A Genetic Enrichment Strategy for Delay of Onset of Alzheimer's Disease Clinical Trials

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Introduction

- One challenge with clinical trials in Alzheimer's Disease (AD) prevention is the timely identification of individuals at near-term risk of cognitive symptom onset, mitigating the prohibitive costs associated with trial size and duration.
- A biomarker algorithm, consisting of genotypes at the apolipoprotein E (APOE) and translocase of outer mitochondrial membrane 40 homolog (TOMM40) rs10524523 ('523) loci and current age, was developed to enrich the TOMMORROW delay of AD-onset clinical study (NCT01931566).
- '523 is a homopolymer of 14–50 thymine (T) residues. For the biomarker algorithm, the '523 alleles were categorized by poly-T length as short (S; < 20 nucleotides), long (L; ≤ 20 to ≤ 29 nucleotides) or very long (VL; > 29 nucleotides).
- The biomarker algorithm is described in Crenshaw *et al.*,[1] and the TOMMORROW study design is described in Burns *et al.*[2] and Roses *et al.*[3] The TOMMORROW study was terminated at futility analysis and study findings are the subject of a manuscript in preparation. Statistical analysis of biomarker algorithm performance compared with biofluid and imaging biomarkers for the prediction of mild cognitive impairment (MCI) due to AD in a 5-year time frame is described in Lutz *et al.*[4]

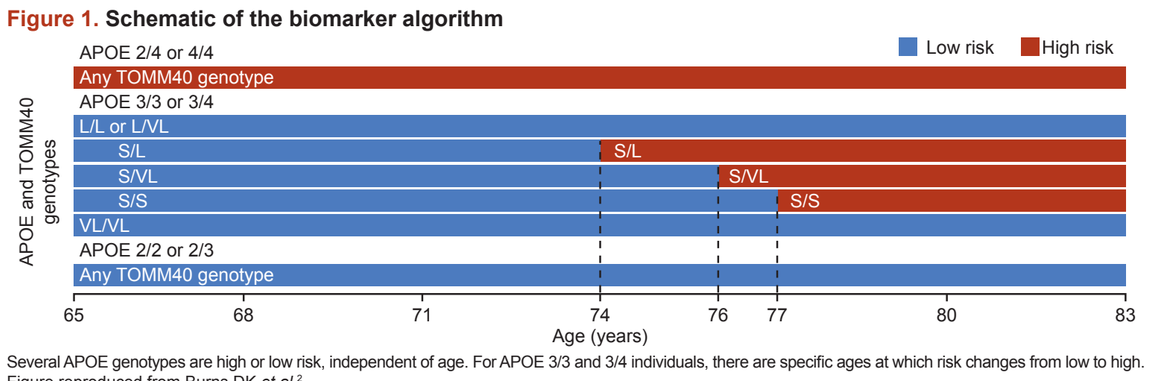
Objectives

- To assess performance of the biomarker algorithm for AD-prevention clinical trial enrichment using data from TOMMORROW.
- To recalibrate the categories for the '523 genotype using the large screening population from TOMMORROW and to reassess biomarker algorithm performance.
- To develop simulation models for utility of the clinical trials incorporating the biomarker algorithm for specific conditions, such as prevalence, event rates (MCI due to AD) and trial length.
- To evaluate the performance of a commercial kit-based assay for the biomarker-algorithm genotypes.

