulation outcomes against observed clinical data from other patient registries, clinical trials, or literature external to those used for model development.[1] In external validation, a model is used to simulate a real scenario, such as a clinical trial, and the predicted outcomes are compared with the real-world outcomes. A key to developing confidence in a model is to perform multiple validations on model components, such as population creation, disease incidence/progression, and occurrence of clinical outcomes.

One therapeutic area which benefits from disease simulation is Alzheimer's disease (AD), in which the vast majority of clinical trials in recent years have been unsuccessful. The clinical and economic value of potential therapies in development can be evaluated using disease simulation; from interventions targeted to attack AD earlier in its progression (during prodromal stage) through the most severe stages of AD.

In this article, we describe two external validation tests of the Alzheimer's Disease Archimedes Condition Event (AD ACE) simulator as an example; the first against the National Alzheimer's Coordinating Center (NACC) dataset, and the second compared to results of the BAN2401-G000-201 trial (Study 201), a recent clinical trial to evaluate safety,


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tolerability, and efficacy of an amyloid-targeted treatment (BAN2401) in subjects with early AD. The two selected sources were independent from the sources used to build the AD ACE simulator.

Disease Simulation with the AD ACE

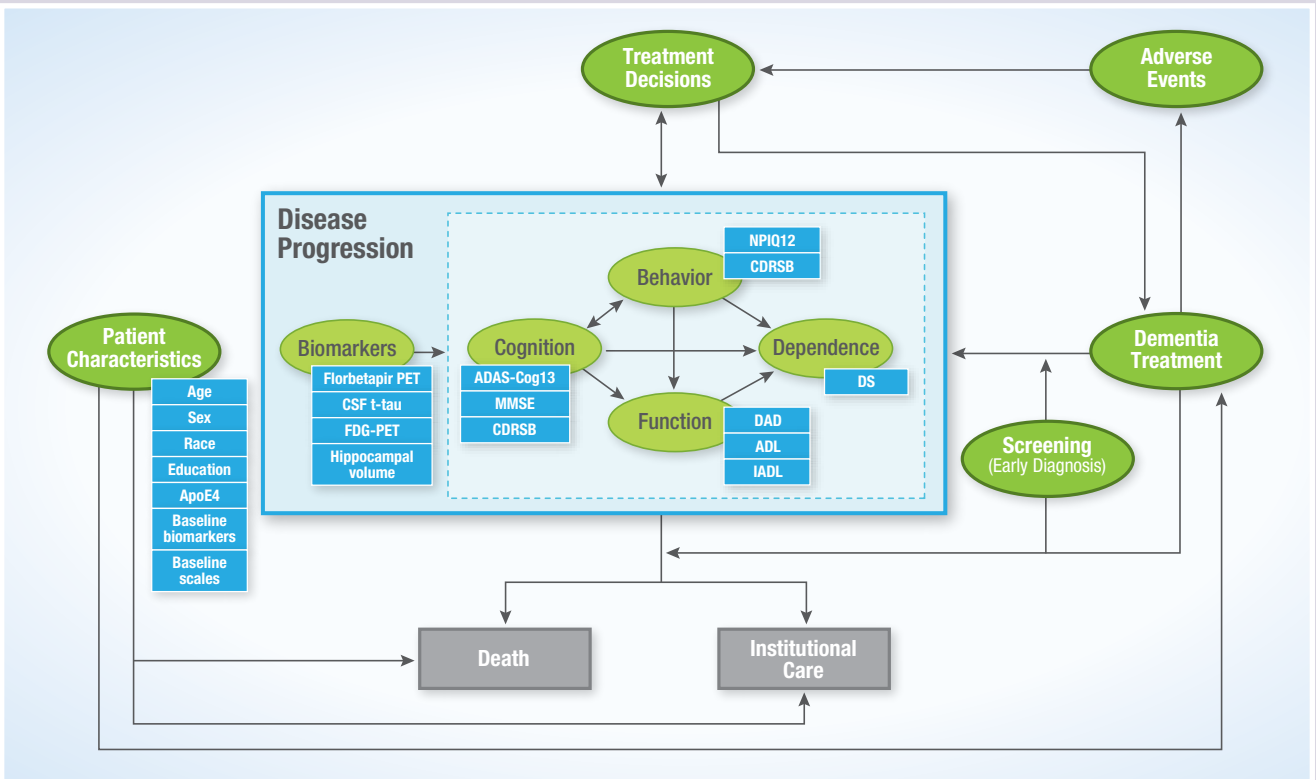
The AD ACE is a discretely integrated, condition event (DICE) simulation of AD.[2] The simulator incorporates measures of the underlying pathophysiology of AD, including measures of amyloid PET (AV45) and tau (CSF t-tau) levels and their connections to clinical presentation of AD, including cognition and behavioral scales (Figure 1). The relationship between changes in these measures over time are quantified using predictive equations derived from long-term observational data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to predict natural history of individuals with normal cognition through to severe AD.[3] The AD ACE can evaluate the impact of disease-modifying treatments (DMTs) and symptomatic treatments on both the clinical and economic consequences of AD. It simulates at the level of individual patient profiles, including explicit quantification of intra- and inter-patient heterogeneity.

