Motor Neuron Disease

A lecture from the Neuromuscular Review Course

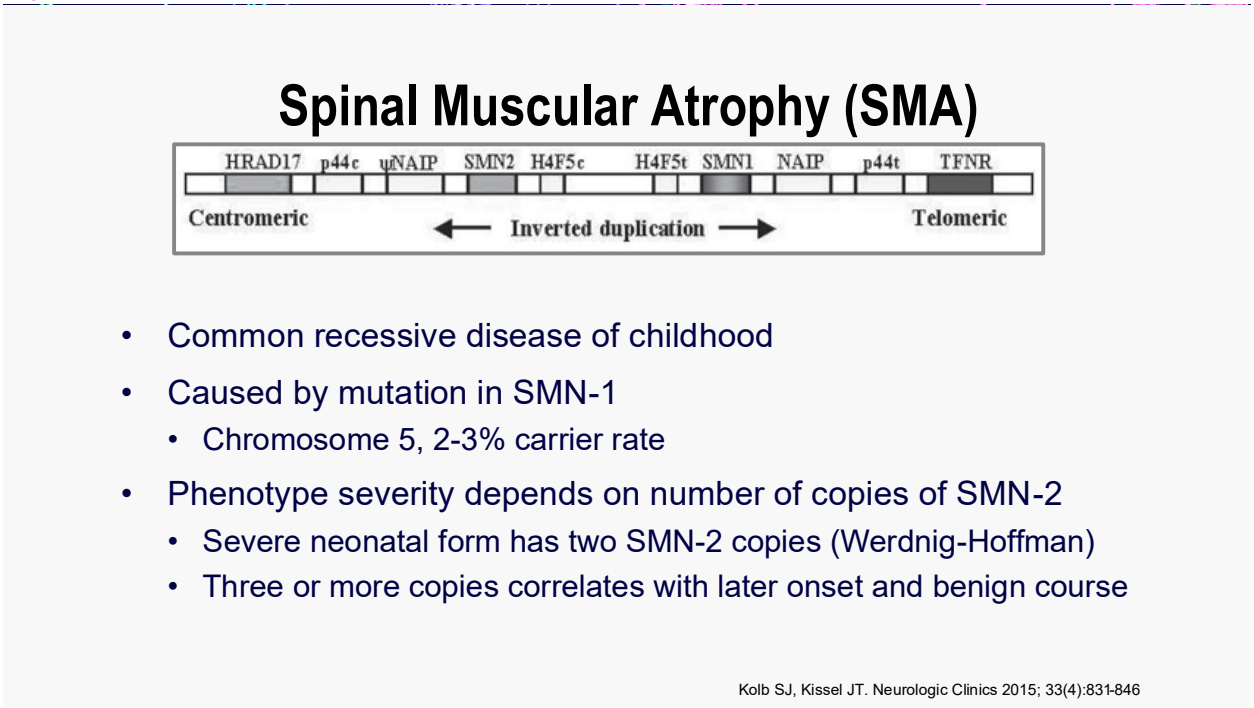
Jonathan S. Katz, MD[1]
Todd D. Levine, MD[2]
David S. Saperstein, MD[3]
Mamatha Pasnoor, MD[4]
Mazen M. Dimachkie, MD[5]
Richard J. Barohn, MD[6]

[1]California Pacific Medical Center
[2]HonorHealth Neurology - Bob Bové Neuroscience Institute
[3]Center for Complex Neurology, EDS and POTS Phoenix Arizona
[4]University of Kansas School of Medicine, Kansas City Kansas
[5]University of Kansas School of Medicine, Kansas City Kansas
[6]University of Missouri School of Medicine, Columbia Missouri

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive, predominantly childhood disease due to a mutation in the SMN-1 gene on chromosome 5.

