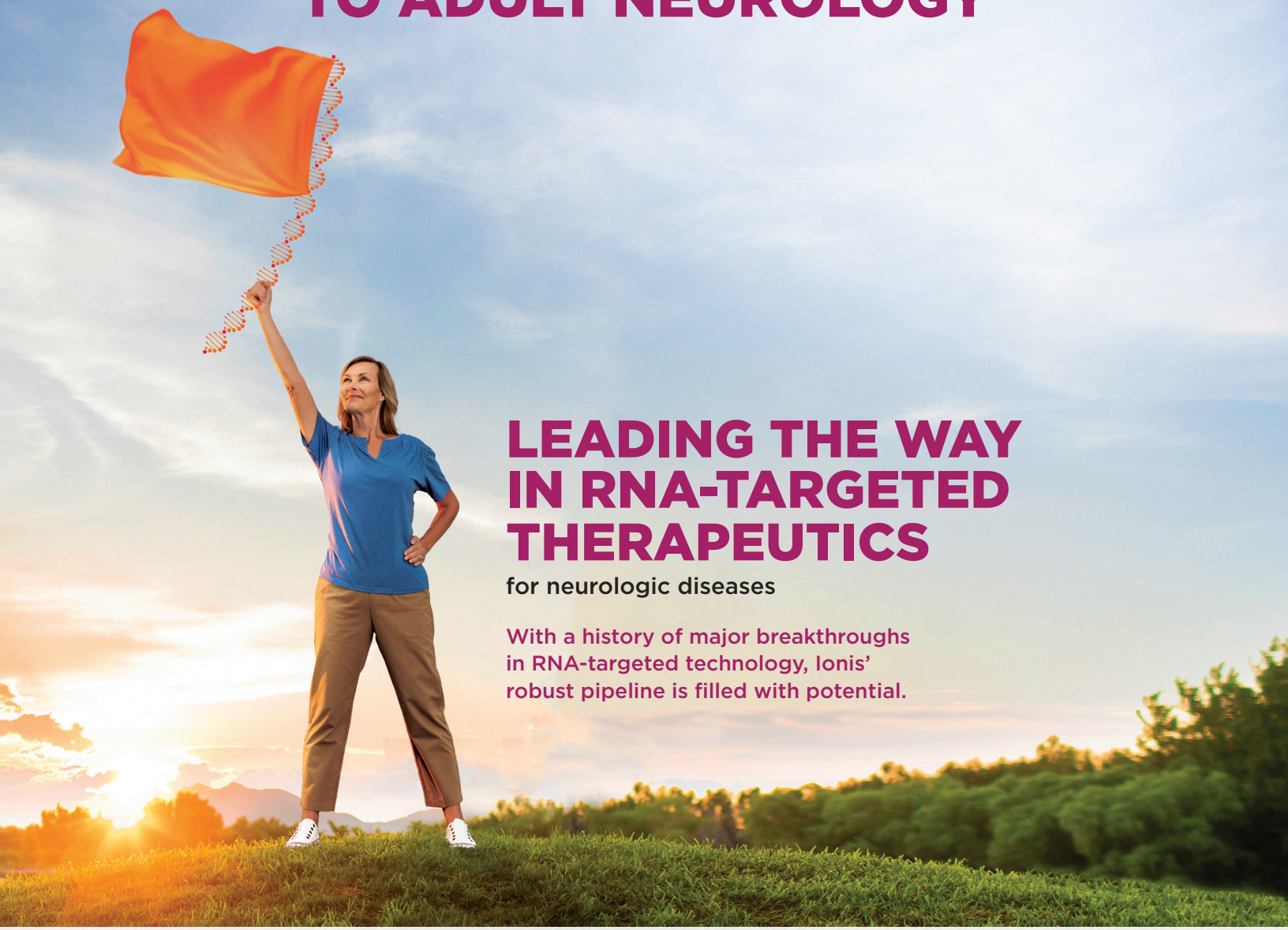
IONIS' COMMITMENT TO ADULT NEUROLOGY



LEADING THE WAY IN RNA-TARGETED THERAPEUTICS

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Angelman Syndrome (AS) Is a Rare and Severe Neurodevelopmental Disorder[1-4]

AS is a rare, monogenic, neurodevelopmental disorder that is caused by a loss of function in the maternally inherited ***UBE3A* gene**.[1-4] The majority of AS cases (~70%-75%) are caused by **deletions in the *UBE3A* gene**, leading to the **most severe symptoms**. Truncations or missense mutations, imprinting center defects, and paternal uniparental disomy can also cause AS.[3-7]

The diagnosed prevalence of AS is approximately 1 in 21,000 people worldwide.[3,6,8,9] AS symptoms and impairments present early in life and persist throughout a normal lifespan, resulting in medical challenges that require lifelong care.[3,5,10-13]

The lack of FDA-approved disease-modifying therapies, combined with the severity of the condition, results in **high unmet clinical needs** for individuals with AS and their families.[14,15]

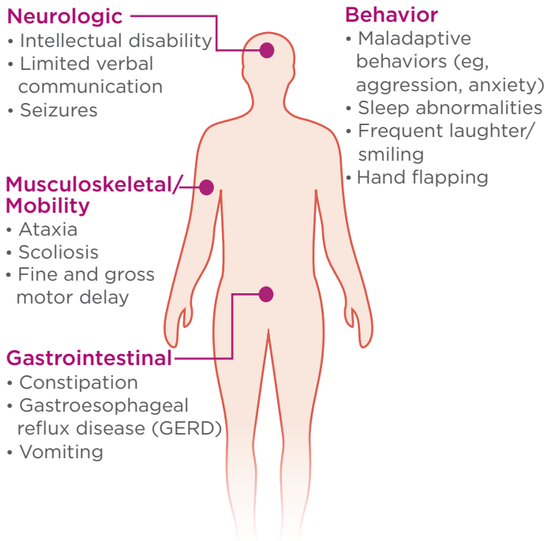
AS Is Characterized by a Range of Impairments, Including Communication, Cognitive, Motor, and Behavioral Manifestations[3,5,13]

AS is characterized by intellectual disability, seizures, communication difficulty, a very happy demeanor with frequent laughter, sleep disturbances, delays in fine and gross motor milestones, and movement issues (Figure 1).[3,5,13]

