

MULTIMODAL AI PREDICTION IN PRE-SYMPTOMATIC ALZHEIMER'S DISEASE ENRICHES FOR CLINICAL PROGRESSION OVER FOUR YEARS



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BACKGROUND

- Individuals with pre-symptomatic Alzheimer's disease (AD) are paradoxically both the optimal target population for disease-modifying AD clinical trials, given their theoretical potential for AD prevention, yet the most challenging population to study for AD clinical trials, given their low and variable rates of short-term clinical decline that inflates sample sizes, costs, and trial duration.
- We evaluated whether a multimodal AI platform (QyPredict®) integrating baseline imaging biomarkers (QyScore®) and standard baseline predictors can identify pre-symptomatic AD individuals at the greatest risk for clinical decline, for the use in clinical trial enrichment.

METHODS

- QyPredict® was trained on a sample of 272 pre-symptomatic AD patients from the A4 Study (mean age: 71.6 ±4.6, 60.0% female, mean MMSE: 28.7±1.3).
- We customised multimodal machine-learning models to predict 4-year clinical progression (defined as CDR-SB decline ≥0.5 points). Models combined baseline PET amyloid burden (either A4-derived or QyScore®-derived), blood p-tau217, QyScore®-derived imaging markers, and demographic, cognitive, and APOE4 data.
- An entirely independent sample of 86 pre-symptomatic AD patients, not involved in any model training, was used for model validation and to derive performance metrics.
- All models were tuned to achieve 100% sensitivity, to eliminate the risk of incorrectly labelling true future decliners as future stable patients.

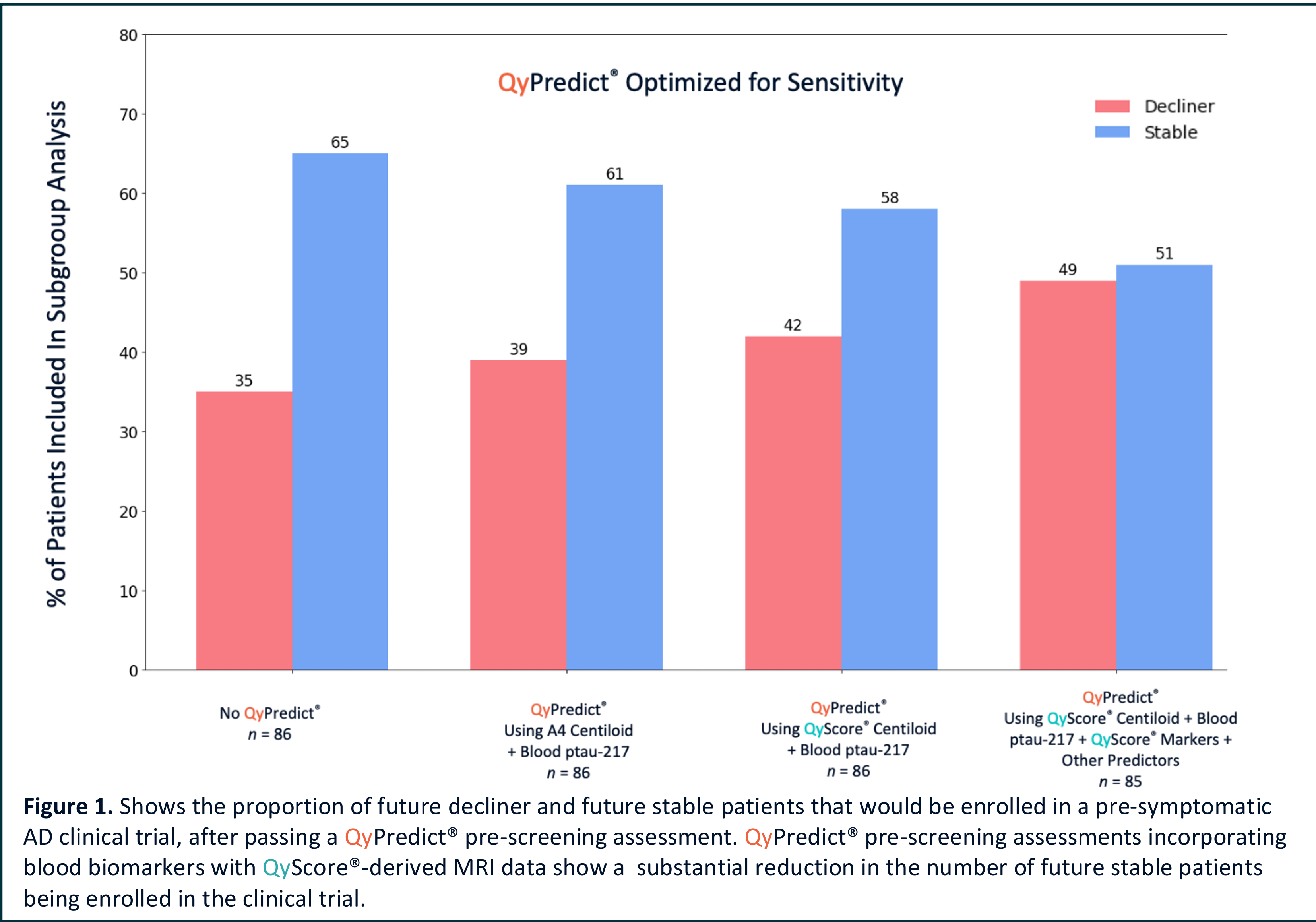
RESULTS

- When tuned for **100% sensitivity** (to minimise missed future decliners), multimodal models achieved up to ~2× higher specificity for identifying future clinical decliners compared to benchmark prescreening using blood p-tau217, which reduced the inclusion of individuals likely to remain clinically stable by ~21% (**Table 1; Figure 1**).
- Moreover, models utilising QyScore®-derived centiloid data saw a boost in predictive performance over models utilising A4-derived centiloid data (**Table 1; Figure 1**).

RESULTS

Table 1. Shows the performance metrics of QyPredict® models, predicting cognitive decline over 4 years in pre-symptomatic AD, trained on different baseline features. All models were tuned to achieve 100% sensitivity, to eliminate the risk of incorrectly excluding true future decliners in a clinical trial pre-screening scenario

Metrics	QyPredict® Using Blood ptau-217 (Benchmark)	QyPredict® Using A4-derived Centiloid + Blood ptau-217	QyPredict® Using QyScore® Centiloid + Blood ptau-217	QyPredict® Using QyScore® Centiloid + Blood ptau-217 + other QyScore®-derived Imaging Markers + demographic + cognitive + APOE4
Balanced Accuracy	58.0%	60.7%	62.5%	71.8%
Sensitivity	100%	100%	100%	100%
Specificity	16.1%	21.4%	25.0%	43.6%
RoC AUC	69.0%	69.3%	70.4%	79.0%
Precision	39.0%	40.5%	41.7%	49.2%
Negative Predictive Value	100%	100%	100%	100%
F1 Score	56.1%	57.7%	58.8%	65.9%



CONCLUSIONS

In **pre-symptomatic AD**, multimodal AI that integrates quantitative imaging with blood biomarkers and baseline risk factors can materially **improve identification of likely progressors at baseline**, potentially increasing trial power and reducing cost by limiting enrolment of non-progressors.

These findings support further validation in larger pre-symptomatic cohorts and prospective evaluation as an enrichment tool aligned with core clinical endpoints.