Predicting amyloid burden at screen in Anti-Amyloid Treatment in Asymptomatic AD (A4) study participants

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Disclosures

- Consultant to Neurotrack & Kyowa Kirin
- Spouse is fulltime employee of Janssen

Background

- Screening for asymptomatic AD is expensive and slow
- For A4, 4,486 individuals received amyloid PET scans in order to identify 1,323 Aβ+ individuals for an **amyloid PET screen fail rate of 71%**
- Number Needed to Screen (NNS) was 3.39 individuals per Aβ+ individual
- Can we use less expensive measures to identify a population at increased risk for asymptomatic AD to make screening for asymptomatic AD more efficient?
- We explore possible approaches using machine learning (Random Forests*) applied to the A4 screening data

*Leo Breiman (2001). Random Forests. *Machine Learning*, 45(1), 5-32.

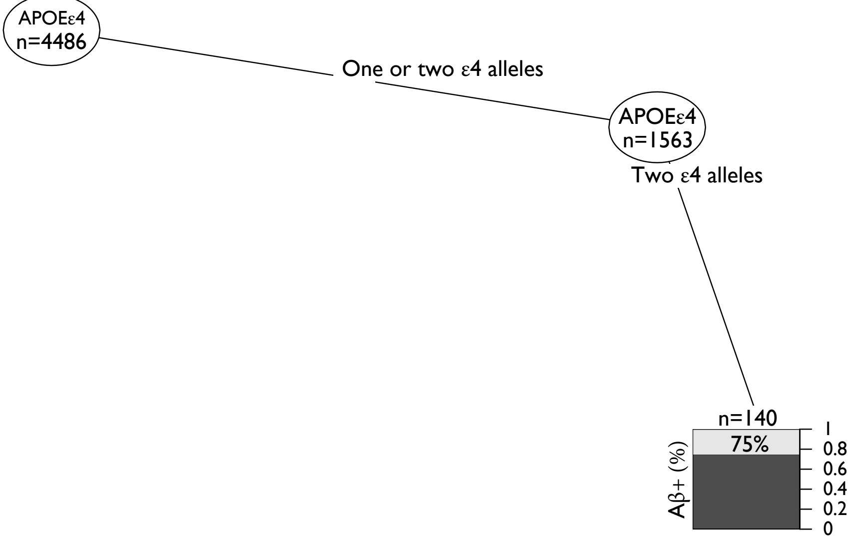
Predictors considered

We considered models with and without APOEε4, as well as:

- Age
- Education
- Sex
- Family Hx (sibling or parent)
- Preclinical Alzheimer's Cognitive Composite (PACC)
- Mini-Mental State Exam (MMSE)
- Free and Cued Selective Reminding (FCSRT)
- LMIa Immediate Recall
- LMIa Delay Recall
- Digit Symbol Substitution (DSST)
- Cognitive Function Instrument (CFI)
- Activities of Daily Living (ADL)

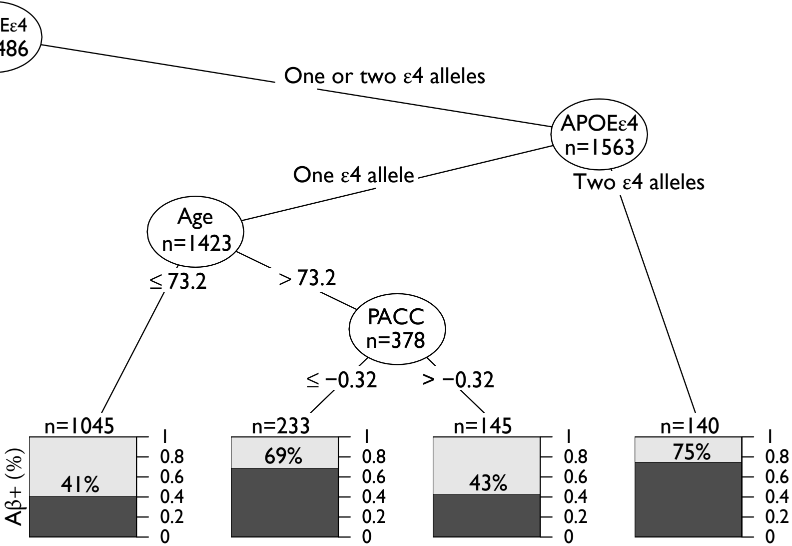
We considered models with either a **binary** (PET elegible or ineligible) and **continuous** (SUVR) outcome

