Enrichment of clinical trials in MCI due to AD using markers of amyloid and neurodegeneration

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ABSTRACT

Objective: To investigate the effect of enriching mild cognitive impairment (MCI) clinical trials using combined markers of amyloid pathology and neurodegeneration.

Methods: We evaluate an implementation of the recent National Institute for Aging–Alzheimer's Association (NIA-AA) diagnostic criteria for MCI due to Alzheimer disease (AD) as inclusion criteria in clinical trials and assess the effect of enrichment with amyloid (A+), neurodegeneration (N+), and their combination (A+N+) on the rate of clinical progression, required sample sizes, and estimates of trial time and cost.

Results: Enrichment based on an individual marker (A+ or N+) substantially improves all assessed trial characteristics. Combined enrichment (A+N+) further improves these results with a reduction in required sample sizes by 45% to 60%, depending on the endpoint.

Conclusions: Operationalizing the NIA-AA diagnostic criteria for clinical trial screening has the potential to substantially improve the statistical power of trials in MCI due to AD by identifying a more rapidly progressing patient population. *Neurology*® 2016;87:1235–1241

GLOSSARY

A+ = amyloid positive; **Aβ** = β-amyloid; **AD** = Alzheimer disease; **ADAS-Cog$_{13}$** = Alzheimer's Disease Assessment Scale Cognitive Subscale; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **FAQ** = Functional Assessment Questionnaire; **HV** = hippocampal volume; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **N+** = neurodegeneration positive; **NIA-AA** = National Institute for Aging–Alzheimer's Association; **RAVLT** = Rey Auditory Verbal Learning Test; **SNR** = signal-to-noise ratio.

Anatomic and pathophysiologic changes in Alzheimer disease (AD) begin years before the emergence of clinical dementia.[1–3] Recent revisions to AD diagnostic criteria have included explicit references to biomarkers for differential diagnosis in the study of subjects for clinical research in both AD and presymptomatic stages.[4–9] In particular, the National Institute for Aging–Alzheimer's Association (NIA-AA) criteria propose positivity on both amyloid and neurodegeneration biomarkers (A+ and N+, respectively).[6,10]

Recent negative phase III clinical trials of antiamyloid therapies did not consider biomarkers for inclusion and recruited a significant portion of amyloid-negative subjects who did not progress substantially on primary endpoints.[11–14] More recent phase II/III trials in prodromal or mild AD implemented enrichment strategies based on amyloid markers.[15,16]

The value of MRI measures of neurodegeneration for trial enrichment has been shown both in isolation and in combination with other measurements,[17–25] has been endorsed by regulatory agencies,[26] and more recently has been emphasized by a post hoc analysis of the failed (A+) Gantenerumab SCarlet RoAD study, showing a treatment effect in a multibiomarker-enriched subpopulation.[15,27]

This article presents an operationalization of the NIA-AA guidelines for mild cognitive impairment (MCI) due to AD[4,6] for enriching clinical trials with the concept of a dual (A+N+)

Supplemental data at Neurology.org

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biomarker strategy.[10,28] Applying established cut points[19,29,30] to define biomarker-positive subpopulations, this study compares the performance of combining both biomarkers (A+N+) compared to screening based on either alone and the resulting improvements in sample size and screen fail fraction and presents total trial time and cost.

METHODS

Study population. The present study was performed on 274 participants with MCI and 444 healthy controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.usc.edu/ADNI).[31]

For the MCI cohort, we selected all participants with amnestic MCI (labeled MCI in ADNI-1 and L-MCI in ADNI-2) who met the following inclusion criteria: 1.5T (ADNI-1) or 3T (ADNI-2) MRI scan available at baseline, baseline assessment of amyloid status (from CSF or AV-45 amyloid PET) available, and clinical scores (Mini-Mental State Examination [MMSE], 13-point Alzheimer's Disease Assessment Scale Cognitive Subscale [ADAS-Cog_{13}]) available at baseline and at month 24.

For the healthy control cohort, used as a normative reference population to define a hippocampal volume (HV) cut point, all participants who had an MRI available at baseline from both ADNI-1 and ADNI-2 were used. We have previously demonstrated minimal differences in HVs calculated from 1.5T and 3T scans on the same participants.[32]

An overview of the included participants, together with key characteristics, is presented in table 1. A more detailed description of ADNI and its study design and the image acquisition parameters are given in appendix e-1 at Neurology.org.

