

FORECAST ALZHEIMER'S DISEASE PROGRESSION TO BETTER SELECT PATIENTS FOR CLINICAL TRIALS

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Objectives

Subject recruitment is a burden that hampers clinical trials, especially in neurodegenerative diseases, where worsening of abilities is subtle, long-term and heterogeneous. Targeting the right patients during trial screening is a way to reduce the needed sample size or conversely to improve the proven effect size.

Methods

From Alzheimer's disease (AD) observational cohorts, we selected longitudinal data that matched AD trials (inclusion and exclusion criteria, trial duration and primary endpoint). We modeled EMERGE, a phase 3 trial in pre-clinical AD, and a mild AD trial, using 4 research cohorts (ADNI, Memento, PharmaCog, AIBL). For each patient, we simulated its treated counterpart by applying an individual treatment effect. It consisted in a linear improvement of outcome for effective decliners, calibrated on our data so to match the expected trial effect size. Next, we built a multimodal AD course map that grasped long-term disease progression in a mixed-effects fashion [1] with [Leaspy](#). We used it to forecast never-seen individuals' outcomes from their screening biomarkers. Based on these individual screening predictions, we selected clinically relevant sub-groups [2]. Finally, we compared the effective sample size that would have been needed for the trial, with and without our selections. We evaluated dispersion of this metric using a bootstrap procedure.

Results

In all investigated setups and cohorts, we found a decrease in needed sample sizes with selection. For EMERGE trial, we showed that selecting patients having a predicted CDR-SoB changed between 0.5 and 1.5 points per year enabled to reduce the needed sample size by 38.2 ± 3.3 %. For the mild AD trial, we showed that selecting patients having a predicted MMSE changed between 1 and 2 points per year enabled to reduce the needed sample size by 38.9 ± 2.2 %.

Conclusions

We build a modelling framework for forecasting individual outcomes from their multimodal screening assessments. Using them as an extra inclusion criterion in clinical trials, we can better control trial population and thus reduce the needed sample size for a given treatment effect.

References

- [1] Schiratti J-B, Allasonniere S, Colliot O, Durrleman S. *A Bayesian mixed-effects model to learn trajectories of changes from repeated manifold-valued observations*. In Journal of Machine Learning Research (JMLR) 18(1):4840-4872. 2017.
- [2] Galasko DR, Gould RL, Abramson IS, Salmon DP. *Measuring cognitive change in a cohort of patients with Alzheimer's disease*. In Stat Med 19(11-12):1421-1432. 2000.

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