Individuals with AS may be asymptomatic at birth, but often have feeding problems in the first months of life, developmental delays between 6 and 12 months, and seizures beginning around 2 to 3 years of age.[3,5,13,16]

Clinical signs and symptoms of AS may vary based on genetic subtype. Expressive communication and cognitive impairment are universal features of AS, with most severe disability seen in those with deletion subtype. Epilepsy is also common in all subtypes, with higher rates in those with deletion subtype and later onset in the nondeletion subtype (>5 years of age). Microcephaly is often seen in those with deletion subtype but not as frequently noted in other subtypes, while hyperphagia is more common in those with uniparental disomy or imprinting defects.[10,17]

Figure 1: Primary Symptoms Associated With AS[3,5,13]



In adulthood, individuals with AS continue to experience AS-related impairments, including cognitive disability, communication difficulties, anxiety, issues with self-care, and further decline in mobility. Sleep, seizures, and hyperactivity often become less significant impairments as individuals with AS age.[3,5,10,11]

Individuals with AS have a near-normal life expectancy but require lifelong care[3,10]

FDA, US Food and Drug Administration; *UBE3A*, ubiquitin protein ligase E3A gene.

1. Kishino T, et al. *Nat Genet*. 1997;15(1):70-73. 2. Matsuura T, et al. *Nat Genet*. 1997;15(1):74-77. 3. Wheeler AC, et al. *Orphanet J Rare Dis*. 2017;12(1):164. 4. Larson AM, et al. *Am J Med Genet A*. 2015;167A(2):331-344. 5. Prasad A, et al. *Am J Med Genet A*. 2018;176(6):1327-1334. 6. Mertz LGB, et al. *Am J Med Genet A*. 2013;161A(9):2197-2203. 7. Hagenaar DA, et al. *J Intellect Disabil Res*. 2024;68(3):248-263. 8. Yakoreva M, et al. *Eur J Hum Genet*. 2019;27(11):1649-1658. 9. Luk HM, et al. *Eur J Med Genet*. 2016;59(6-7):315-319. 10. Duis J, et al. *Mol Genet Genomics Med*. 2022;10:e1843. 11. Khan N, et al. *Qual Life Res*. 2023;32(7):2059-2067. 12. Willgoss T, et al. *Child Psychiatry Hum Dev*. 2021;52(4):654-668. 13. Clayton-Smith J, et al. *J Med Genet*. 2003;40(2):87-95. 14. Wheeler AC, et al. *J Neurodev Disord*. 2023;15(1):37. 15. Angelman syndrome. National Organization for Rare Disorders. Updated February 14, 2018. Accessed December 12, 2024. https://rarediseases.org/rare-diseases/angelman-syndrome/?filter=ovr-ds-resources/ 16. Williams CA, et al. *Am J Med Genet*. 1995;56:237-238. 17. Keute M, et al. *Mol Psychiatry*. 2021;26(7):3625-3633.

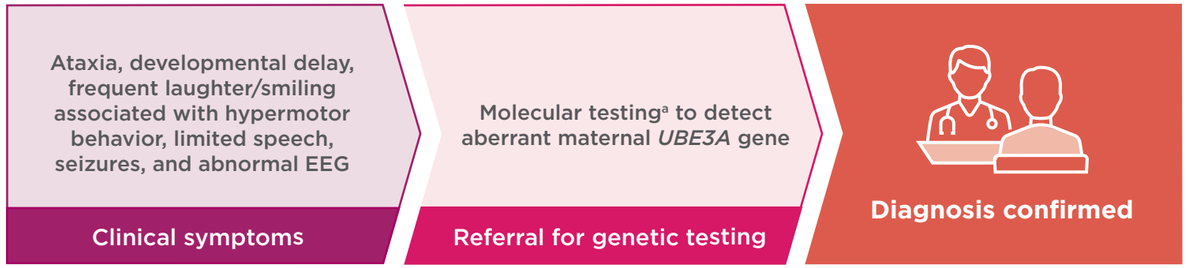
Prompt Diagnosis and Interventions Targeting the Underlying Pathophysiology of Angelman Syndrome (AS) Are Critical Unmet Needs[1-3]

Patients may experience a delay in diagnosis of up to ~3 years after symptom onset[5,6]

Disorders with overlapping symptomology[4]

- Alpha-thalassemia
- Lennox-Gastaut syndrome
- Infant autism spectrum disorder
- Mowat-Wilson syndrome
- Rett syndrome
- X-linked intellectual disability

Figure 2: Diagnosis Is Made by Clinical Observation Followed by Confirmatory *UBE3A* Genetic Testing[1-4,7]



Further diagnostic and screening efforts are needed to identify individuals with AS early in life, as they often experience developmental delays in early childhood[6]

There Are No Disease-Modifying Treatment Options Available for Individuals With AS[2,3,5]

Current treatments provide only symptomatic relief

Expressive communication[1,2,8]
- Speech therapy
- Augmentative and Alternative Communication
- Individualized education plan

Sleep[1,2,8]
- Treatment of contributing problems (eg, GERD, epilepsy, anxiety, obstructive sleep apnea)
- Sleep hygiene
- Sleep aid medications

Behavior[1,2,8]
- Physical and occupational therapy
- Hydrotherapy

Seizures[8]
- Antiseizure medications
- Low carbohydrate diet

[a]Tests include methylation studies, chromosome microarray, uniparental disomy studies, imprinting center studies, and gene sequencing.[3,4,9]

EEG, electroencephalogram; GERD, gastroesophageal reflux disease; *UBE3A*, ubiquitin protein ligase E3A gene.