Biomarker measures. Amyloid deposition measured through PET imaging and CSF analyses of β-amyloid (Aβ) levels has been shown to be highly concordant and to show a similar diagnostic accuracy.[33] Consequently, the selection of either marker is driven mainly by geographic availability and cost, as well as patient and doctor preferences.[33] For the purpose of identifying participants as amyloid positive or negative, we used CSF Aβ42 for participants from ADNI-1 and florbetapir-PET for participants from ADNI-2; cut points derived from both biomarkers have been shown to perform consistently.[30,33] Specifically, ADNI-1 participants were considered A+ with Aβ42 levels ≤192 pg/mL, while ADNI-2 participants were considered A+ with a florbetapir-PET standardized uptake value ratio >1.11 for the mean of 6 predefined regions of interest relative to the whole cerebellum. Appendix e-2 presents results from the ADNI-2 cohort on the concordance between amyloid positivity from the 2 biomarkers and its impact on patient selection. However, our cost estimates are based on the assumption that PET imaging is used to determine amyloid positivity for our simulated clinical trial scenarios.

HV was calculated with the learning embeddings for atlas propagation (LEAP) algorithm[34] incorporated into the CE-marked medical device Assessa (www.assessa.com). HV was adjusted for age and head size as measured by intracranial volume, and left and right hippocampi were averaged for each subject (details are presented in appendix e-3). After a detailed validation of HV cut points,[19] participants were considered N+ if their adjusted HV was smaller than the 25th percentile of the age-matched healthy subject cohort.

Combinatorial enrichment strategies. We examined the following enrichment strategies: NIA-AA I (A+), enrichment by abnormal amyloid alone (neurodegeneration status undetermined); NIA-AA II (N+), enrichment by low HV alone (amyloid status undetermined); and NIA-AA III (A+N+), enrichment by both

Table 1 Subject characteristics

	ADNI-1 MCI	ADNI-2 MCI	Combined MCI
Female, n (%)	152 (34)	122 (48)	274 (41)
Age, y	74.7 ± 7.5	71.4 ± 8.0	73.2 ± 7.9
A+, %	76 (CSF)	72 (CSF),[a] 68 (PET)[a]	74 (all CSF),[a] 72 (CSF/PET)[a]
ApoE ε4 carriers, %	53	55	54
MMSE BL/M24	26.9 ± 1.8/25.3 ± 3.9	27.7 ± 1.8/25.7 ± 3.4	27.3 ± 1.9/25.5 ± 3.7
CDR-SOB BL/M24	1.51 ± 0.84/2.98 ± 2.13	1.74 ± 1.02/2.77 ± 2.21	1.61 ± 0.93/2.89 ± 2.16
ADAS-Cog_{13} BL/M24	18.0 ± 6.8/22.4 ± 9.7	18.7 ± 6.8/21.8 ± 10.7	18.3 ± 6.8/22.1 ± 10.2
HV	1,632 ± 301	1,730 ± 326	1,675 ± 314
	ADNI-1 CN	ADNI-2 CN	Combined CN
Female, n (%)	222 (48)	222 (53)	444 (50)
Age, y	76.3 ± 5.1	72.8 ± 6.0	74.5 ± 5.8
MMSE BL	29.1 ± 1.0	29.0 ± 1.3	29.0 ± 1.2
CDR-SOB BL	0.00 ± 0.09	0.02 ± 0.13	0.01 ± 0.11
ADAS-Cog_{13} BL[b]	9.53 ± 4.16	8.87 ± 4.33	9.21 ± 4.25
HV	1,956 ± 254	1,953 ± 243	1,954 ± 246

Abbreviations: A+ = amyloid positive; ADAS-COG_{13} = Alzheimer's Disease Assessment Scale Cognitive Subscale; ADNI = Alzheimer's Disease Neuroimaging Initiative; BL = baseline; CDR-SOB = Clinical Dementia Rating-Sum of Boxes; CN = cognitively normal; HV = hippocampal volume; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; M24, month 24.
[a] Eight subjects are CSF+/PET−, and 4 are PET+/CSF−.
[b] ADAS-Cog measurement was available in only 219 and 208 CN participants in ADNI-1 and ADNI-2, respectively.