Classification tree* with APOEε4

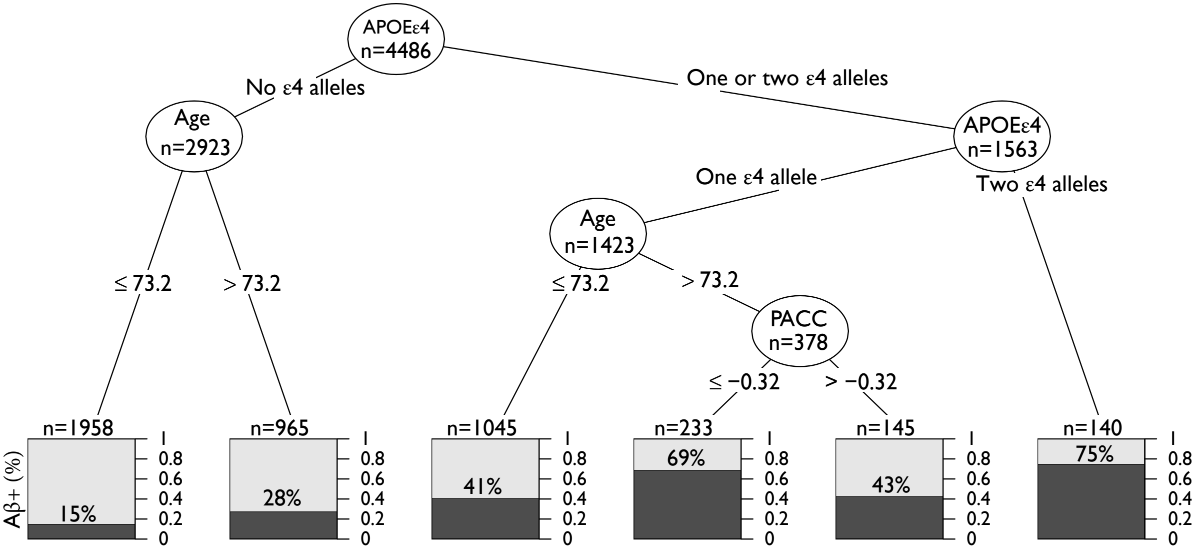


*Breiman, Friedman, Olshen, Stone. (1984). Classification and regression trees.

