

Article

ALS - FTD

Frontotemporal Dementia and Motor Neuron Disease: A Shared Clinical and Biological Landscape

Motor neuron disease (MND) and frontotemporal dementia (FTD) have traditionally been treated as separate disorders — one primarily motor, the other primarily cognitive and behavioural. A growing body of clinical, genetic, and pathological evidence instead positions them as points on a single disease spectrum. Cognitive and behavioural change occurs in up to 75% of MND patients, and up to a quarter meet formal criteria for FTD; conversely, 15% of patients presenting with FTD go on to develop MND. The C9orf72 repeat expansion is one of the strongest shared genetic drivers identified to date, and TDP-43 pathology — present in the great majority of MND cases and around half of FTD cases — spreads along converging anatomical trajectories in each disease. This shared biology already carries direct implications for diagnosis, screening, and the therapies now being trialled across both conditions.

ALS: Amyotrophic lateral sclerosis; ALS-CBS: ALS Cognitive Behavioural Screen; ASO: Antisense oligonucleotide bvFTD: Behavioural variant of frontotemporal dementia; ECAS: Edinburgh Cognitive and Behavioural ALS Screen; FTD; Frontotemporal dementia; MND: Motor neuron disease; PBA: Pseudobulbar affect; SSRIs selective serotonin reuptake inhibitors

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Frontotemporal Dementia and Motor Neuron Disease: A Shared Clinical and Biological Landscape

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Motor Neuron Disease and Frontotemporal Dementia

Motor neuron disease (MND) and frontotemporal dementia (FTD) rank among neurology's most formidable diseases, and both are set to become more common as populations age. Worldwide, MND affects roughly 1.7 people per 100,000 each year, with a prevalence of around 5.1 per 100,000. FTD is the leading cause of dementia under age 60, with an incidence of ~2.3 and a prevalence of 9.2 per 100,000.[1]

Amyotrophic lateral sclerosis (ALS) is the most common MND subtype, though the term is often used interchangeably with MND to denote the entire syndrome. ALS is rapidly progressive and fatal within 2–5 years;[2] with current therapies extending survival by only ~6 months.[3,4] FTD is also universally fatal, with no disease-modifying treatment.[5] Drugs for Alzheimer's disease show no benefit, or in some cases have been reported to worsen neuropsychiatric symptoms of FTD.[5]

Though MND is generally characterised by progressive motor decline and FTD cognitive and behavioural changes, MND and FTD are increasingly understood to be part of the same disease spectrum, with clinical, genetic and pathological overlap **(Fig.1)**.

Cognitive and behavioural abnormalities occur in 50–75% of MND patients, with 15–25% meeting formal criteria for FTD, most commonly the behavioural variant (bvFTD).[6,7] When observing patients with FTD, ~15% have a clinical diagnosis of definite MND.[8] Cognitive involvement in MND and motor dysfunction in FTD are both frequently under-recognised, risking incomplete phenotyping on either side of the spectrum.

Clinical Overlap

Executive impairment is the most common cognitive change in MND, seen in about 20–25% of cases, while non-executive deficits — language or memory problems — affect around 5–10%.[9,10] Behavioural change is even more widespread: using the Motor Neuron