1. Wheeler AC, et al. *Orphanet J Rare Dis*. 2017;12(1):164. 2. Angelman syndrome. National Organization for Rare Disorders. Updated February 14, 2018. Accessed December 12, 2024. https://rarediseases.org/rare-diseases/angelman-syndrome/?filter=ovr-ds-resources/ 3. Madaan M, Mendez MD. *StatPearls.* Treasure Island (FL): StatPearls Publishing; January 2024. 4. Maranga C, et al. *FEBS J*. 2020;287(11):2154-2175. 5. Wheeler AC, et al. *J Neurodev Disord*. 2023;15(1):37. 6. Williams CA, et al. *Am J Med Genet*. 1995;56:237-238. 7. Clayton-Smith J, et al. *J Med Genet*. 2003;40(2):87-95. 8. Duis J, et al. *Mol Genet Genomic Med*. 2022;10(3):e1843. 9. Testing and Diagnosis. Angelman Syndrome Foundation. Accessed December 12, 2024. https://www.angelman.org/what-is-as/testing-and-diagnosis/

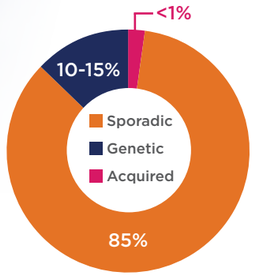
Prion Disease (PrD) Is a Rare, Progressive, Fatal Neurodegenerative Disease[1,2]

PrD, also known as transmissible spongiform encephalopathies, describes a group of rare neurodegenerative diseases characterized by rapid, progressive neurological decline.[1,2]

PrD can occur via several etiologies (**Figure 1**)[1]:
- **Sporadic**, with no known exposure or genetic cause
- **Genetic**, due to variants in the prion protein gene (*PRNP*)
- **Acquired** from an exogenous source

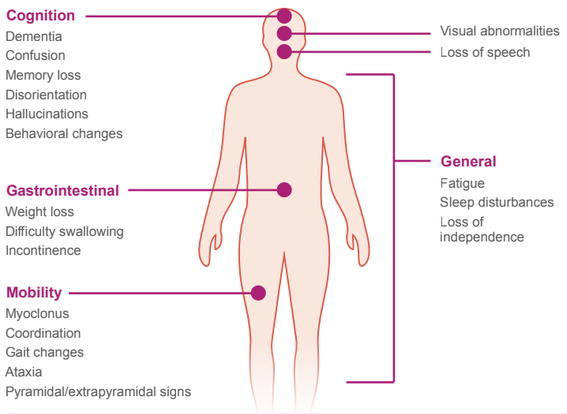
Misfolded prion protein scrapie (PrP^{Sc}) is the cause of disease in all types of PrD.[1]

Figure 1: Etiology of PrD[1]



PrD Is Typically Characterized by Rapidly Progressive and Nonspecific Cognitive, Motor, Cerebellar, and Visual Symptoms[1,3]

Figure 2: PrD Has a Range of Symptoms[3-6,a]



Types of PrD include[1]
- Creutzfeldt-Jakob disease (CJD)
- Fatal familial insomnia
- Gerstmann-Sträussler-Scheinker disease
- Variant CJD (vCJD)

Age of disease onset is unpredictable but can be influenced by disease subtype. PrD onset generally occurs later in life (50 to 80 years of age) but has been diagnosed in people <20 and >80 years of age.[3,4,7,8]

Progressive neurological decline and death (**Figure 3**) typically occur within ~1 year of symptom onset, though some types of PrD have a longer duration.[2,7]

Disease progression can be assessed with the 20-point Medical Research Council Prion Disease Rating Scale, which measures[4]:

- Cognitive function
- Speech
- Mobility
- Personal care/feeding
- Continence

Figure 3: Illustration of Disease Progression and Common Functional/Cognitive Milestones in PrD[4]

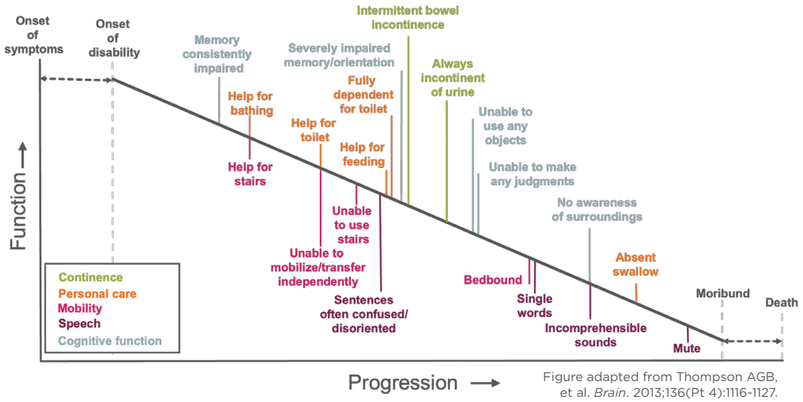


Figure adapted from Thompson AGB, et al. *Brain*. 2013;136(Pt 4):1116-1127.

[a]Not a complete list of symptoms. Not all patients will experience all symptoms shown.

1. Altuna M, et al. *Medicina (Kaunas)*. 2022;58(4):473. 2. Bonda DJ, et al. *Neurosurg Focus*. 2016;41(1):E10. 3. Geschwind MD. *Continuum (Minneap Minn)*. 2015;21 (6 Neuroinfectious Disease):1612-1638. 4. Thompson AGB, et al. *Brain*. 2013;136(Pt 4):1116-1127. 5. Appleby BS, Yobs DR. *Handb Clin Neurol*. 2018;153:399-408. 6. Ford L, et al. *Int Psychogeriatr*. 2019;31(8):1181-1190. 7. Sun Y, et al. *Clin Epidemiol*. 2020;12:1073-1081. 8. Chen C, et al. *PLoS One*. 2013;8(5):e62553.