Figure 1

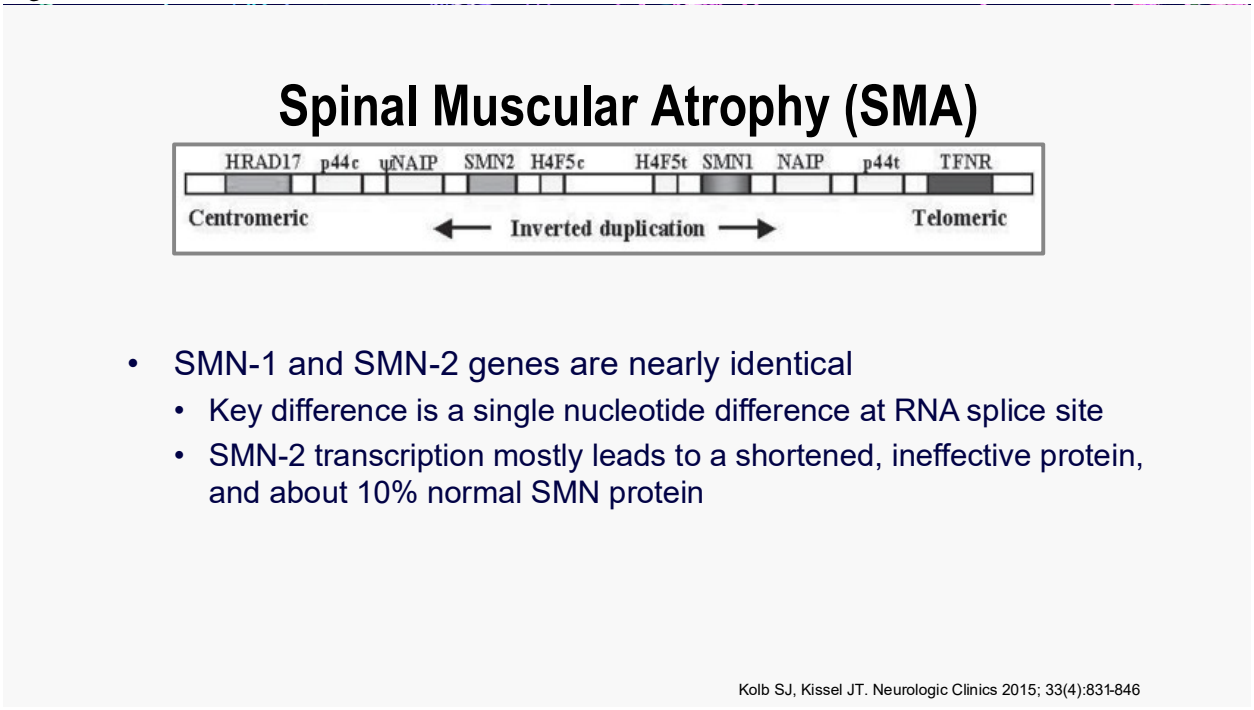


The SMN-1 gene is located in the inverted region of chromosome 5 and has a carrier rate of 2–3%. Before the gene was identified, the diagnosis was clinical, with supportive information from electromyography (EMG) and muscle biopsy. Infants were described as “floppy babies” who would not live through the first year of life. Historically, the infantile form of SMA was referred to as Werdnig-Hoffman disease. Later childhood and adult forms were also identified in the pre-genetic era.

The phenotype for most SMA patients, whether infants, children, or adults, is symmetric proximal and distal pure motor weakness without sensory loss, which corresponds to the neuropathic pattern 7 (NP7) phenotype (Barohn et al., 2024, 2025).

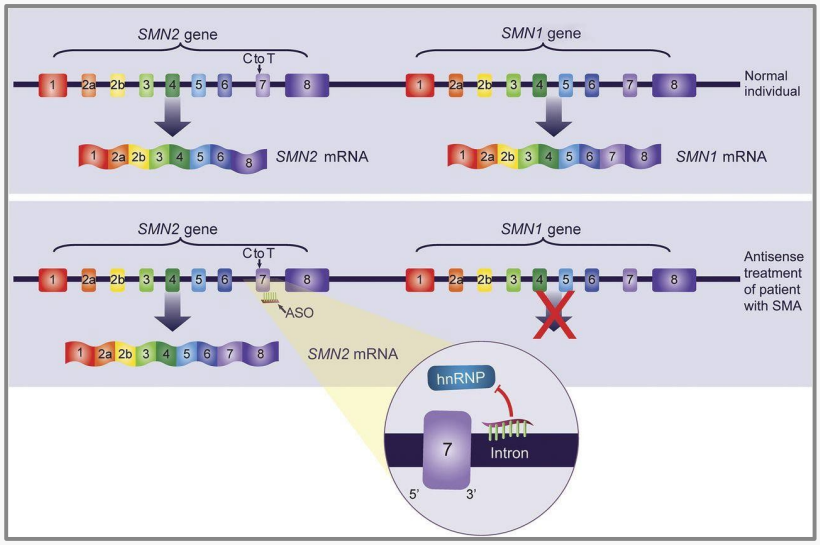
When the gene was discovered in 1995, two genes encoding the same protein were identified in the same region: SMN-1 and SMN-2 (Lefebvre et al., 1995). These genes differ by a single nucleotide at an RNA splice site. As a result, the SMN-2 gene produces a shortened and largely ineffective protein with only minimal activity.