Methods

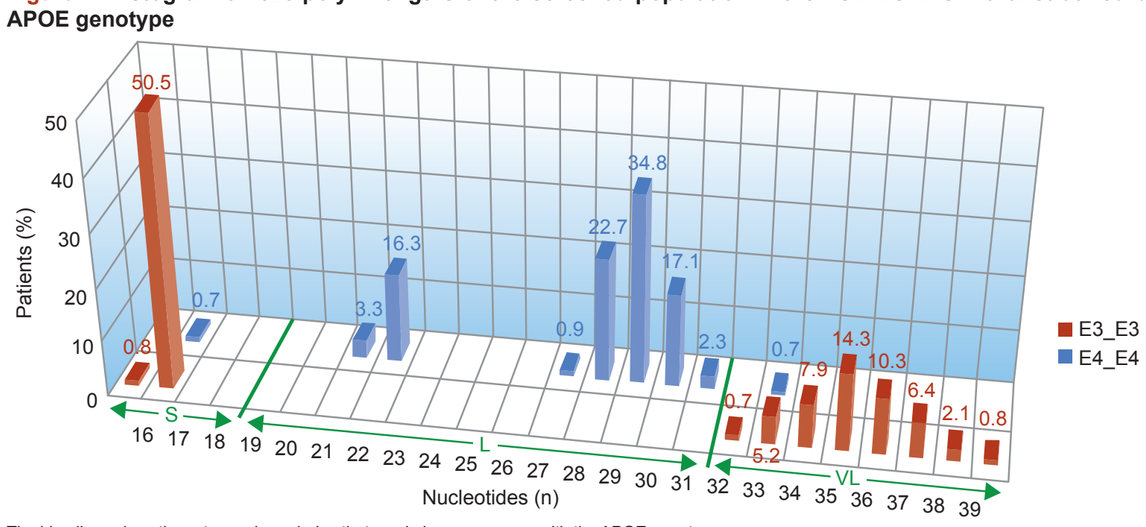
- The TOMMORROW study provided a large data set to assess APOE-'523 haplotypes. The original biomarker algorithm used phased genetic information from 150 individuals to map specific '523 T lengths to the three defined categories (S, L and VL). Because phased haplotype data were not available from the samples genotyped in the TOMMORROW study, an optimized calibration of the categories for poly-T length was performed using APOE 3/3 and 4/4 homozygous individuals (n = 1625). By maximizing the genetic congruency between the APOE and '523 genotypes, based on the strong linkage disequilibrium of these variants, the calibration of the categorical boundaries was optimized.
  - The distribution of T lengths around each of the three categories was determined, and 2% of the cumulative distribution from the tails was removed to set the T length thresholds.
  - The recalibrated mapping based on the TOMMORROW data set was: S, < 19 nucleotides; L, ≤ 19 to ≤ 31 nucleotides; and VL, > 31 nucleotides.
- The study cohort for the assessment of biomarker algorithm performance consisted of 1803 individuals, including 50 with adjudicated MCI due to AD diagnoses.
- The performance (hazard ratio [HR], sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) of the biomarker algorithm using the optimized '523 categories was compared with the original trial results for TOMMORROW. Likelihood ratios (LR) are reported, weighted by prevalence for positive prediction (+) and negative prediction (–). Receiver operating characteristics (ROC) curves were calculated for combinations of the three components of the biomarker algorithm.
- The data generated from the TOMMORROW study were used to develop a simulation model to evaluate the clinical utility of the biomarker algorithm for AD-prevention trial design. To enable accurate prediction of event rates at various time points of the study, a locally estimated scatterplot smoothing model was fit through observed event rates in the TOMMORROW study and used to predict event rates at 36, 48 and 60 months. The predicted event rates, as well as the prevalence of the biomarker algorithm high-risk group, were then used to determine the number of individuals that needed to be enrolled or screened, respectively, to achieve 1 or 300 event(s) within 5 years.
- The AmplideX PCR/CE TOMM40 kit (Asuragen, USA) and prototype APOE PCR/CE reagents (Asuragen, USA) were used to compare TOMM40 and APOE genotype assays with the results obtained using a clinical trial assay (CTA). For the congruency evaluation, 60 DNA samples representing all six APOE genotypes and 25 different TOMM40 '523 T lengths (16–42 nucleotides) were analyzed.

Figure 1. Schematic of the biomarker algorithm



Several APOE genotypes are high or low risk, independent of age. For APOE 3/3 and 3/4 individuals, there are specific ages at which risk changes from low to high. Figure reproduced from Burns DK *et al.*[2]
APOE, apolipoprotein E; L, long; S, short; TOMM40, translocase of outer mitochondrial membrane 40 homolog; VL, very long.