Prompt Diagnosis and Treatments That Target the Underlying Pathophysiology Are Critical Unmet Needs for Patients With Prion Disease (PrD)[1-3]

up to 82% of patients are misdiagnosed on first assessment following symptom onset[3]

49% were previously diagnosed with cerebrovascular disease[4,a]

3.8 misdiagnoses on average before a PrD diagnosis is made[3]

Common Misdiagnoses[3-6,b]

- Viral encephalitis
- Depression
- Alzheimer's disease
- Dementia (unspecified)
- Paraneoplastic/ autoimmune disorders
- Peripheral vertigo
- Stroke

PrD Diagnosis Is Based on Clinical, Imaging, and/or Laboratory Findings[7,8]

A probable diagnosis is based upon the following[7,8,c]:
Neuropsychiatric disorder PLUS positive RT-QuIC in CSF or other tissues OR:
- Rapidly progressive dementia with ≥2 of 4 key clinical features[d]
- AND a positive result on at least one of the following laboratory tests:
  - a typical EEG (periodic sharp wave complexes) during an illness of any duration
  - a positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years
  - High signal in caudate/putamen on MRI brain scan or ≥2 cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging or fluid attenuated inversion recovery
- AND without routine investigations indicating an alternative diagnosis[7]

Key clinical features that may raise suspicion of PrD and prompt timely and appropriate workup include[9]

1. **Rapidly progressive cognitive impairment**
2. Myoclonus
3. Visual or cerebellar signs
4. Pyramidal/extrapyramidal signs

Probable genetic PrD can be diagnosed based on the presence of a progressive neuropsychiatric disorder and either a pathogenic *PRNP* variant or definite or probable diagnosis of PrD in a first-degree relative.[9]

Treatment and Management Approaches Focus on Minimizing Symptoms and Maintaining Favorable Quality of Life[2]

Currently, there is no cure for patients with PrD that can stop, reverse, or address accumulation of PrP^{Sc}, the underlying pathogenic cause of disease.[1,2,10]

Disease management for PrD includes both pharmacologic and nonpharmacologic interventions that focus on managing symptoms and improving quality of life.[2]

[a]In a retrospective observational study of adults with CJD.[4] [b]Not a complete list. [c]Guidelines presented are from the CDC and ECDC and are specific for sporadic CJD.[7,8] [d]Four key clinical features comprise myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, and akinetic mutism.[7,8]
CDC, Centers for Disease Control and Prevention; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; ECDC, European Centre for Disease Prevention and Control; EEG, electroencephalogram; MRI, magnetic resonance imaging; *PRNP*, prion protein gene; PrP^{Sc}, prion protein scrapie; RT-QuIC, real-time quaking-induced conversion.

1. Shim KH, et al. *Prion*. 2022;16(1):265-294. 2. Appleby BS, Yobs DR. *Handb Clin Neurol*. 2018;153:399-408. 3. Paterson RW, et al. *Arch Neurol*. 2012;69(12):1578-1582. 4. Brown D, et al. Poster presented at: Prion 2023; October 16-20, 2023; Faro, Portugal. 5. Weeks K, et al. Poster presented at: 2023 Annual Meeting of the American Academy of Neurology; April 22-27, 2023; Boston, MA. 6. Day GS, et al. Poster presented at: 2023 Annual Meeting of the American Academy of Neurology; April 22-27, 2023; Boston, MA. 7. Centers for Disease Control and Prevention. CJD Diagnostic Criteria. Updated May 13, 2024. Accessed November 21, 2024. https://www.cdc.gov/creutzfeldt-jakob/hcp/clinical-overview/diagnosis.html 8. European Centre for Disease Prevention and Control. EU case definition. Accessed November 21, 2024. https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/variant-creutzfeldt-jakob-disease/eu-case-definition/ 9. The National CJD Research & Surveillance Unit. Accessed November 21, 2024. https://www.cjd.ed.ac.uk/sites/default/files/criteria_0.pdf 10. Altuna M, et al. *Medicina (Kaunas)*. 2022;58(4):473.

Multiple System Atrophy (MSA) Is a Progressive, Fatal, Rare Neurodegenerative Disease Caused by Misfolding and Accumulation of α-Synuclein[1,2]

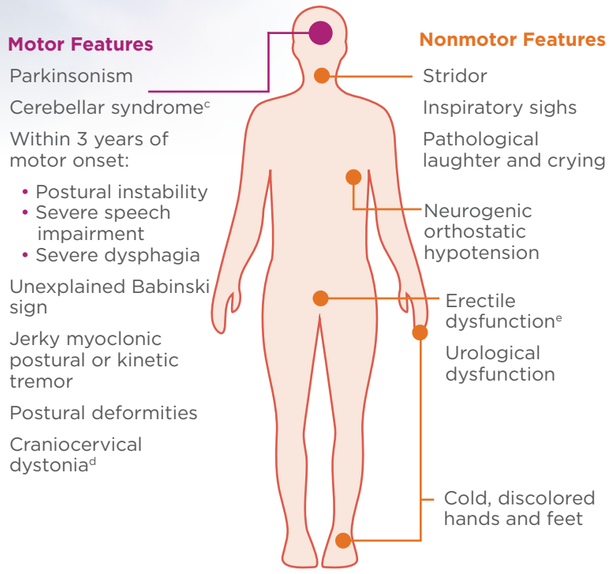
MSA is an adult-onset α-synucleinopathy with a diverse pathological spread of α-synuclein and varied clinical presentation.[2-4] Among synucleinopathies, MSA is associated with the lowest survival rates.[5,a]

MSA is characterized by and broadly sorted into two categories, parkinsonism (MSA-P) and cerebellar (MSA-C), although the majority of patients have a mixed/autonomic presentation.[2,6]

Diagnostic guidelines denote key red flag symptoms of MSA for clinicians to be aware of that can help determine which α-synucleinopathy a patient has (**Figure 1**).[4]

MSA has an average age of onset of 63 years and a median survival of 9.8 years.[7]

Figure 1: Red Flag Symptoms of MSA[4,b]



MSA Is Associated With "Prion-Like" α-Synuclein Accumulation and Propagation[3,4,8]

Figure 2: Pathological Spreading of α-Synuclein Neuronal Inclusions in MSA[9]

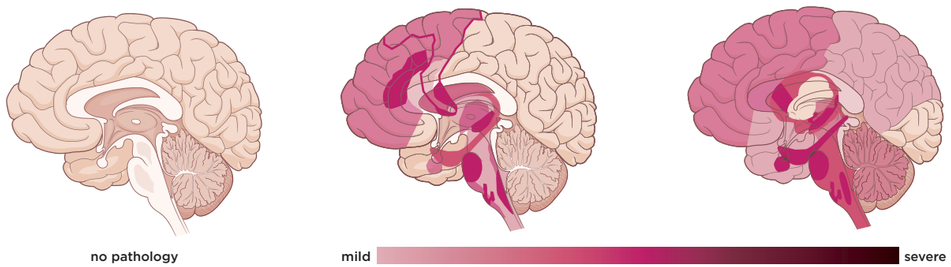


Figure adapted from Halliday GM. *Brain.* 2015;138(Pt 8):2116-2119.