Figure 2



All patients with autosomal recessive SMA have a mutation in the SMN-1 gene, but patients may have multiple copies of the SMN-2 gene. The severity of the phenotype depends on the number of SMN-2 copies present. Fewer copies (1 or 2) lead to a severe, usually infantile phenotype. Patients with 3 to 5 copies of the SMN-2 gene have a less severe phenotype because they produce more of the ineffective protein, which delays or mitigates clinical severity.

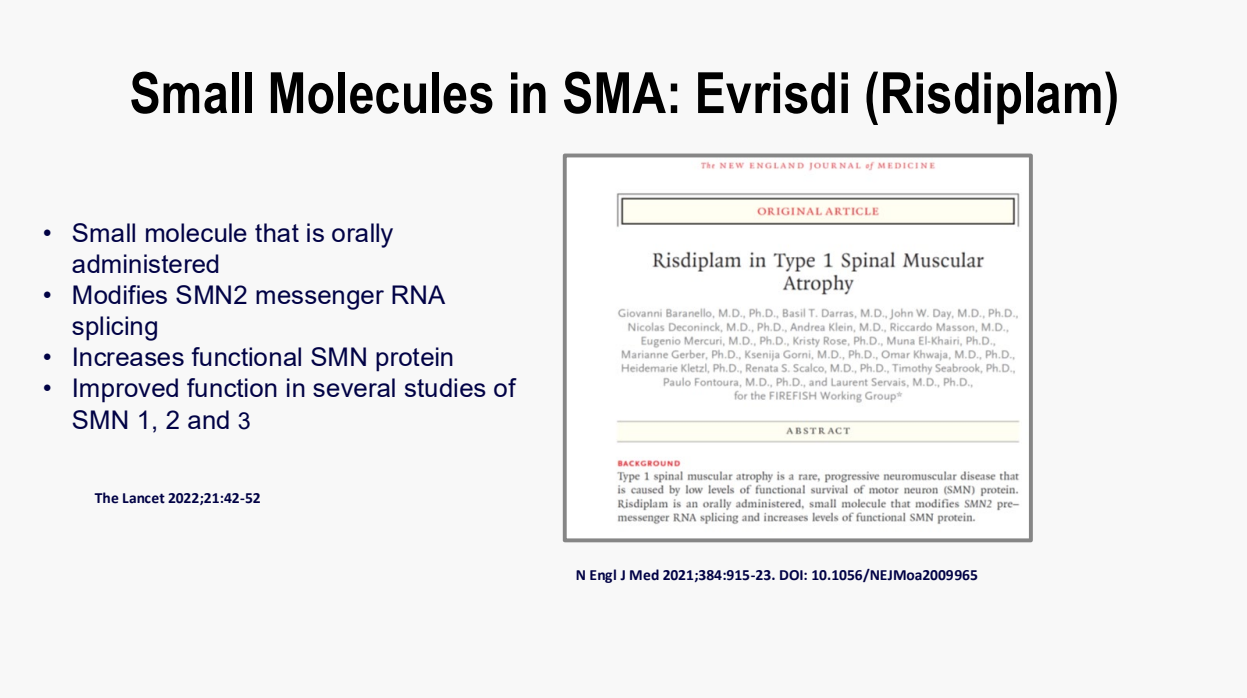
Figure 3



https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm

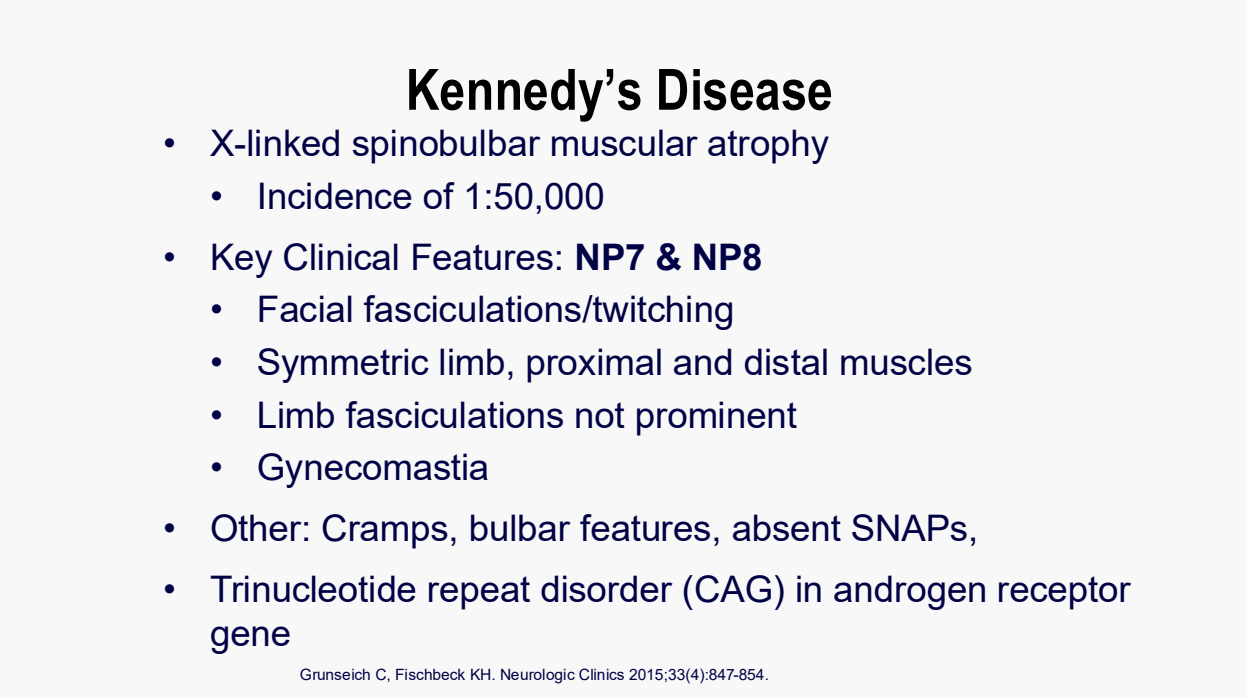
The first breakthrough therapy for SMA was an antisense oligonucleotide drug called nusinersen (Finkel et al., 2016). Nusinersen promotes increased protein production by modifying SMN-2 gene splicing, increasing functional SMN protein levels. This therapy works by converting a severe phenotype into a more benign one.

Figure 4



Nusinersen is administered intrathecally. Subsequently, an oral therapy that modifies SMN-2 messenger RNA and increases functional SMN protein production was FDA-approved. This drug is called evrysdi (Risdiplam). Antisense therapy was followed by gene replacement therapy, onasemnogene abeparvovec (Zolgensma), which was approved by the FDA in 2019 (Mendell et al., 2017).