Classification tree with APOEε4



Classification tree with APOEε4

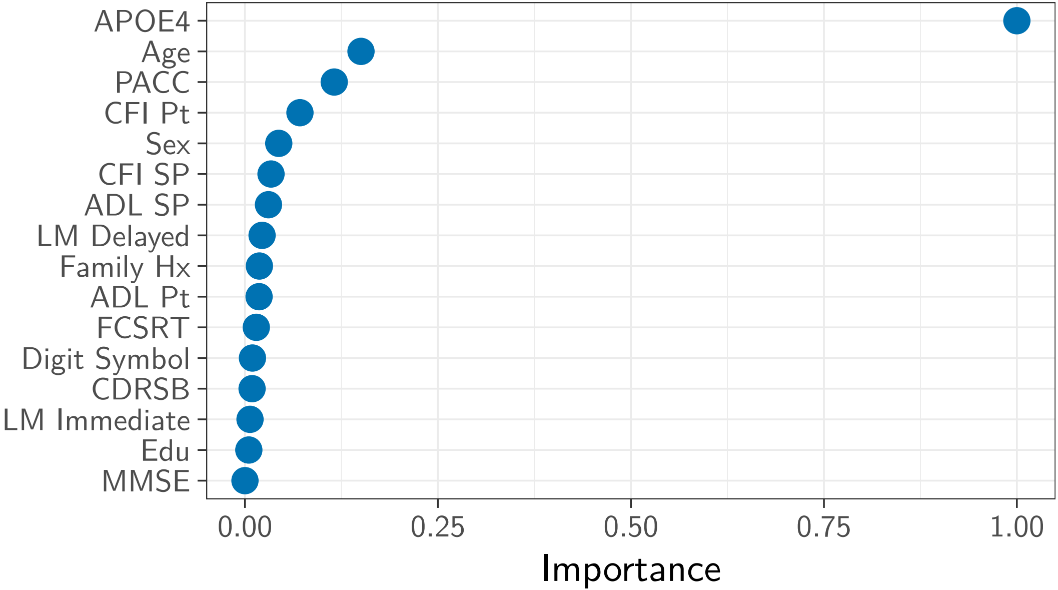


Random forests*

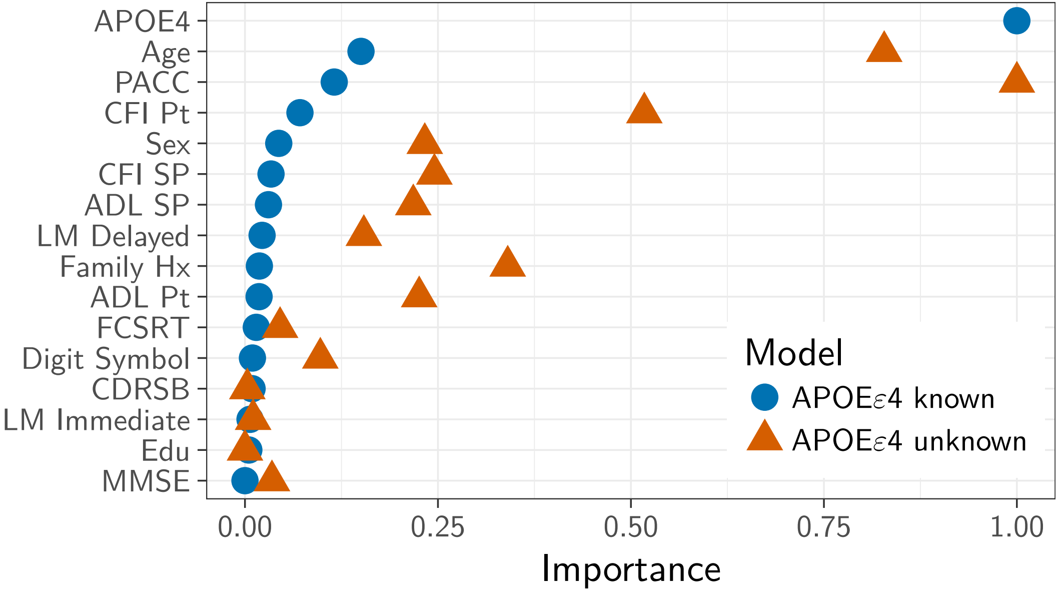
- Consist of many trees "grown" on random subsamples (like bootstrapping)
- Predictions are based on the consensus among the trees
- Subsampling allows for built-in cross-validation
- Difficult to visualize & summarize
- *Variable importance*: relative contribution of each predictor to predictive accuracy
- Imbalanced data (only 29.5% A$\beta+$), so A$\beta+$ observations were up-weighted when fitting models

*Leo Breiman (2001). Random Forests. *Machine Learning*, 45(1), 5-32.