Alpha-synuclein, encoded by *SNCA*, forms aggregates and glial cytoplasmic inclusions.[3,10,11]

Increased *SNCA* copy number variations lead to greater α-synuclein inclusions in people with MSA that correlate with earlier onset of disease.[11-13]

MSA is a progressive disease in which clinical symptoms and α-synuclein pathology both increase in severity as the disease progresses.[9,14]

[a]Among people with clinically diagnosed synucleinopathies with parkinsonism.[5] [b]Essential clinical features for all patients are sporadicity, progressive course, and adult onset (>30 years).[4] [c]Defined as at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features.[4] [d]Induced or exacerbated by L-dopa in the absence of limb dyskinesia.[4] [e]In males <60 years of age.[4]
SNCA, synuclein alpha gene.
1. Koga S, et al. *Mol Neurodegener*. 2021;16(1):83. 2. Wenning GK, et al. *Lancet Neurol.* 2013;12(3):264-274. 3. Chelban V, et al. *J Neurol.* 2020;267(9):2754-2770. 4. Wenning GK, et al. *Mov Disord*. 2022;37(6):1131-1148. 5. Savica R, et al. *JAMA Neurol.* 2017;74(7):839-846. 6. Figueroa JJ, et al. *Mov Disord.* 2014;29(9):1151-1157. 7. Low PA, et al. *Lancet Neurol*. 2015;14(7):710-719. 8. Woerman AL, et al. *Cold Spring Harb Perspect Med*. 2018;8(7):a024588. 9. Halliday GM. *Brain.* 2015;138(Pt 8):2116-2119. 10. Yamasaki TR, et al. *J Biol Chem.* 2019;294(3):1045-1058. 11. Perez-Rodriguez D, et al. *Acta Neuropathol Commun.* 2019;7(1):219. 12. Tseng FS, et al. *J Transl Med.* 2023;21(1):104. 13. Garcia-Segura ME, et al. *Mov Disord.* 2023;38(2):338-342. 14. Reddy K, Dieriks BV. *Mol Neurodegener*. 2022;17(1):77.

Prompt Diagnosis and Treatments That Target the Underlying Pathophysiology Are Critical Unmet Needs in Multiple System Atrophy (MSA)[1-3]

MSA is frequently misdiagnosed because of its varied clinical manifestations, notably at the onset of disease, with up to 38% of patients not receiving an accurate diagnosis of MSA.[2,4]

Diagnosis of MSA is delayed by an average of 3.7 years.[5]

Possible prodromal MSA is a diagnostic type in which patients exhibit clinical signs or symptoms but have not yet reached the threshold for clinical diagnosis (**Table 1**).[1]

Table 1: Clinical Characteristics of Premortem Diagnosis of MSA[1,6,a]

	Core Clinical Features		MRI	Supportive Clinical Features
Clinically Established	**Autonomic dysfunction (defined as at least one of the following):** • Unexplained voiding difficulties with postvoid urinary residual volume >100 mL • Unexplained urinary urge incontinence • Neurogenic OH[b] within 3 minutes of standing or head-up tilt test	**AND at least one:** • Poorly L-dopa-responsive parkinsonism • Cerebellar syndrome[c]	Yes	≥2
Clinically Probable	**At least two of the following:** **1.** Autonomic dysfunction defined as (at least one of): • Unexplained voiding difficulties with postvoid urinary residual volume • Unexplained urinary urge incontinence • Neurogenic OH[b] within 10 minutes of standing or head-up tilt test	**2.** Parkinsonism **3.** Cerebellar syndrome[c]	Not Required	≥1[d]
Possible Prodromal	**At least one of the following:** • Rapid eye movement sleep behavior disorder • Neurogenic OH[b] within 10 minutes of standing or head-up tilt test • Urogenital failure	**AND at least one:** • Subtle parkinsonian signs • Subtle cerebellar signs	N/A	N/A

Current Standard-of-Care Treatment for MSA Is to Minimize Symptoms[2]

As MSA progresses, patients are at an increased risk of falls, wheelchair dependency, loss of coherent speech, and feeding by nasogastric tube or gastrostomy tube.[7]

Medications to manage MSA are focused on controlling symptoms, including for parkinsonism, autonomic lability, bladder and bowel dysfunction, and mood problems.[2,3]

Current options do not prevent or reduce disease progression, presenting a need for effective therapeutic agents.[3]

[a]Essential clinical features for all patients are sporadicity, progressive course, and adult onset (>30 years).[1] [b]≥20/10 mm Hg blood pressure drop.[1] [c]Defined as at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features.[1] [d]Excluding erectile dysfunction as an isolated feature.[1]
L-dopa, levodopa; MRI, magnetic resonance imaging; N/A, not applicable; OH, orthostatic hypotension.
1. Wenning GK, et al. *Mov Disord.* 2022;37(6):1131-1148. 2. Chelban V, et al. *J Neurol.* 2020;267(9):2754-2770. 3. Reddy K, Dieriks BV. *Mol Neurodegener*. 2022;17(1):77. 4. Koga S, et al. *Neurology.* 2015;85(5):404-412. 5. Foubert-Samier A, et al. *Neurobiol Dis*. 2020;139:104813. 6. Goh YY, et al. *Pract Neurol*. 2023;23(3):208-221. 7. Wenning GK, et al. *Lancet Neurol*. 2013;12(3):264-274.