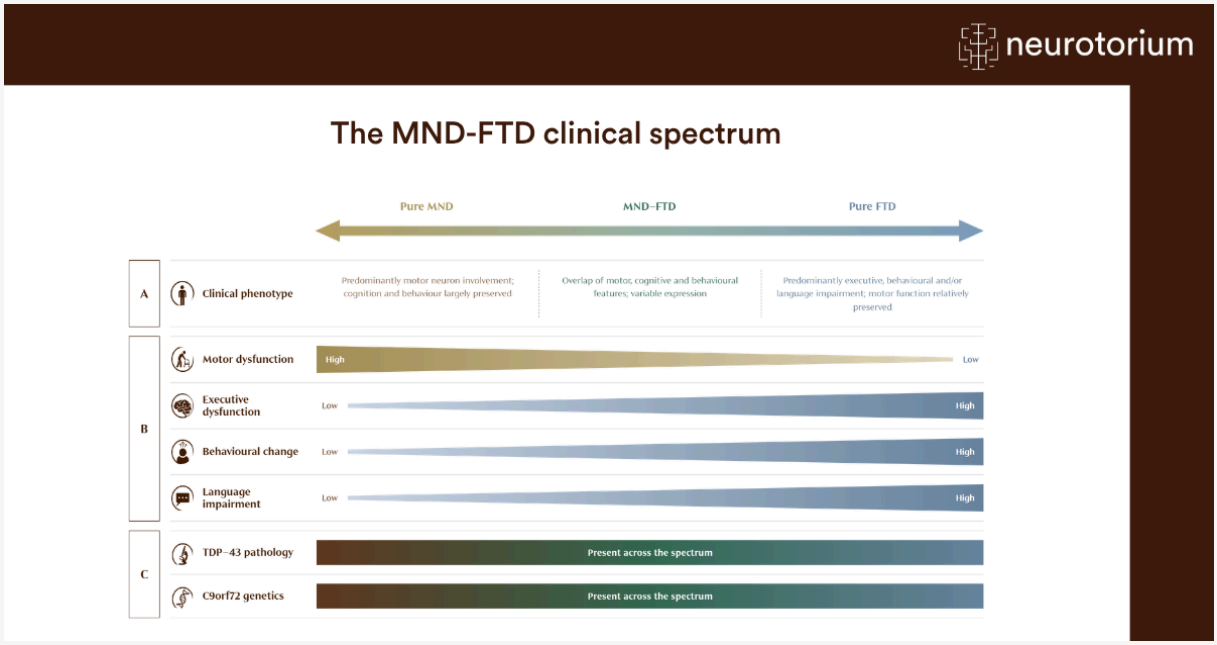


Figure 1. The MND-FTD clinical spectrum
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Disease Behavioural Instrument, disturbances have been identified in around 75% of patients.[11] In some cases, these behavioural symptoms don't follow motor decline — they precede it, appearing roughly 12 months before motor dysfunction sets in.[12]

Apathy is the most common of these behavioural changes, being moderate-to-severe in at least half of the cases, independent of any underlying mood or anxiety disorder.[13] Disinhibition, a blunted sense of empathy, aggression, and agitation have all been reported too, in both MND and combined FTD-MND.[14]

The overlap between the two diseases runs in both directions and shows up early. Population and clinic-based cohort studies find that 10–15% of MND patients already meet criteria for FTD at baseline, while 15% of patients who present with FTD go on to develop MND — and a further 30–40% show subtle clinical or neurophysiological signs of motor system involvement even without a formal MND diagnosis.[15] Progression is more rapid in patients with combined FTD-MND than in those with MND alone, with bulbar onset and low educational status being identified as potential risk factors for cognitive decline.[9]

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Genetic and Pathological Overlap

In MND, 10-15% of cases are classified as familial,[16] with up to 60% of FTD patients reporting a family history of dementia.[17] Both figures are probably underestimates, with apparently sporadic cases carrying pathogenic variants likely representing unrecognised familial cases, missed through incomplete family history rather than genuinely arising de novo mutations.[16]

The C9orf72 hexanucleotide repeat expansion is the most common cause of both familial MND and familial FTD, and is the strongest single piece of genetic evidence for overlap between the two diseases.[18] It is present in ~40% of familial MND and ~25% of familial FTD.[19]

Penetrance of the expansion has not been definitively established, and clinical presentation and prognosis vary widely among carriers.[20] Whether an asymptomatic carrier will develop FTD, MND, or a combination cannot currently be predicted. However, brain imaging may help: early studies suggest scans showing damage in specific brain regions could be developed into risk biomarkers.[21] Patients with C9orf72 mutations who have a predominant MND syndrome can still exhibit pathological features consistent with FTD, and those with a predominant FTD syndrome can show pathology in the motor system.[22]

Three mechanisms have been proposed for how the C9orf72 expansion drives disease — haploinsufficiency, toxic RNA foci, and dipeptide repeat toxicity.[23] Evidence supports all three, but none conclusively enough to stand alone, suggesting several mechanisms may act together to drive the pathophysiology of MND/FTD.[24]

C9orf72 mutations are associated with TDP-43 inclusions; cytoplasmic and nuclear TDP-43 inclusions are characteristic of both MND and FTD, and TDP-43 pathology is consistently identified as the shared hallmark linking the two diseases.[25,5] This pathology is present in over 90% of MND patients, and in around half of all FTD cases.[24,26]

TDP-43 deposition follows a different, but converging anatomical path in FTD and MND **(Fig. 2)**. In bvFTD, pathology begins in the frontal lobe and amygdala (stage 1), then spreads through the rest of the frontal and anterior temporal lobes — including the hippocampus, thalamus, and related subcortical structures (stage 2) — before reaching cortical, brainstem, and spinal motor regions at stage 3, and finally the visual cortex at stage 4. In MND, the sequence runs in roughly the opposite direction. Deposition starts in upper motor neurons in the cortex or lower motor neurons in the spinal cord and lower brainstem (stage 1), then extends to posterior frontal and parietal regions and the brainstem reticular formation (stage 2), to the anterior frontal lobe, basal forebrain, thalamus, and substantia nigra (stage 3), and finally to the anterior temporal lobe, including the hippocampus, at stage 4.[27,28]