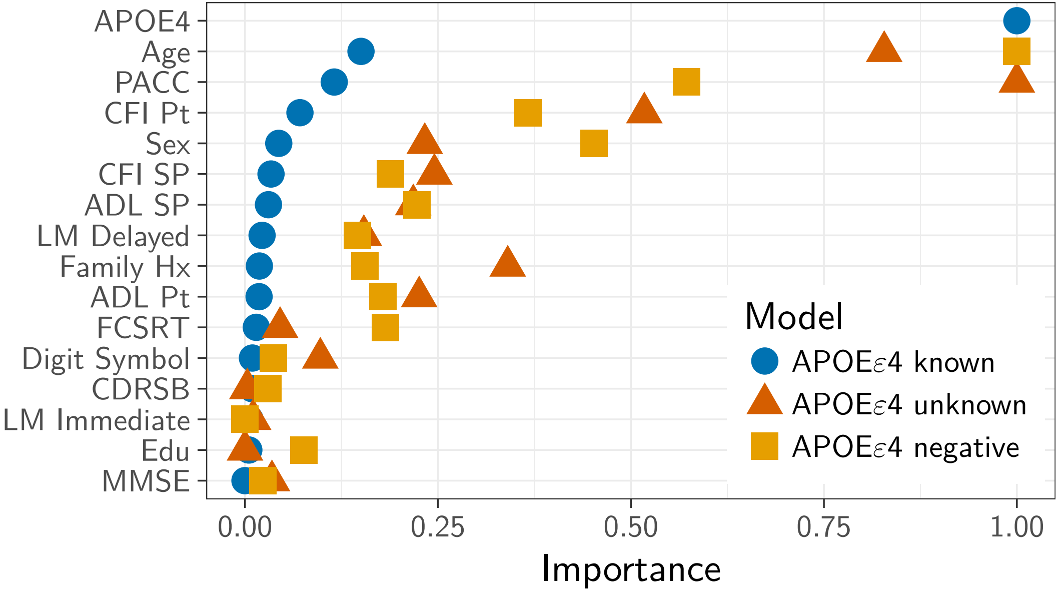
Predictor importance in random forest of SUVR



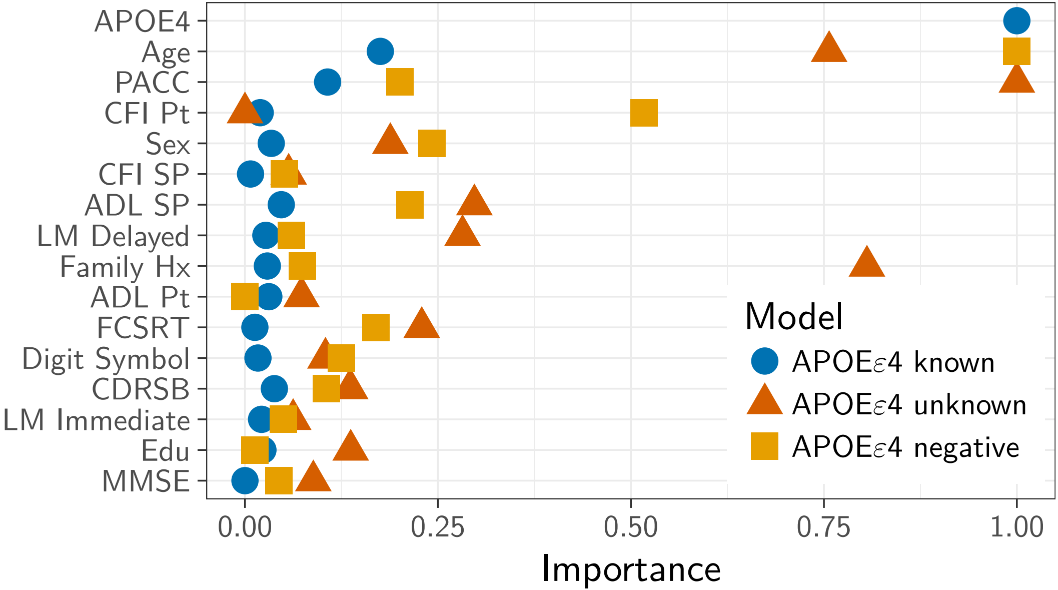
Predictor importance in random forest of SUVR