amyloid and HV. For comparison, the performance of the following 4 enrichment strategies is presented in appendix e-4: exploratory I, enrichment by ApoE ε4 status alone (ε4 carriers only included); exploratory II, enrichment based on a clinical functional deficit (Functional Assessment Questionnaire [FAQ] >0); exploratory III, enrichment based on a deficit in global cognition beyond that specified as part of the diagnostic criteria (ADAS-Cog_{13} >15); and exploratory IV, enrichment based on a more stringent definition of memory deficit (Rey Auditory Verbal Learning Test [RAVLT] <35).

Experiments. The effect of biomarker-based enrichment was assessed with respect to the 2-year change in widely used clinical scales of global cognition, MMSE and ADAS-Cog_{13}, in terms of 2 key trial characteristics: the rate and homogeneity of clinical progression in the included trial cohort and the additional screen failure fraction due to the biomarker selection criteria. As a joint measurement of rate and homogeneity of clinical progression, we defined a signal-to-noise ratio (SNR) as the mean 2-year change on the clinical scale in the included group divided by the SD of the 2-year change. On the basis of representative values from multisite trial operations, we also estimated how the change and interplay of these key measurements influence required sample sizes, the number of participants who need to undergo screening to obtain the required sample size, and indicative overall trial duration and cost.[19] Calculations of the latter take into account the tradeoff between increased screen failures and the reduced number of participants needed to be randomized. Sample size calculations were performed for a 25% reduction in the worsening of either MMSE or ADAS-Cog_{13} at 80% power and 5% significance. Detailed models for sample size, number needed to screen, and trial time and cost are presented in appendix e-3. Although amyloid positivity is defined from CSF (ADNI-1 participants) and PET imaging (ADNI-2 participants) in this work, the use of PET imaging is assumed in the cost calculation.

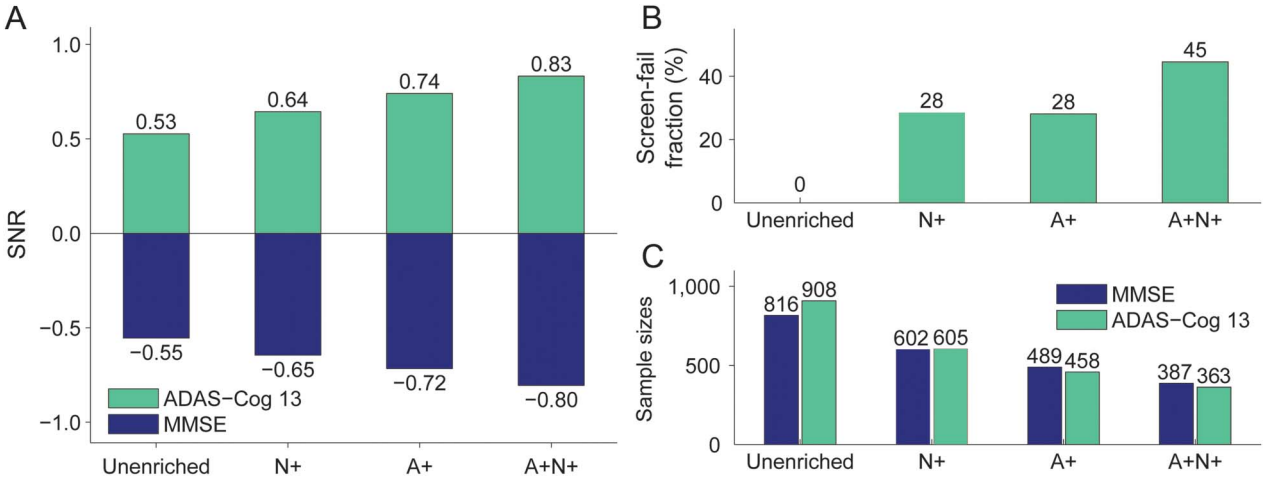
RESULTS All 3 NIA-AA–based enrichment strategies yielded increased 2-year SNRs for both MMSE and ADAS-Cog_{13} (figure 1A) compared to the unenriched population. Enrichment with HV (N+) showed the smallest improvement, followed by enrichment based on amyloid positivity (A+), whereas enrichment based on both biomarkers (A+N+) provided the overall best enrichment performance. SNR was increased by 18% (MMSE) and 25% (ADAS-Cog_{13}) by N+ enrichment, 31% and 38%, respectively, by A+ enrichment, and 45% and 57%, respectively, by A+N+ enrichment.