External Validation Against NACC Dataset

The National Alzheimer's Coordinating Center (NACC) maintains a database of participant information collected from the 29 Alzheimer's disease centers funded by the National Institute on Aging (NIA). It is unique in the United States (U.S.) for its size and capacity to support collaborative research in AD. The standardized Uniform Data Set (UDS), which collects prospective and longitudinal clinical data, includes over 38,000 subjects as of June 2018. The UDS provides a standard set of measures collected longitudinally to characterize participants with mild AD and mild cognitive impairment (MCI) in comparison with non-demented controls.

Simulated measures of cognition (i.e., CDRSB and MMSE) from the AD ACE were compared to observed mean trajectories from NACC in three subgroups: 1) normal cognition or subjective memory complaint (CN-SMC), 2) MCI, and 3) mild AD. The NACC subgroups were defined based on reported baseline cognition level and observed trajectories were computed for each subgroup based on all NACC patients with at least three visits (including baseline visit). A total of 385 patients were identified in NACC for inclusion in the external validation (40 CN-SMC, 125 MCI, 220 mild AD). Population average trajectories were computed for each subgroup independently, adjusting each visit timing to the nearest six-month timepoint. No imputation was performed for missing data, so the population average trajectories included different sets of patients at each time point.

Figure 1. AD ACE Model Diagram

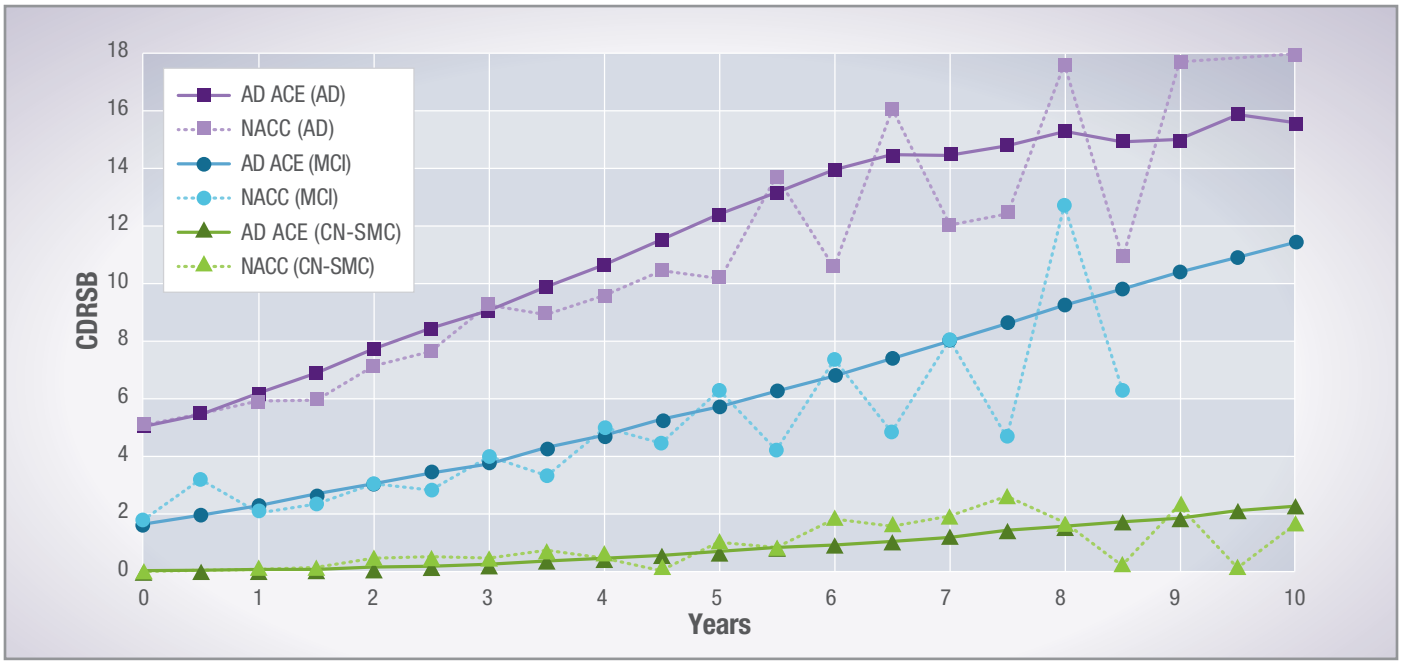


ADAS-Cog13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; **ADL** = Activities of Daily Living; **APOE4** = Apolipoprotein E4; **CDRSB** = Clinical Dementia Rating Sum of Boxes; **CSF t-tau** = Cerebrospinal Fluid Total-tau; **DAD** = Disability Assessment Scale for Dementia; **DS** = Dependence Scale; **FDG-PET** = Fluorodeoxyglucose–Positron Emission Tomography; **Florbetapir PET** = Florbetapir Positron Emission Tomography; **IADL** = Instrumental Activities of Daily Living; **MMSE** = Mini-Mental State Examination; **NPI-Q12** = Neuropsychiatric Inventory Questionnaire 12

Individual baseline ADNI patient profiles (1,735 total) were then filtered in the AD ACE based on the range of cognition scores observed in the NACC for each subgroup. The filtered subgroups in the AD ACE were well-matched with the NACC subgroups in terms of mean age and cognitive levels (CDRSB and MMSE) at baseline (Year 0 in Figures 2 and 3). The simulations sampled 500 patients from each subgroup in the AD ACE and simulated each patient over a 10-year time horizon outputting all measures of disease progression each six months. No modifications or fitting was performed in the disease simulation for these analyses.

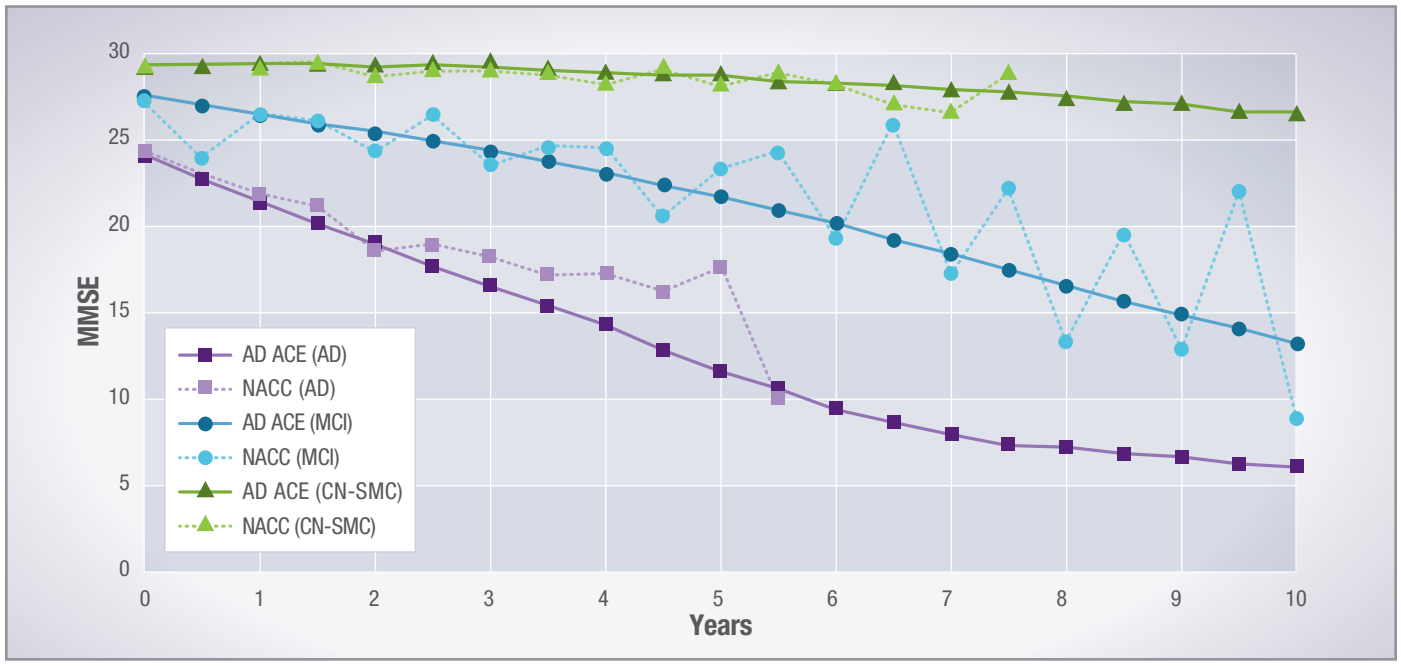
The simulated trajectories for CDRSB and MMSE agree well with the mean trajectories from NACC in all subgroups (Figures 2 and 3). The observed NACC trajectories show greater variance at late times as patient counts decrease