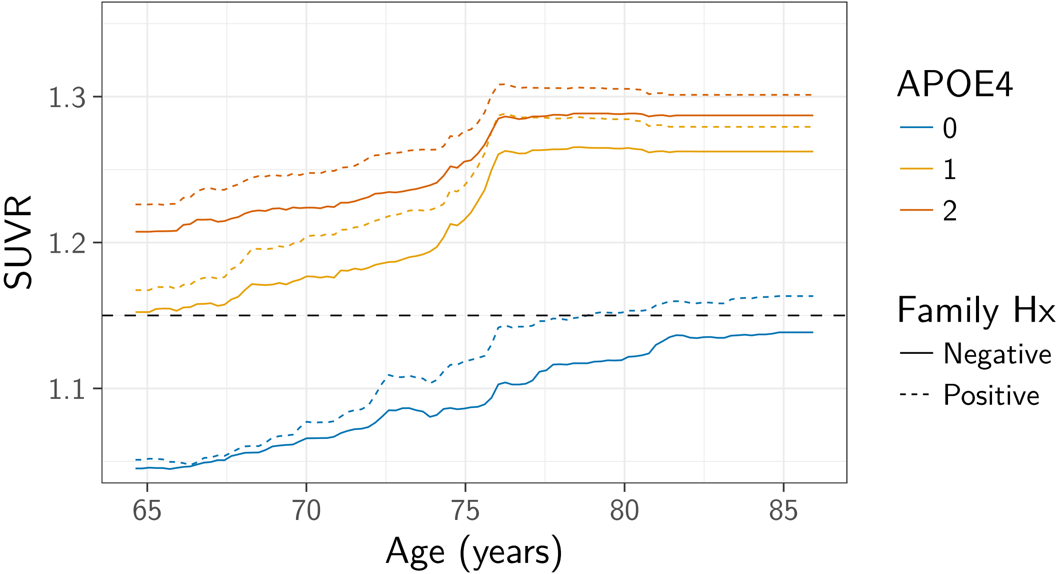
Predictor importance in random forest of SUVR



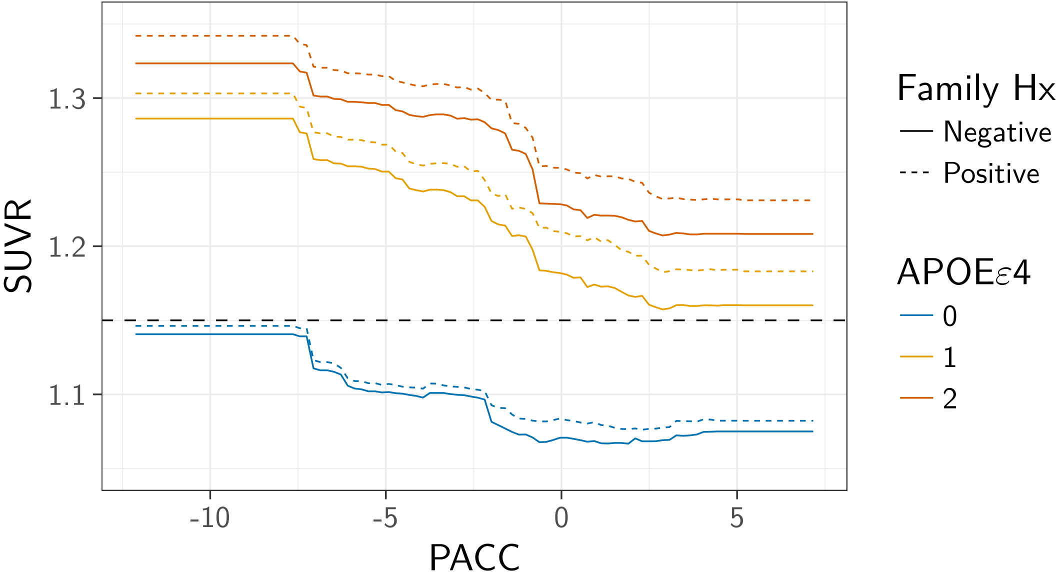
Predictor importance in random forest of (binary) amyloid eligibility