Figure 2. Histogram of '523 poly-T lengths of the screened population in the TOMMORROW trial stratified by APOE genotype



The blue lines show the category boundaries that maximize congruency with the APOE genotype.
'523, rs10524523; APOE, apolipoprotein E; L, long; S, short; T, thymine; VL, very long.

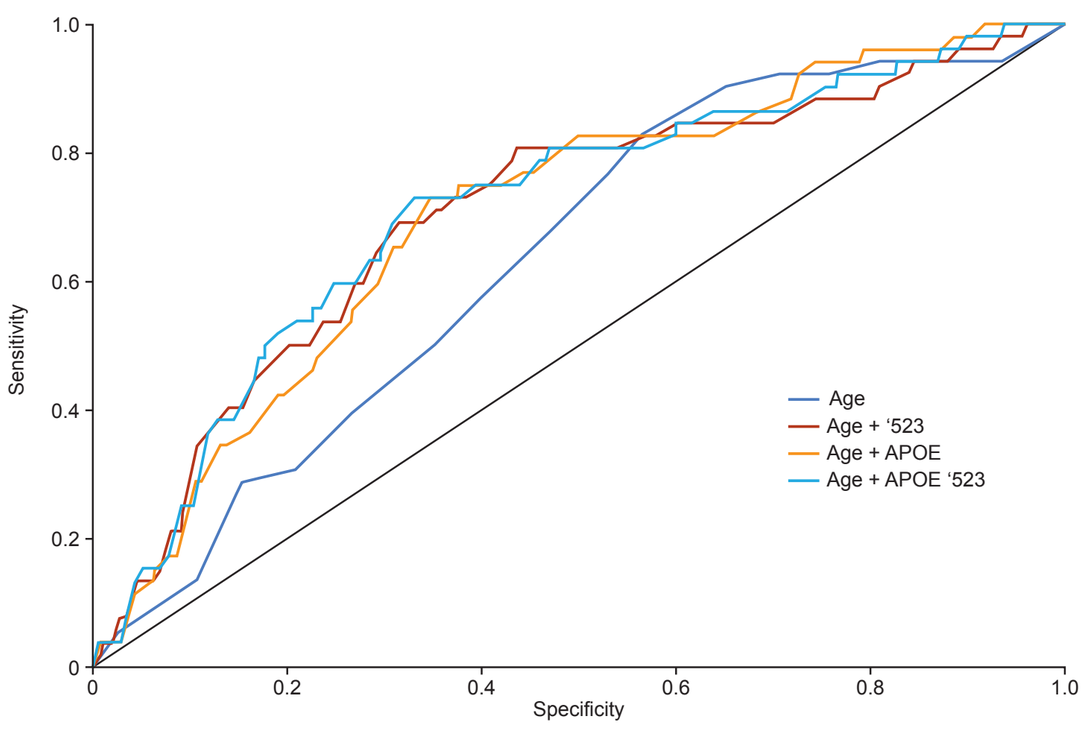
Table 1. Performance of the biomarker algorithm for the prediction of conversion to MCI based on TOMMORROW data, for the original version and for the version with recalibrated '523 categorical genotypes

Statistic	Original	Recalibrated
High risk/low risk, HR (95% CI), *p*	3.3 (1.2–9.0), 0.023	**4.3 (1.3–13.7), 0.015**
PPV	3 (2–4)	**3 (2–4)**
NPV	99 (97–99)	**99 (97–99)**
Prevalence	0.03 (0.02–0.04)	**0.03 (0.02–0.04)**
Sensitivity	0.90 (0.78–0.96)	**0.94 (0.82–0.98)**
Specificity	0.23 (0.21–0.24)	**0.21 (0.20–0.24)**
LR[a] (+)	0.03 (0.02–0.04)	**0.03 (0.03–0.05)**
LR[a] (–)	0.01 (0.01–0.03)	**0.01 (0.01–0.02)**

[a]Weighted by prevalence.
'523, rs10524523; CI, confidence interval; HR, hazard ratio; LR, likelihood ratio; MCI, mild cognitive impairment; NPV, negative predictive value; PPV, positive predictive value.