Figure 2. Mean CDRSB Trajectories for NACC vs. AD ACE for Different AD Disease Severity Levels



CN = Cognitively Normal; SMC = Significant Memory Concern; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MMSE = Mini-Mental State Examination; CDRSB = Clinical Dementia Rating Scale-Sum of Boxes; NACC = National Alzheimer's Coordinating Center; AD ACE = Alzheimer's Disease Archimedes Condition Event

Figure 3. Mean MMSE Trajectories for NACC vs. AD ACE for Different AD Disease Severity Levels



CN = Cognitively Normal; SMC = Significant Memory Concern; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MMSE = Mini-Mental State Examination; CDRSB = Clinical Dementia Rating Scale-Sum of Boxes; NACC = National Alzheimer's Coordinating Center; AD ACE = Alzheimer's Disease Archimedes Condition Event

and the population of patients at each time point becomes less consistent.

External Validation Against BAN2401-G000-201 Trial (Study 201) Results

Eisai and Biogen recently announced positive topline results from the Phase II study with BAN2401, an anti-amyloid antibody, in 856 patients with early AD.[4] The BAN2401 study 201 achieved statistical significance on key endpoints evaluating efficacy after 18 months of treatment in patients receiving the highest treatment dose (10 mg/kg biweekly) as compared to placebo on reduction of amyloid PET (positron emission tomography) standardized uptake value ratio (SUVR) accumulated in the brain (-0.30 adjusted mean change from baseline) and on slowing progression in key cognition scales (ADCOMS 30%, CDRSB 26%, ADAS-cog13 47%). Dose-dependent changes from baseline were observed across the PET results and the clinical endpoints.

To initiate the external validation of AD ACE against the reported BAN2401 study 201 results, a set of 610 ADNI patient profiles were initially selected in the AD ACE