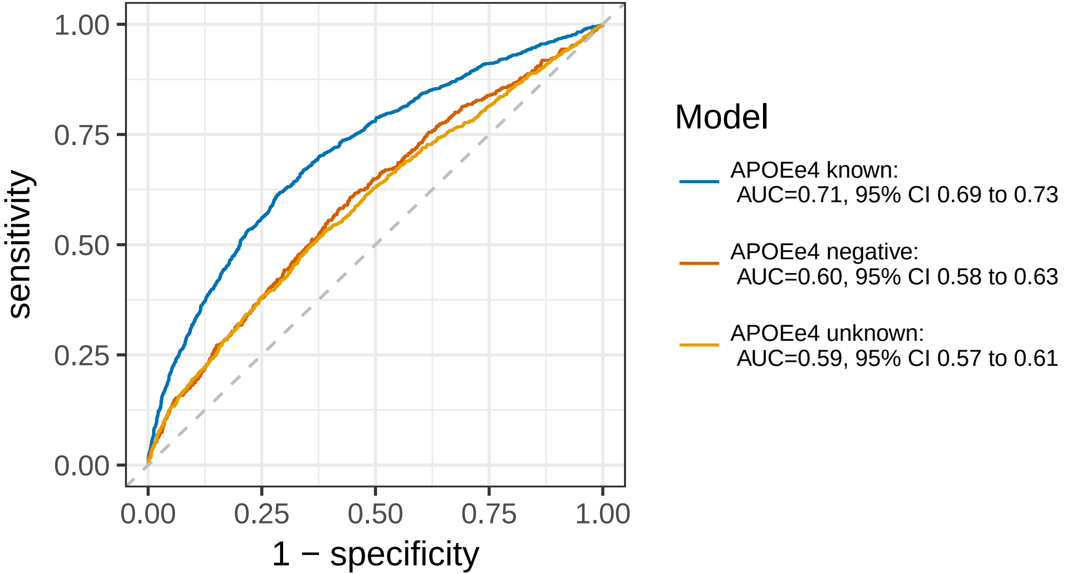
Predicted SUVR by APOEε4, Family Hx & age



Predicted SUVR by APOEε4, Family Hx & PACC



ROC curves for random forest models of amyloid SUVR



Predictive accuracy for APOEε4 known, unknown, or negative

Applying cutoff of 1.15 to out-of-sample predicted SUVR, and comparing to observed Aβ status:

APOEε4	Accuracy	Sensitivity	Specificity	NPV	PPV	NNS*	NNS reduction
known	68.8%	58.4%	73.2%	80.8%	47.6%	2.10	38.1%
unknown	63.9%	38.5%	74.5%	74.4%	38.8%	2.58	23.9%
negative	79.5%	11.8%	95.4%	82.1%	37.8%	2.65	49.4%

*Number Needed to Screen (NNS) to identify an A$\beta+$ individual, which was 3.39 individuals in A4 (5.24 for $\varepsilon 4-$).

Summary of predictive performance

- Machine learning algorithms have potential to reduce number needed to screen by [38% | 24% | 49%] when APOEε4 is [known | unknown | negative], and greatly reduce screening costs.
- However, sensitivity is only [58% | 38% | 12%], meaning [42% | 62% | 88%] of A$\beta+$ subjects would be falsely screened out (sensitivity can be improved by lowering the cutoff applied to predicted SUVR.)
- Predictive performance was similar regardless of whether we modelled binary or continuous outcomes, though Family Hx was more important in binary model without APOE.

Summary of predictor importance

- As expected APOE, Age, Cognition (both performance and subjective concerns), and Family Hx were important.
- The importance of cognitive composite in this *cross-sectional* analysis suggests *longitudinal* cognitive change might improve performance.

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- Site PIs and coordinators
- Study participants and families
- A4 Study Team list at A4STUDY.org