People With Down Syndrome (DS) Are at High Genetic Risk of Developing Alzheimer's Disease (AD)[1-3]

Alzheimer's disease, a neurodegenerative condition, is the most common form of dementia and one of the leading causes of disability and mortality.[3-5] The greatest risk factor for AD is aging; as the global population ages, the prevalence of AD increases.[5,6]

AD occurs in two predominant types[7]

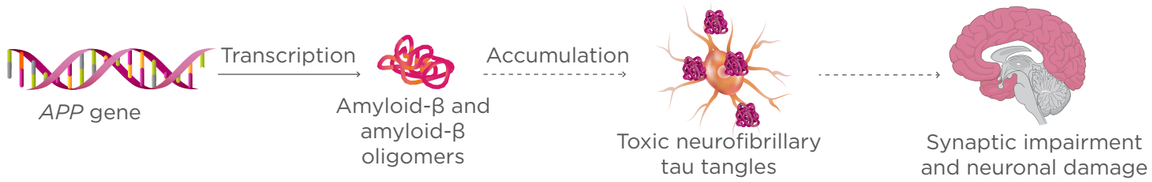
1. **Sporadic/late-onset (SAD)**
2. **Early-onset familial (EO-FAD)**

Genes associated with EO-FAD[7,8]

APP *PSEN1* *PSEN2*

EO-FAD accounts for approximately 5% to 6% of AD cases, but genetics influence susceptibility in approximately half of SAD cases[9,10]

Figure 1: The Amyloid Cascade Hypothesis Explains the Role of *APP* in AD Progression[7]



Almost all adults with DS have AD neuropathology by the age of 40 due to triplication of *APP*, with variability in the prevalence of dementia[1,2]

Down syndrome is caused by the presence of all or part of **a third copy of chromosome 21.**[11]

The triplication of *APP*, on chromosome 21, is both sufficient and necessary to produce **early onset AD in people with DS.**[1]

Biomarker changes are hypothesized to occur **years before any clinical symptoms present (Figure 2).**[1,2]

Baseline assessment of cognitive and adaptive functioning at 30 years of age is recommended in individuals with DS to assist AD monitoring and diagnosis.[12]

Figure 2: Timeline to Symptomatic AD-DS[13]

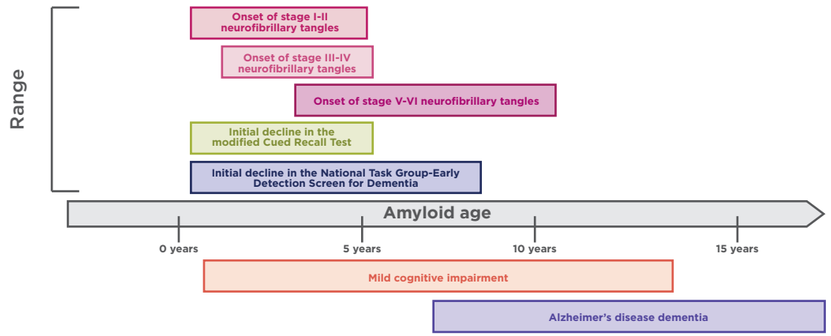


Figure adapted from Schworer EK, et al. *Lancet Neurol.* 2024;23(12):1214-1224.

APP, amyloid-β precursor protein gene; *PSEN1*, presenilin 1 gene; *PSEN2*, presenilin 2 gene.

1. Fortea J, et al. *Lancet Neurol*. 2021;20(11):930-942. 2. Lott IT, Head E. *Nat Rev Neurol*. 2019;15(3):135-147. 3. National Institute on Aging. Alzheimer's disease fact sheet. https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet/ 4. Lei P, et al. *J Biol Chem*. 2021;296:100105. 5. Wang X, et al. *J Alzheimers Dis*. 2019;68(1):33-38. 6. National Institute on Aging. What causes Alzheimer's disease? Accessed February 3, 2025. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-causes-alzheimers-disease/ 7. Selkoe DJ, Hardy J. *EMBO Mol Med*. 2016;8(6): 595-608. 8. Jin SC, et al. *Alzheimers Res Ther*. 2012;4(4):34. 9. Mendez MF. *Continuum (Minneap Minn)*. 2019;25(1):34-51. 10. Pimenova AA, et al. *Biol Psychiatry*. 2018;83(4):300-310. 11. Akhtar F, Bokhari SRA. *StatPearls*. Treasure Island (FL): StatPearls Publishing; January 2024. 12. Antonarakis SE, et al. *Nat Rev Dis Primers*. 2020;6(1):9. 13. Schworer EK, et al. *Lancet Neurol*. 2024;23(12):1214-1224.

Prompt Diagnosis and Interventions Targeting the Pathophysiology of Alzheimer's Disease in Down Syndrome (DS-AD) Are Critical Unmet Needs[1]

The average life expectancy for people with DS is now approximately 60 years and continues to increase, **leading to a high risk of dementia as they age (Figure 3).**[2,3]

DS-AD is considered a genetic form of AD, placing any asymptomatic individual with DS at stage 0 on the AD continuum.[4]

>90%

estimated lifetime risk of dementia in people with DS[1]

Unmet Quality-of-Life Needs Expressed by People With DS and Caregivers[5]

Only 7/39 studies in a systematic review reported adults with DS had a good quality of life.

- Full independence
- Desire for relationships
- Community involvement
- Educational services and programs
- Ability to communicate
- Right to privacy
- Same respect/quality as nondisabled counterparts
- Facilities to meet the needs of people with DS-AD as parent caregivers age

Decline in activities of daily living is seen in people with early prodromal DS-AD, possibly because the skills involved are more cognitively demanding in this population.[1]

Variability of baseline cognitive function in DS makes the diagnosis of DS-AD challenging.[1,4]

- Consultations for cognitive decline are often done only when activities of daily living are substantially affected or when behavioral problems emerge
- The diagnosis of DS-AD uses the consensus approach for diagnosis typically used for SAD as a guideline, and is dependent on the clinical examination, neuropsychological tests, and biomarkers

People with DS have not been included in clinical trials for AD medications, leading to unknown safety in this population and lack of recommendations.[1,6]

Currently, there is insufficient data on the use of FDA-approved treatment options for people with DS-AD, despite it being the leading cause of death in the DS population.[1]

FDA, US Food and Drug Administration; SAD, sporadic Alzheimer's disease.

1. Fortea J, et al. *Lancet Neurol*. 2021;20(11):930-942. 2. Iulita MF, et al. *JAMA Netw Open*. 2022;5(5):e2212910. 3. Akhtar F, Bokhari SRA. *StatPearls*. Treasure Island (FL): StatPearls Publishing; January 2024. 4. Jack CR Jr, et al. *Nat Med*. 2024 Aug;30(8):2121-2124. 5. Ijezie OA, et al. *PLoS One*. 2023;18(5):e0280014. 6. Rafii MS, Fortea J. *JAMA*. 2023;330(22):2157-2158.