Figure 4. Mean Change from Baseline in CDRSB for Different Placebo Populations

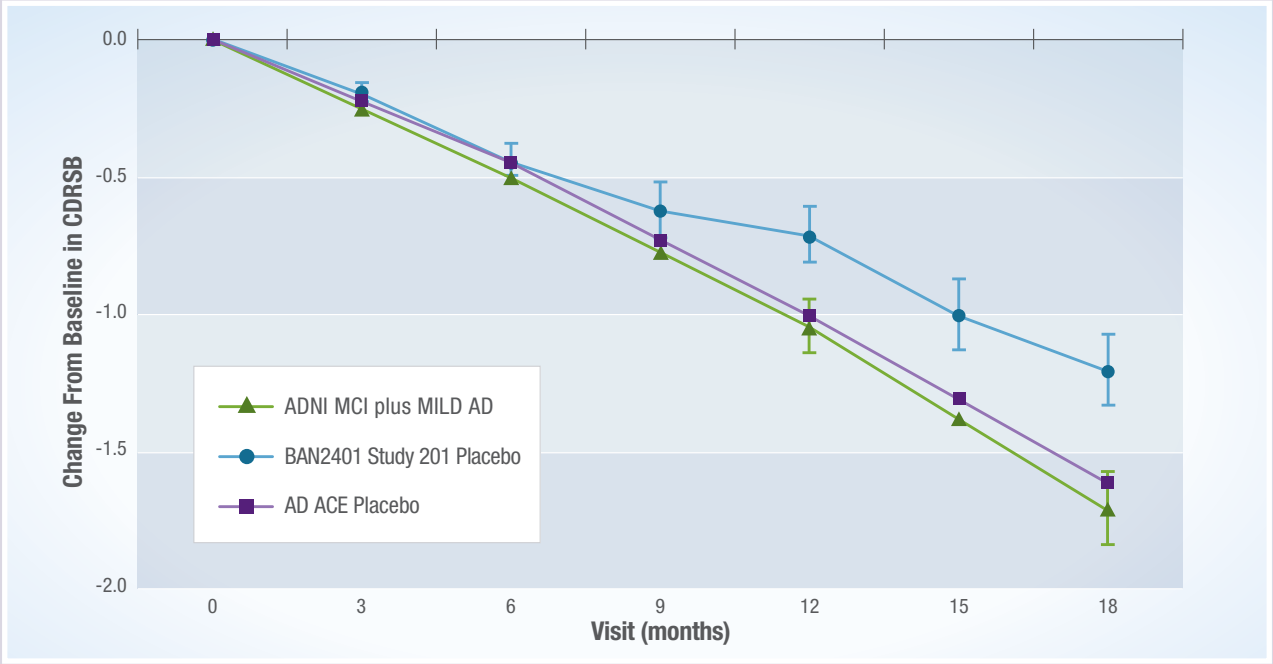
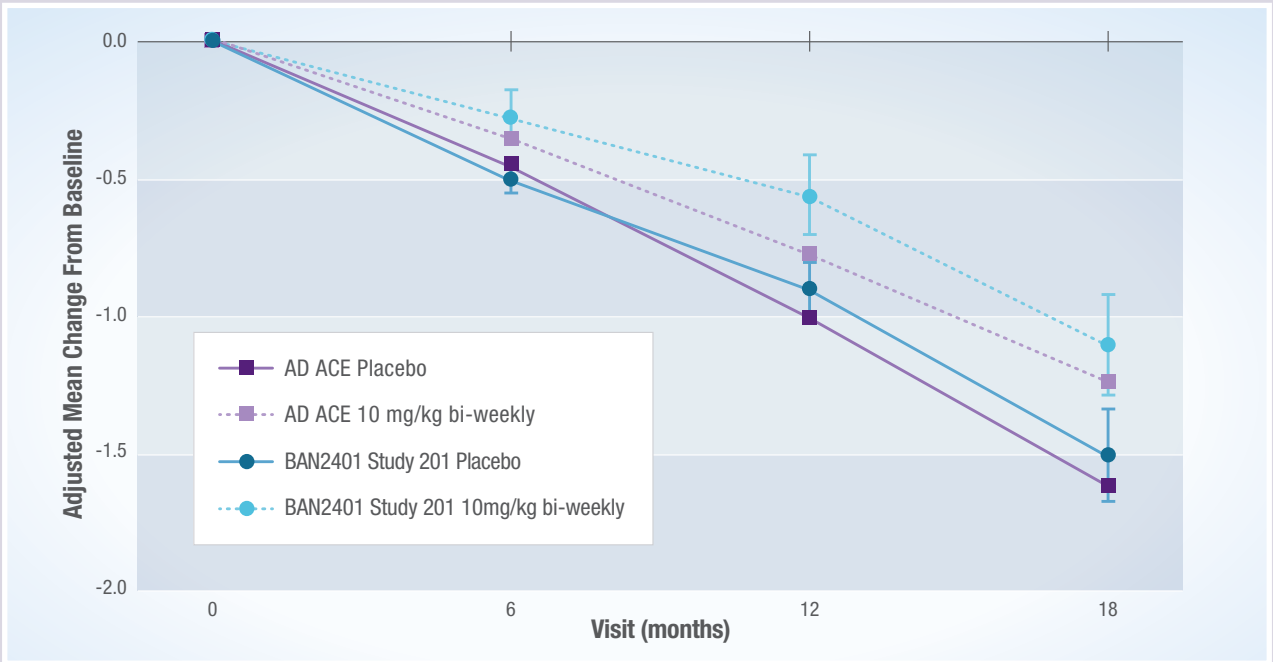