The biomarker screen fail fractions were 28% for enrichment by A+ or N+ alone and 45% for the combined A+N+ enrichment (figure 1B). However, the required sample size to enroll was substantially reduced, by 26% (MMSE) and 33% (ADAS-Cog_{13}) for N+ enrichment, by 40% and 50% for A+ enrichment, and by 53% and 60% for A+N+ enrichment (figure 1C). In terms of overall estimated trial duration and cost, all 3 enrichment strategies resulted in quicker, cheaper clinical trials (table 2). That is, the gain due to the reduced sample size more than compensated for the increased screen fail rate. Performing N+ enrichment before A+ enrichment leads to a further reduction in trial cost (table 2).

Two-year change on both clinical scales showed a nominally more rapid progression in the selected cohort relative to the unenriched cohort for all 3 enrichment methods, and this was statistically significant with the use of the A+ and A+N+ enrichment schemes for both scales ($p < 0.05$; figure 2). The excluded group showed substantially slower clinical progression rates for both scales using all 3 enrichment schemes ($p < 0.01$). When shorter 6-month and 12-month trials were simulated, SNR was increased for both measures by amounts similar to that found for the 24-month trial (appendix e-5).

Detailed results for the comparator enrichment strategies, based on ApoE ε4 genotype, cognition (ADAS-Cog_{13}), function (FAQ), and memory (RAVLT), are

Figure 1 Trial characteristics for different enrichment strategies



Signal-to-noise ratio (SNR; A), screen fail fraction (B), and required sample sizes (C) for trials using different enrichment strategies. A+ = amyloid positive; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale Cognitive Subscale; MMSE = Mini-Mental State Examination; N+ = neurodegeneration positive.

Table 2 Screen failure fraction (SFF), 2-year change on clinical outcome measures (mean ± SD), 2-year signal-to-noise ratio (SNR: mean/SD), number of participants who need to undergo screening (NNS), trial cost, and overall trial duration

	Unenriched		N+		A+		N+ then A+		A+ then N+	
	MMSE	ADAS-Cog_{13}	MMSE	ADAS-Cog_{13}	MMSE	ADAS-Cog_{13}	MMSE	ADAS-Cog_{13}	MMSE	ADAS-Cog_{13}
SFF, %	0		28		28		28–>45		28–>45	
2-y change	−1.77 ± 3.19	3.87 ± 7.35	−2.17 ± 3.37	5.00 ± 7.77	−2.40 ± 3.35	5.58 ± 7.54	−2.76 ± 3.43	6.49 ± 7.80	−2.76 ± 3.43	6.49 ± 7.80
SNR	−0.55	0.53	−0.65	0.64	−0.72	0.74	−0.80	0.83	−0.80	0.83
Sample size, n	816	908	602	605	489	458	387	363	387	363
NNS	2,332	2,593	2,404	2,415	1,945	1,819	1,994	1,867	1,994	1,867
Cost, $1,000,000	74	83	59	59	58	54	48	45	51	48
Time, y	4.9	5.2	5	5	4.4	4.3	4.5	4.3	4.5	4.3

Abbreviations: A+ = amyloid positive; ADAS-COG_{13} = Alzheimer's Disease Assessment Scale Cognitive Subscale; MMSE = Mini-Mental State Examination; N+ = neurodegeneration positive.