Overlap in deposition of TDP-43 in MND and FTD is greatest for type B TDP-43 pathology, which occurs in most patients with MND but only a fraction of those with FTD, and may account for the overlap in clinical

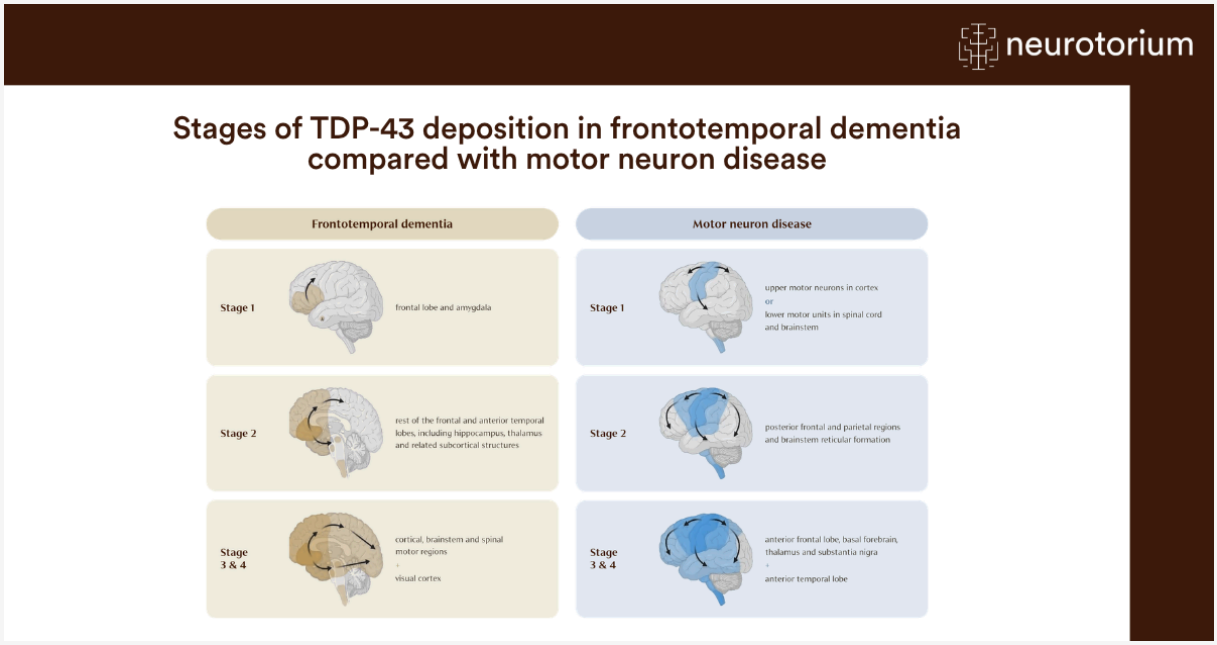


Figure 2. Stages of TDP-43 deposition in frontotemporal dementia compared with motor neuron disease

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Clinical and Therapeutic Implications

The international consensus criteria for possible bvFTD require three of six clinically discriminating features: disinhibition, apathy or inertia, loss of sympathy or empathy, perseverative or compulsive behaviours, hyperorality, and a dysexecutive neuropsychological profile.[29] These criteria make no reference to motor features, but the Gold Coast Criteria — the more recently established diagnostic criteria for ALS — acknowledge the overlap directly: ALS may include cognitive, behavioural, and/or psychiatric abnormalities, though these are not essential for diagnosis.[30] Separate consensus criteria have also been developed specifically for diagnosing frontotemporal cognitive and

