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Disease progression models in an international familial frontotemporal dementia cohort reveal the temporal ordering of clinical and biomarker changes and inform clinical trial design

State of the Art: Familial frontotemporal lobar degeneration (f-FTLD) is rare and therefore efficient clinical trial design is critical. Disease progression models (DPM) of the temporal ordering of clinical and biomarker changes can be used to optimize selection of trial endpoints and identify high-risk presymptomatic participants most likely to exhibit measurable disease progression during a trial.

Methodology: A Bayesian repeated-measures DPM incorporated longitudinal clinical status (CDR®+NACC-FTLD-SB), neuropsychological scores, regional brain atrophy, and plasma neurofilament light chain (NfL) in 796 mutations carriers (GRN, MAPT, or C9orf72) and 412 non-carrier controls from ALLFTD and GENFI. Evidence-based simulations were conducted to estimate sample sizes required for prevention and early symptomatic clinical trials.

Results: DPM curves were similar in ALLFTD and GENFI cohorts. Disease progression in C9orf72 was slow, with significant atrophy >10 years before and NfL elevations within 10 years of symptom onset. All measures progressed more rapidly in GRN; NfL elevations, followed by atrophy, occurred within 10 years of onset. In MAPT, atrophy began 0-10 years before, but NfL increased just prior to onset. In prevention trial simulations, atrophy and NfL were the best endpoints, whereas clinical measures were feasible endpoints in early symptomatic trials. Employing DPM-based patient selection led to sizeable reductions in sample sizes.

Conclusion: Endpoint selection should be specific to disease stage and mutation, and DPMs would facilitate more efficient trials. F-FTLD prevention trials are feasible but will likely require global recruitment. The similarity in progression across consortia suggests these models may have utility for designing international trials.