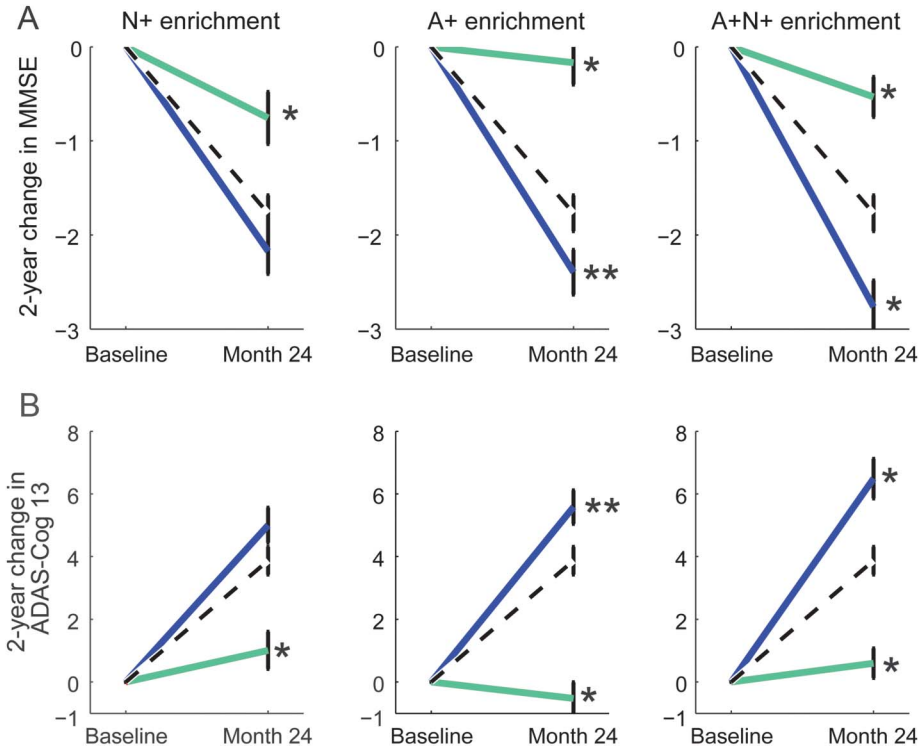
presented in appendix e-4. Briefly, enrolling ApoE ε4 carriers (a strong risk factor for amyloid positivity) yielded an improvement in SNR of 24% (MMSE) and 28% (ADAS-Cog_{13}) at a screen failure rate of 46%. Enriching with ADAS-Cog_{13} >15 improved the SNR by 40% on MMSE at the cost of an additional 31% screen failure rate, while FAQ-based enrichment gave an SNR increase of 40% (MMSE) and 20% (ADAS-Cog_{13}) with an associated screen failure rate of 30%. Enriching with RAVLT <35 gave an SNR increase of 23% (MMSE) and 36% (ADAS-Cog_{13}) at the cost of an additional 32% screen failure rate. A corresponding reduction in sample sizes was observed with all 4 of these alternative, non–biomarker-based enrichment strategies.

DISCUSSION These results demonstrate the effect of using the current NIA-AA research diagnostic criteria as an enrichment strategy for amnestic MCI clinical trials. Compared to previous work that looked at multibiomarker enrichment, we explicitly examined the effects of these diagnostic criteria using specific, established cut points on both measures. With a view to operationalizing these criteria, we also assessed their effect on trial design by exploring the changes in a set of practical trial characteristics, including time and cost, using parameters from recent trials. Although these input values may vary, our findings of a substantial relative improvement in trial parameters should be relatively robust to realistic differences in these inputs and the assumptions underlying our model.

The presented results show that enrichment with either biomarker individually (A+ or N+) increases the SNR of the change in clinical endpoint measures and reduces the required sample sizes and the projected trial cost. When combined enrichment (A+N+) is applied, the SNR values increase and the required sample sizes decrease relative to no enrichment by 45% to 60%, depending on the clinical endpoint. The mean 2-year change in ADAS-Cog_{13} in the enriched population was increased from 3.9 points (unenriched) to 5.0 to 6.5 points, and the mean decrease in MMSE increased from 1.8 points (unenriched) to 2.2 to 2.8 points. These results show that when a trial with fixed power is designed, biomarker enrichment does not increase the number of participants who need to be screened because the reduction in the required sample size outweighs the increased screen failure rate. Projected trial durations were overall predicted to be no longer than in the unenriched scenario. These results were robust to trial duration because simulations with shorter follow-up times resulted in very similar relative characteristics of the enriched population (appendix e-5).

