Preparing for the age of therapeutic trials in frontotemporal lobar degeneration

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There is a rapidly growing field of therapeutic development for familial forms of FTLD and Peakman et al address the important need for adequate clinical tools to measure treatment effect.

Frontotemporal lobar degeneration (FTLD) comprises a spectrum of heterogenous clinicopathological neurodegenerative disorders and neuropathological examination at autopsy remains the gold standard for diagnosis.[1] However, detection of pathogenic mutations in genes known to associate with either FTLD-Tau or FTLD-TDP neuropathology in ~20%–30% of all FTLD with familial disease provides an accurate antemortem molecular diagnosis in these individuals, even in the presymptomatic stage. Therefore, several clinical trials for agents targeting disease-specific mechanisms associated with forms of familial FTLD are planned or currently underway. Reliable clinical outcome measures to detect and track early disease are crucial to facilitate the success of these efforts. Peakman *et al*[2] perform a detailed cross-sectional and longitudinal analysis of two commonly used clinical rating scales (ie, extended clinical dementia rating scale (CDR+NACC FTLD) and the Frontotemporal Dementia Rating Scale (FRS)) in the large international Genetic FTD Initiative (GENFI) cohort to address this critical issue.

The main findings include overall good correlation of the scales with each other, and with other metrics of disease severity. However, there was some disagreement between scales in classifying the earliest stages of symptomatic disease. In longitudinal analysis over approximately 1 year of follow-up, there was measurable decline on both FRS and CDR+NACC FTLD sum-of-boxes score, particularly in mild to moderate global CDR+NACC FTLD symptomatic stages (scores=1–2). Notably, annualised change was low for both in the early presymptomatic 0.5 stage and did not differ from controls. Finally, using presymptomatic stage 0.5 patient data in a proof-of concept power analysis, the authors find relatively large sample sizes may be needed to detect a moderate effect size on both scales in a therapeutic trial. While both scales have been highly influential and important in improving diagnosis and research in symptomatic patients, these data suggest that additional approaches may be needed in presymptomatic familial FTLD.

This is a rigorous and important study that is exemplary of the importance of coordinated international collaborative efforts to facilitate success of therapeutic trials in rare conditions such as familial FTLD, including GENFI and other ongoing FTLD clinical trial readiness programmes such as ALLFTD (NCT04363684) and the FTD disorders registry (www.ftdregistry.org). The authors clearly articulate the potential limitations of the study, including the relative few presymptomatic patients who became symptomatic (ie, undergo phenoconversion) during observation and the lack of individual-item responses in FRS to help resolve discrepancies between scales. Moreover, they thoughtfully posit that augmentation of clinical assessments to include motor and neuropsychiatric features may improve the characterisation of presymptomatic disease. Indeed, the clinical heterogeneity of FTD results in varying overlapping clinical features[1] thus, interdisciplinary collaborations are needed across neurologic and psychiatric subspecialties to improve clinical assessments in FTLD. Emerging digital technologies to objectively measure clinical outcomes may be another avenue to track early disease progression,[3] such as automated speech analysis.[4] The power analyses performed in this study used a traditional 1:1 randomisation design and thus, did not account for the diverse and complex clinical trial strategies currently proposed[3] or implemented in FTLD trials.[5] As such, the authors suggest a stratification process using biomarkers of underlying neurodegeneration[6] to enrich presymptomatic familial FTLD cohorts with those individuals at highest risk for phenoconversion that may improve statistical power. Future longitudinal analysis that includes more phenoconversion data, when available, will help clarify this important issue. While this study focused on familial FTLD, it is important to note that the majority of patients with sporadic FTLD are often excluded from therapeutic trials, in part, due to relatively poor diagnostic accuracy of most clinical FTD syndromes for a specific underlying pathology. Thus, brain donation and translational research using postmortem human brain tissue to validate and develop novel tissue-sensitive biomarkers for specific forms of FTLD neuropathology[1] are critical to accelerate discoveries and prepare for the rapidly growing field of therapeutic trials in FTLD.

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Funding This work was supported by grants from NIH grants R01-NS109260, P01-AG066597, P30-AG10124, U19-AG062418 and the Penn Institute on Aging.

Disclaimer DJI receives research support to conduct therapeutic trials from Alector and Prevail.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Irwin D. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2021-327497

Received 1 August 2021
Accepted 8 August 2021

Linked

► http://dx.doi.org/10.1136/jnnp-2021-326868

J Neurol Neurosurg Psychiatry 2021;**0**:1–2. doi:10.1136/jnnp-2021-327497

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REFERENCES

1 Irwin DJ, Cairns NJ, Grossman M, *et al*. Frontotemporal lobar degeneration: defining phenotypic diversity through personalized medicine. *Acta Neuropathol* 2015;129:469–91.
2 Peakman G, Russell LL, Convery RS, *et al*. Comparison of clinical rating scales in genetic frontotemporal dementia within the GENFI cohort. *J Neurol Neurosurg Psychiatry* 2021. doi:10.1136/jnnp-2021-326868. [Epub ahead of print: 05 Aug 2021].
3 Friedman LG, McKeehan N, Hara Y, *et al*. Value-generating exploratory trials in neurodegenerative dementias. *Neurology* 2021;96:944–54.
4 Cho S, Nevler N, Ash S, *et al*. Automated analysis of lexical features in frontotemporal degeneration. *Cortex* 2021;137:215–31.
5 Desmarais P, Rohrer JD, Nguyen QD, *et al*. Therapeutic trial design for frontotemporal dementia and

related disorders. *J Neurol Neurosurg Psychiatry* 2019;90:412–23.

6 Meeter LH, Dopper EG, Jiskoot LC, *et al*. Neurofilament light chain: a biomarker for genetic frontotemporal dementia. *Ann Clin Transl Neurol* 2016;3:623–36.