Figure 5. Adjusted Mean Change from Baseline in CDRSB for BAN2401 Study 201 vs. AD ACE



based on reported inclusion criteria in the BAN2401 study 201. Mean demographic and baseline characteristics in the filtered AD ACE profile were closely aligned with the placebo and BAN2401 arms of the trial as shown in Table 1. Next, we sampled 1,000 patients from the filtered ADNI profile and simulated each patient with and without treatment over 18 months and reported all measures of disease progression each six months. In the treatment arm, the baseline amyloid PET SUVR was adjusted by -0.30 after treatment initiation to mimic the 10 mg/kg bi-weekly regimen in the trial. No modifications or fitting was performed in the disease simulation for these analyses.

For the placebo arm, the AD ACE predicted a change of 1.61 points in CDRSB after 18 months (see Figure 4), which is consistent with the rate of progression reported for the placebo arm of BAN2401 Study 201 (1.2±0.1) and within the confidence bounds of what was reported for the ADNI MCI plus mild AD placebo population (1.7±0.1). For the treatment arm, the cognitive decline in CDRSB over 18 months was slowed by 23% in AD ACE compared to the 26% reported in the trial results (see Figure 5). The AD ACE also predicted a slowdown in cognitive decline on ADAS-cog13 consistent with, but lower, than what was reported in the trial results (30% vs 47%).

Discussion

Disease simulation can provide valuable insights during drug development in AD. For a simulation to inform decision-making, however, potential users need to know whether a model is reliable or generalizable to the setting and population of interest. External validation is essential in ensuring confidence in the simulator, and consequent results, being used for decision making.

In this article we presented the results of two external validations of the AD ACE – against a well-known AD dataset and a recent clinical trial. The results of the external validations indicated that AD ACE could closely match cognitive declines observed in both the NACC dataset and BAN2401 study 201. Specifically, the NACC validation showed generalizability of AD ACE to different populations by comparing model results with real-world results, while the BAN2401 study 201 validation demonstrated predictive validity of AD ACE by comparing model results with observed outcomes in a recent trial.

Table 1. Baseline Characteristics of Individuals in BAN2401 Study 201 (Placebo and BAN2401 arms) vs. AD ACE (Mean ± Standard Deviation)

	Placebo (N=238)	BAN2401 (N=587)	AD ACE (N=610)
ADAS-cog13	22.6±7.7	22.2±7.4	22.96±7.66
CDRSB	2.89±1.45	2.95±1.37	2.63±1.64
MMSE	26.0±2.3	25.6±2.4	25.95±2.16
PET SUVR	1.40±0.16	1.41±0.16	1.37±0.14
Age	71.1	71.4	74.1±7.2
Age Range	50 - 89	50 - 90	54 - 90
% Male	42%	54%	57%
% MCI	65%	64%	64%
% APOE4 +	71%	72%	73%
CDR Global = 0.5	84%	86%	89%

ADAS-cog13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; **CDRSB** = Clinical Dementia Rating Scale-Sum of Boxes; **MMSE** = Mini-Mental State Examination; **PET SUVR** = Positron Emission Tomography Standardized Uptake Value Ratio; **MCI** = Mild Cognitive Impairment; **APOE4** = Apolipoprotein E4

These results help provide context for appropriate applications of the AD ACE, but in a broader sense, they support the strength of using disease simulation to help make impactful decisions during the drug development process. While simulation is not always the answer, results like what we see from the external validation of the AD ACE clearly show that it can definitely be part of the equation for key stakeholders when evaluating the future of life changing medical treatments. ■

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