Criteria	Diagnostic category	Key required features
Gold Coast ALS diagnosis criteria[30]	Single diagnostic entity (replaces definite / probable / possible)	• Progressive motor impairment, preceded by normal motor function • UMN + LMN dysfunction in ≥1 body region, OR LMN dysfunction alone in ≥2 regions • Investigations exclude other disease processes
Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in ALS[29]	ALS-FTD (bvFTD / PNFA / SD)	Meets full Neary (1998) criteria for bvFTD, PNFA or SD
	ALSbi — behavioural impairment	≥2 non-overlapping supportive features (Neary and/or Hodges criteria), from ≥2 sources (patient, caregiver, questionnaire)
	ALSci — cognitive impairment	Impairment ≤5th percentile on ≥2 distinct executive-function tests (formal neuropsychological testing required)
FTDC bvFTD criteria[31]	Possible bvFTD	≥3 of 6 features required: • (A) early disinhibition • (B) early apathy/inertia • (C) early loss of sympathy/empathy • (D) early perseverative/stereotyped/ compulsive behaviour • (E) hyperorality/dietary change • (F) executive deficits with relative sparing of memory and visuospatial skills
	Probable bvFTD	• Meets possible bvFTD • + significant functional decline • + imaging consistent with bvFTD (frontal/ anterior temporal atrophy on MRI/CT, or hypoperfusion/hypometabolism on PET/ SPECT)
	bvFTD with definite FTLD pathology	Possible or probable bvFTD + histopathological confirmation (biopsy/ autopsy) OR known pathogenic mutation

Table 1. Key diagnostic criteria for ALS and the ALS-FTD spectrum

Abbreviations: UMN = upper motor neuron; LMN = lower motor neuron; bvFTD = behavioural variant frontotemporal dementia; PNFA = progressive non-fluent aphasia; SD = semantic dementia; ALSbi = ALS with behavioural impairment; ALSci = ALS with cognitive impairment; FTLD = frontotemporal lobar degeneration; FTDC = International Behavioural Variant FTD Criteria Consortium.

behavioural syndromes in MND. These span four axes: clinical diagnosis of MND (axis I), behavioural and cognitive deficits (axis II), non-motor manifestations (axis III), and disease modifiers (axis IV) **(Table 1)**.[31]

Two cognitive screening tools have been developed specifically for MND. The ALS Cognitive Behavioural Screen (ALS-CBS) measures executive dysfunction while accounting for motor deficits[32] and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), which assesses executive function, verbal fluency, language, and visuospatial function.[33]

The FDA-approved MND drugs each produce only modest slowing of progression.[3,4] FTD management remains symptomatic relying on selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics for behavioural symptoms.[5] Antisense oligonucleotide (ASO) technologies to reduce mutant gene expression including C9orf72 have been evaluated in clinical trials34, along with trials indirectly targeting C9orf72 through other pathways.[35]

No therapies have been specifically studied for abnormal behaviours in this combined syndrome, though symptomatic antipsychotic treatment may be used for agitation, aggression, or sexualised behaviours.[20] Recently, the FDA has approved the first medication targeting pseudobulbar affect (PBA), characterised by sudden bouts of uncontrollable crying or laughter, which is frequently seen in FTD-MND.[5]

The well-established multidisciplinary care model for MND[36] offers a natural starting point for FTD-MND, and extending it to the combined syndrome is already common practice. Confirming which elements translate directly is a clear opportunity for future work: Riluzole's specific role in FTD-MND has not yet been directly studied, and interventions known to help in MND — non-invasive ventilation and enteral feeding — remain to be evaluated in this group, where compliance may need particular attention.[2] Better characterising the link between respiratory insufficiency, quality of life, and cognitive decline is a further avenue worth pursuing. Earlier recognition of carer burden as the disease progresses, supported by counselling and, later, regular respite and psychological support, is an area where FTD-MND care stands to build meaningfully on what's already established for MND.

Conclusion

MND and FTD are now widely recognised as part of a single disease spectrum, rather than as separate conditions. This is supported by their shared genetic driver (C9orf72), a common pathological substrate (TDP-43), and overlapping patterns of disease spread. It is also reflected in current clinical practice: diagnostic criteria on both sides increasingly account for features of the other domain, screening tools have been developed specifically for MND-associated cognitive change, and clinical trials are now testing therapies that target the shared C9orf72 mutation. Recognising MND and FTD as points on one spectrum, rather than through separate diagnostic pathways, supports earlier diagnosis and better coordinated care.

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References

1. Urso D, Giannoni-Luza S, Brayne C, Ray N, Logroscino G. Incidence and prevalence of frontotemporal dementia: A systematic review and meta-analysis. JAMA Neurology. 2025;82(11):1144-1152.

2. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. Lancet (London, England). 2011;377(9769):942-955.

3. Brooks BR, Berry JD, Ciepielewska M, et al. Intravenous edaravone treatment in ALS and survival: An exploratory, retrospective, administrative claims analysis. eClinicalMedicine. 2022;52.

4. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). The Cochrane database of systematic reviews. 2012;2012(3):Cd001447.

5. Neylan KD, Miller BL. New approaches to the treatment of frontotemporal dementia. Neurotherapeutics. 2023;20(4):1055-1065.