Kennedy's Disease
Figure 5

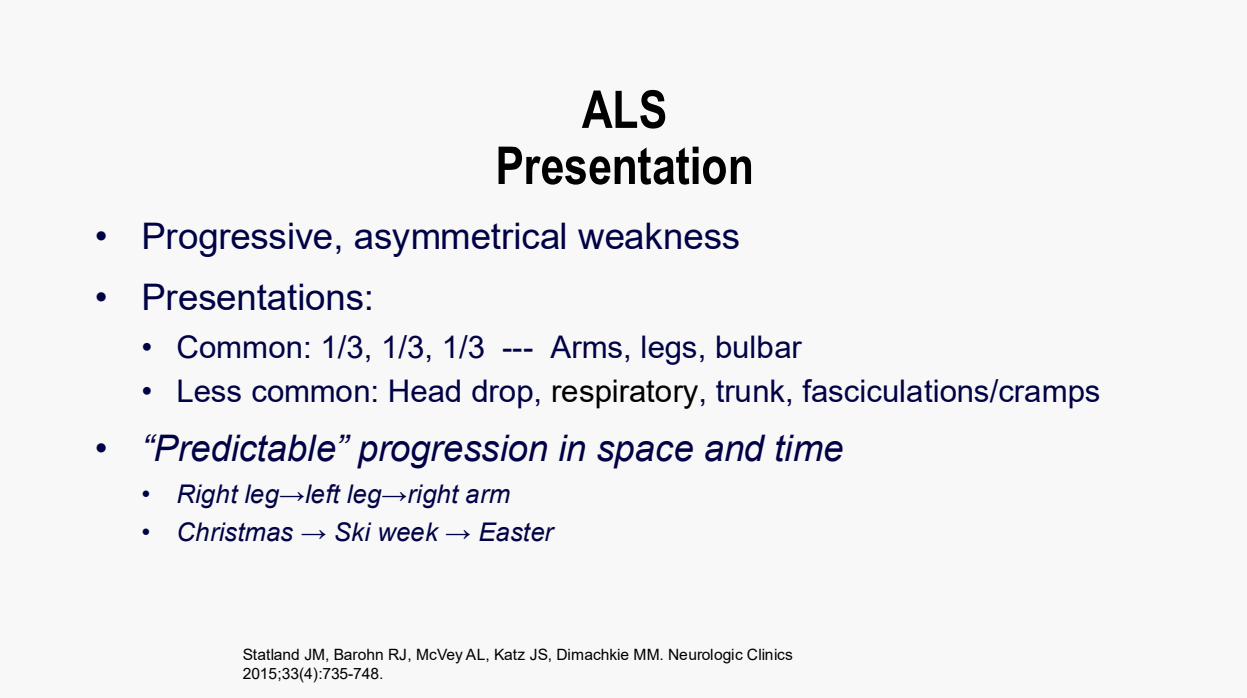


Kennedy's disease is an adult-onset spinal muscular atrophy that affects only men because the affected gene is located on the X chromosome (Grunseich & Fischbeck, 2015; La Spada et al., 1991). It is also referred to as spinal bulbar muscular atrophy, although the severity of bulbar involvement is variable. Kennedy's disease is rare, with an estimated prevalence of 1 in 50,000. It presents with proximal and distal pure motor weakness along with some degree of bulbar involvement, usually consisting of tongue or facial muscle atrophy, fasciculations, and dysarthria. Because of the combination of extremity and bulbar involvement, this condition falls into both the NP7 and NP8 categories.