Results

Figure 3. ROC curves for components of the biomarker algorithm using the recalibrated '523 categorical genotypes



Curves are derived from models that include combinations of age, APOE and '523 genotype, and are fit to the TOMMORROW trial data for conversion to MCI due to AD. '523, rs10524523; AD, Alzheimer's disease; APOE, apolipoprotein E; MCI, mild cognitive impairment; ROC, receiver operating characteristic.

Table 2. Utility of the biomarker algorithm for clinical trial enrichment

Description	Prevalence,[a,b] %	Trial length, months	Predicted event rate,[b] %	Cohort size required to enroll converters, n		Screen for 300 converters	Enrollment improvement,[c] %
				1 converter	300 converters		
All[d]	100	36	3.31	31	9300	9300	
Recalibrated biomarker	30	36	3.93	26	7800	25 500	16.1%
All[d]	100	48	4.10	25	7500	7500	
Recalibrated biomarker	30	48	4.97	21	6300	20 400	16.0%
All[d]	100	60	4.51	23	6900	6900	
Recalibrated biomarker	30	60	5.87	18	5400	17 100	21.7%

The recalibrated biomarker algorithm is based on the optimized '523 categorical genotypes.
[a]For the high-risk group (age 65–83 years). [b]Estimated from the TOMMORROW trial data. Individuals who transition from normal cognition to MCI due to AD are termed converters. [c]Represents the reduction in the enrolled population needed to achieve 300 converters. [d]General population without enrichment.
'523, rs10524523; AD, Alzheimer's disease; MCI, mild cognitive impairment.

Table 3. Comparison of the APOE and '523 genotyping assays with the TOMMORROW CTA

Measure	Concordance[a]	Percentage, %
APOE genotype	60/60	100
TOMM40 '523 T length	57/60	95
TOMM40 '523 categorical genotype	58/60	97
Biomarker algorithm[b]	60/60	100

[a]Agreement on the genotype call ('523 T length or categorical call, APOE genotype). [b]High-risk or low-risk classification based on genotype and age.
'523, rs10524523; APOE, apolipoprotein E; CTA, clinical trial assay; T, thymine; TOMM40, translocase of outer mitochondrial membrane 40 homolog.

Summary of findings

- **Using phase 3 clinical trial data, the TOMMORROW biomarker algorithm demonstrated the ability to enrich delay of onset of AD studies with individuals who are more likely to develop MCI during an acceptable timeframe, with the potential for significant cost savings resulting from a smaller study size (Tables 1, 2).**
- **The original mapping of '523 T lengths to categories was: S, < 20 nucleotides; L, ≤ 20 to ≤ 29 nucleotides; and VL, > 29 nucleotides. The recalibrated mapping based on the TOMMORROW dataset was: S, < 19 nucleotides; L, ≤ 19 to ≤ 31 nucleotides; and VL, > 31 nucleotides (Figure 2).**
- **The HR for the time-to-event comparison between the high-risk and low-risk placebo groups improved from 3.3 (95% confidence interval [CI]: 1.2–9.0, *p* = 0.023) to 4.3 (95% CI: 1.3–13.7, *p* = 0.015), using the recalibrated '523 categorical genotype calls (Table 1).**
- **The NPV for the algorithm is strong (99%), while the small number of conversion events relative to the high-risk group size during the study greatly reduces the PPV (3%) (Table 1).**
- **Age, a well-established risk factor for AD, is an important component of the biomarker algorithm (Figures 1, 3).**
- **Applying the recalibrated biomarker algorithm to a future delay of AD onset clinical trial would reduce high-risk enrollment by 22% for a 5-year interventional study versus an all-comers enrollment strategy (Table 2).**
- **In a congruency study, strong concordance was observed between the Asuragen genotyping assays for APOE and TOMM40 '523 and the clinical trial assays used in the TOMMORROW study (Table 3).**
- **This study provides an evaluation of the biomarker algorithm used prospectively for an AD prevention clinical trial. Differences in population characteristics for the study cohort compared with the memory-clinic cohorts used to develop the biomarker algorithm are apparent and important to investigate. Early termination of the TOMMORROW trial had an impact on the evaluation of biomarker performance.**

References

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Disclosures

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