Several recent trials have enrolled amyloid-positive participants only. Our results show that using HV-

Figure 2 Time course graphs for different enrichment strategies



Change in Mini-Mental State Examination (MMSE; A) and Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog 13; B) for the unenriched sample (dashed black line), enriched sample (solid blue line), and excluded sample (solid green line). Whiskers present SE. Significance of the difference between included and excluded groups and the unenriched sample is shown as $^{**}p < 0.05$ and $^{*}p < 0.01$. A+ = amyloid positive; N+ = neurodegeneration positive.

based enrichment in addition further reduces sample sizes by ≈20% and cost by ≈25% when the cheaper exclusion criterion (MRI) is administered first because PET imaging is then required in fewer participants. Because an MRI scan is typically acquired at screening for other reasons, the added operational complexity of automated and rapid computation of a HV estimate is minimal but can lead to significant savings in trial cost. Automatically derived HV provides robust enrichment with relatively little sensitivity to the cut point used.[19] To confirm this in the present study, we compared enrichment with a cut point at the 40th percentile (as an alternative to the 25th percentile used above) of HV in the healthy control population. Screen failure rate changes from 28% to 24%, yet the assessed trial characteristics change by <10% (details are given in appendix e-2). While HV is an important downstream biomarker of AD and therefore can help to identify patients close to accelerated clinical decline,[1] it is not directly linked to Aβ, one of the hallmarks in the amyloid cascade hypothesis of AD.[35] HV alone therefore cannot replace an amyloid marker to accurately select patients in amyloid targeting therapies but can complement it to help to identify subpopulations more likely to progress on primary trial endpoints. Even when not defining a specific exclusion criterion on HV, it can be a valuable stratification or subgrouping measure as shown by the recently presented post hoc analysis of the MCI Gantenerumab SCarlet RoAD study in which all the enrolled participants were amyloid positive but a significant treatment effect was observed only in the subgroup of participants predicted to progress more rapidly with a model that used HV and clinical scales.[15]

Our cost analysis assumed that PET imaging was used to determine amyloid status. Although some reports suggest that CSF levels of Aβ become abnormal earlier in the disease stage,[33] the results presented in appendix e-6 confirm previous publications that showed high concordance between amyloid markers from CSF and PET.[33,36] A recent systematic comparison of PET and CSF concludes that choices can be based on other factors such as availability, cost, and doctor/patient preferences because both have equally high diagnostic accuracy.[36] While a CSF analysis can potentially be incorporated more easily with other biomarkers, it is highly invasive and requires careful standardization; PET imaging, on the other hand, requires highly advanced instruments and is less available in clinical practice in some countries.[36]

In a separate analysis, this article shows how alternative enrichment strategies that avoid imaging measurements can also increase the longitudinal progression rate of a patient population thus selected. The proposed

models were applied to enrichment with ApoE e4 status and measures of global cognition and function that are widely used in clinical trials of mild AD and have furthermore been shown to perform well in the prodromal stage of the disease.[37] The results using ApoE e4 status and measurements of cognition, memory, and function (appendix e-4) show an enrichment performance similar to that obtained with the 2 imaging biomarkers and following the NIA-AA criteria.

A limitation of the presented work is its validation on the ADNI study alone. Even though inclusion and exclusion criteria in ADNI were defined to be comparable to those in clinical trials, it is unclear how well the recruited participants compare to a typical clinical trial population, let alone a real-world treatment population. However, preliminary results from current clinical studies using biomarker enrichment (e.g., aducanumab) and the post-hoc analysis of the SCarlet RoAD study discussed above provide additional evidence for the benefit that single-biomarker and multibiomarker enrichment strategies can have.

Integrating different biomarkers, clinical measurements, and patient attributes into integrated disease progression models represents a next step toward a more detailed understanding of disease progression and the efficient use of available measurements for trial inclusion, as well as the selection of suitable patients once treatment is available.

AUTHOR CONTRIBUTIONS

Robin Wolz: study concept and design, collation of data, analysis and interpretation of data. Adam J. Schwarz: study concept and design, interpretation of data, critical revision of manuscript for intellectual content. Katherine R. Gray: collation of data, analysis of data. Peng Yu: study concept and design, analysis and interpretation of data. Derek L.G. Hill: study concept and design, critical revision of manuscript for intellectual content, study supervision.

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DISCLOSURE

R. Wolz, K. Gray, and D. Hill are employees and shareholders of IXICO. A. Schwarz is an employee and shareholder of Eli Lilly. P. Yu is a former employee of Eli Lilly. Go to Neurology.org for full disclosures.

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