Fused in Sarcoma Amyotrophic Lateral Sclerosis (FUS-ALS) Is One of the Most Severe and Aggressive Types of Genetic ALS[1]

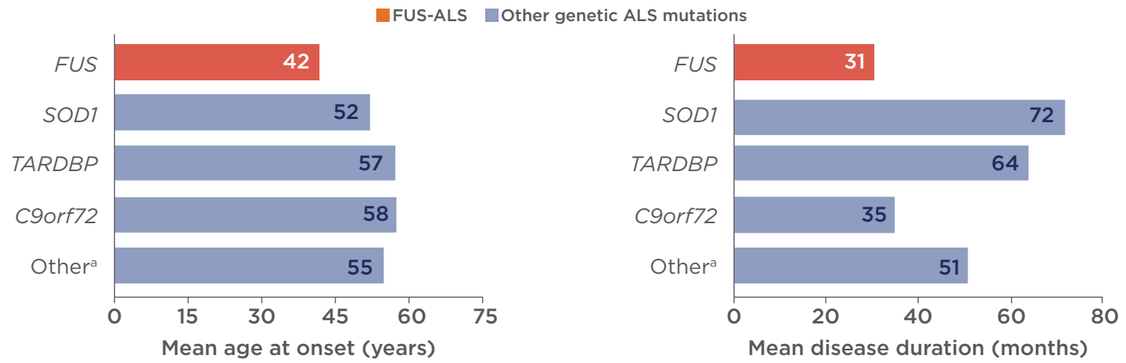
ALS is a neurodegenerative disorder that occurs from loss of upper and lower neurons, leading to progressive paralysis and death.[1]

FUS variants are 1 of the 5 most common causes of genetic ALS[2]

Genetic ALS: ALS due to a genetic variant in patients with and without a family history of the disease makes up >10% of all cases of ALS.[2]

People living with FUS-ALS are generally younger at disease onset and have a shorter duration of survival than people living with other forms of genetic ALS.[1,3,4] More than 60% of people living with FUS-ALS are <45 years of age.[5] In addition to FUS-ALS being severe and aggressive, patients may also present with frontotemporal dementia.[1,6] The mean survival of patients with FUS-ALS is 31 (±25, standard deviation) months following symptom onset (**Figure 1**).[1]

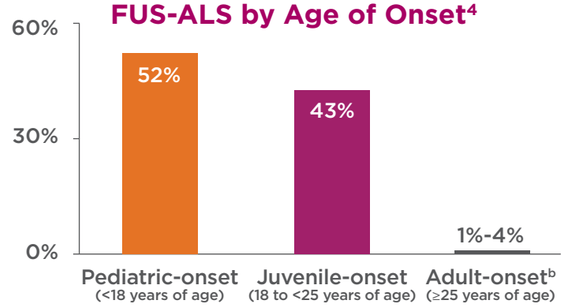
Figure 1: Age of Onset and Disease Duration by Known Variants Associated With Genetic ALS[1]



The majority of people living with FUS-ALS have onset in adolescence. **While juvenile- and pediatric-onset ALS are rare, *FUS* variants are the leading cause of these cases (Figure 2).**[4,7] In patients with pediatric-onset FUS-ALS, disease onset generally occurs during adolescence.[4] Patients with FUS-ALS have a mean age of onset of 42 years.[1]

The type of *FUS* variant can affect the severity and rate of disease progression, as well as the age of disease onset.[8]

Figure 2: Percentage of People Living With ALS Diagnosed With FUS-ALS by Age of Onset[4]



[a]"Other" is an average of less prevalent mutations that are known to cause genetic ALS. Mutations include *CCNF*, *UBQLN2*, *KIF5A*, *ANG*, *PFN1*, *ATXN2*, *VAPB*, *OPTN*, *SQSTM1*, *NEK1*, *SETX*, *TBK1*, *TUBA4A*, *FIG4*, *MATR3*, *VCP*, *SPG11*, *hnRNPA1*, and *ALS2*.[1] [b]FUS-ALS accounts for 1% of ALS cases with no known family history and 4% of cases with a known family history.[4]

ALS, amyotrophic lateral sclerosis; *FUS*, fused in sarcoma gene.

1. Connolly O, et al. *J Pers Med.* 2020;10(3):58. 2. Salmon K, et al. *Brain*. 2022;145(4):1207-1210. 3. Sharma A, et al. *Nat Commun.* 2016;7:10465. 4. Picher-Martel V, et al. *J Child Neurol.* 2020;35(8):556-562. 5. Shang Y, Huang EJ. *Brain Res.* 2016;1647:65-78. 6. Ling SC, et al. *Neuron*. 2013;79(3):416-438. 7. Grassano M, et al. *Neurol Genet*. 2022;8(5):e200011. 8. Naumann M, et al. *Ann Clin Transl Neurol.* 2019;6(12):2384-2394.

Early Diagnosis and Treatment Are Critical for People With Fused in Sarcoma Amyotrophic Lateral Sclerosis (FUS-ALS)[1]

A diagnosis of FUS-ALS can be delayed from months to years because of variability in clinical presentation, lack of biomarkers, and paucity of genetic testing[2,3]

Consensus guidelines published by the American Neurological Association regarding ALS genetic testing and counseling recommend that all persons with ALS be offered genetic testing with an ALS gene panel that includes screening for *FUS* variants.[4]

A diagnosis of ALS may be delayed by a median of ~9 to 24 months.[3]

ALS may be misdiagnosed in up to 68% of cases because of the variability in clinical presentation and lack of biomarkers.[3,5]

Genetic testing rates in ALS often don't reflect the true burden of genetic variants in ALS.[6]

A genetic test is required to confirm a diagnosis of FUS-ALS because the initial symptoms are nonspecific.[2,3]

Genetic testing may shorten the time it takes to diagnose, provide insight into the type of ALS, inform treatment choices, and provide opportunities for people to participate in research or clinical trials.[1,7-9]

Earlier care and treatment by a collaborative multidisciplinary team is associated with a modest improvement in quality of life and survival[10]