6. Lillo P, Savage S, Mioshi E, Kiernan MC, Hodges JR. Amyotrophic lateral sclerosis and frontotemporal dementia: A behavioural and cognitive continuum. Amyotroph Lateral Scler. 2012;13(1):102-109.

7. Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2012;83(1):102-108.

8. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. Neurology. 2002;59(7):1077-1079.

9. Montuschi A, Iazzolino B, Calvo A, et al. Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. J Neurol Neurosurg Psychiatry. 2015;86(2):168-173.

10. Elamin M, Bede P, Byrne S, et al. Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology. 2013;80(17):1590-1597.

11. Mioshi E, Hsieh S, Caga J, et al. A novel tool to detect behavioural symptoms in ALS. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014;15(3-4):298-304.

12. Mioshi E, Caga J, Lillo P, et al. Neuropsychiatric changes precede classic motor symptoms in ALS and do not affect survival. Neurology. 2014;82(2):149-155.

13. Lillo P, Garcin B, Hornberger M, Bak TH, Hodges JR. Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis. Arch Neurol. 2010;67(7):826-830.

14. Meier SL, Charleston AJ, Tippett LJ. Cognitive and behavioural deficits associated with the orbitomedial prefrontal cortex in amyotrophic lateral sclerosis. Brain. 2010;133(11):3444-3457.

15. Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor Neuron dysfunction in frontotemporal dementia. Brain. 2011;134(9):2582-2594.

16. Dharmadasa T, Scaber J, Edmond E, et al. Genetic testing in motor neurone disease. Pract Neurol. 2022;22(2):107.

17. Rohrer JD, Guerreiro R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73(18):1451-1456.

18. Abramzon YA, Fratta P, Traynor BJ, Chia R. The Overlapping Genetics of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. Front Neurosci. 2020;14:42.

19. Van Mossevelde S, Engelborghs S, van der Zee J, Van Broeckhoven C. Genotype-phenotype links in frontotemporal lobar degeneration. Nat Rev Neurol. 2018;14(6):363-378.

20. Burrell JR, Halliday GM, Kril JJ, et al. The frontotemporal dementia-motor neuron disease continuum. Lancet. 2016;388(10047):919-931.

21. van Veenhuijzen K, Tan HHG, Nitert AD, et al. Longitudinal Magnetic Resonance Imaging in Asymptomatic C9orf72 Mutation Carriers Distinguishes Phenoconverters to Amyotrophic Lateral Sclerosis or Amyotrophic Lateral Sclerosis With Frontotemporal Dementia. Ann Neurol. 2025;97(2):281-295.

22. Hsiung GY, DeJesus-Hernandez M, Feldman HH, et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Brain. 2012;135(Pt 3):709-722.

23. Taylor JP, Brown RH, Jr., Cleveland DW. Decoding ALS: from genes to mechanism. Nature. 2016;539(7628):197-206.

24. Thonhoff JR, Greene EP, Appel SH. Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. In: Gendelman HE, Ikezu T, eds. Neuroim Pharmacology and Therapeutics; 2024:705-718.

25. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;314(5796):130-133.

26. Ling SC, Polymenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. Neuron. 2013;79(3):416-438.

27. Brettschneider J, Del Tredici K, Toledo JB, et al. Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. Annals of Neurology. 2013;74(1):20-38.

28 Brettschneider J, Del Tredici K, Irwin DJ, et al. Sequential distribution of pTDP-43 pathology in behavioral variant frontotemporal dementia (bvFTD). Acta Neuropathologica. 2014;127(3):423-439.

29. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(Pt 9):2456-2477.

30. Shefner JM, Al-Chalabi A, Baker MR, et al. A proposal for new diagnostic criteria for ALS. Clinical Neurophysiology. 2020;131(8):1975-1978.

31. Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2009;10(3):131-146.

32. Woolley SC, York MK, Moore DH, et al. Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS). Amyotroph Lateral Scler. 2010;11(3):303-311.

33. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(1-2):9-14.

34. van den Berg LH, Rothstein JD, Shaw PJ, et al. Safety, tolerability, and pharmacokinetics of antisense oligonucleotide BIIB078 in adults with C9orf72-associated amyotrophic lateral sclerosis: a phase 1, randomised, double blinded, placebo-controlled, multiple ascending dose study. Lancet Neurol. 2024;23(9):901-912.

35. Babu S, Nicholson KA, Rothstein JD, et al. Apilimod dimesylate in C9orf72 amyotrophic lateral sclerosis: a randomized phase 2a clinical trial. Brain. 2024;147(9):2998-3008.

36. Miller R, Jackson C, Kasarskis E, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73(15):1227-1233.