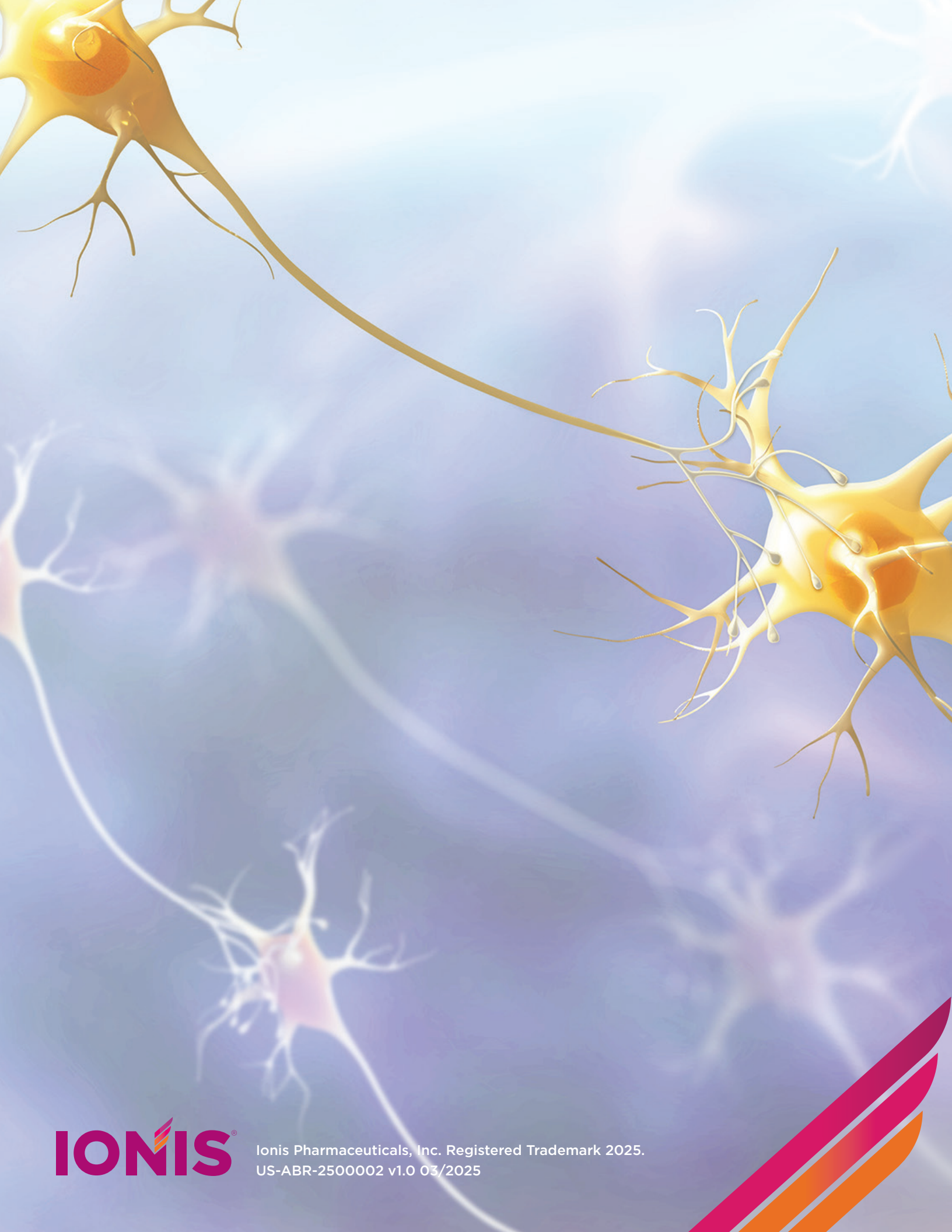
People with FUS-ALS should have their care managed by a collaborative multidisciplinary team of healthcare professionals, which may include[2,10]

- Neurologists
- Nurses
- Pulmonologists
- Speech therapists
- Physical and occupational therapists
- Respiratory therapists
- Nutritionists/dietitians
- Psychologists
- Social workers
- Genetic counselors

None of the FDA–approved treatments available for ALS specifically target FUS or its associated underlying disease pathology.[11-16]

ALS, amyotrophic lateral sclerosis; FDA, US Food and Drug Administration; *FUS*, fused in sarcoma gene.

1. Salmon K, et al. *Brain*. 2022;145(4):1207-1210. 2. Siddique N, Siddique T. In: *GeneReviews®*. University of Washington, Seattle; 1993-2021. March 23, 2001. Updated September 28, 2023. Accessed November 21, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1450/ 3. Longinetti E, Fang F. *Curr Opin Neurol*. 2019;32(5):771-776. 4. Roggenbuck J, et al; ALS Genetic Testing and Counseling Guidelines Expert Panel. *Ann Clin Transl Neurol*. 2023;10(11):2074-2091. 5. Richards D, et al. *J Neurol Sci*. 2020;417:117054. 6. Vajda A, et al. *Neurology*. 2017;88(10):991-999. 7. Zhang L, Hong H. *Pharmaceutics*. 2015;7(4):542-553. 8. Roggenbuck J, et al. *Genet Med*. 2017;19(3):267-274. 9. Klein CJ, Foroud TM. *Mayo Clin Proc*. 2017;92(2):292-305. 10. Chen JJ. *Am J Manag Care*. 2020;26(9 suppl):S191-S197. 11. Chia R, et al. *Lancet Neurol*. 2018;17(1):94-102. 12. Hergesheimer R, et al. *Expert Opin Pharmacother*. 2020;21(9):1103-1110. 13. FDA approves treatment of amyotrophic lateral sclerosis associated with a mutation in the Sod1 gene. US Food and Drug Administration. April 25, 2023. Accessed November 21, 2024. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-amyotrophic-lateral-sclerosis-associated-mutation-sod1-gene/ 14. Yadav A, et al. *J Neuroinflammation*. 2021;18(1):238. 15. Kusaczuk M. *Cells*. 2019;8(12):1471. 16. Qalsody. Package insert. Biogen MA Inc. Updated April 2023. Accessed November 21, 2024. https://www.biogencdn.com/us/pdfs/qalsody-prescribing-information.pdf



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