Kennedy's disease is slowly progressive. Patients often do not know the exact date of onset owing to the extremely insidious progression. They typically present to clinic after gradual worsening begins to affect daily activities and function. The disease is frequently diagnosed when a patient presents with symmetric extremity weakness and additional features such as perioral muscle twitching or gynecomastia is identified. This constellation of findings should prompt the clinician to order genetic testing for Kennedy's disease.

These patients may also complain of muscle cramps and symptoms of laryngospasm. Interestingly, although they have no sensory symptoms or signs, they can have absent sensory nerve action potentials (SNAPs). The underlying mutation is an increased number of trinucleotide repeats in the androgen receptor gene. At this time there is no FDA-approved therapy for Kennedy's disease.

Amyotrophic Lateral Sclerosis
Diagnosis of ALS
Figure 6



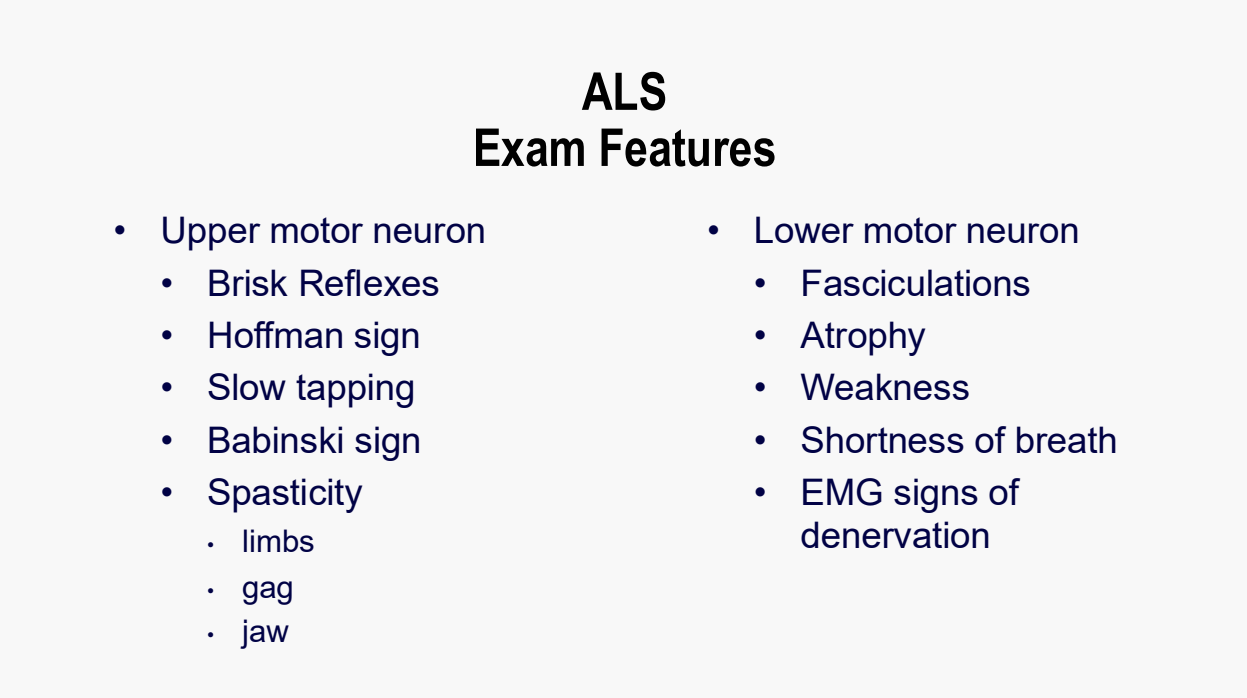
Amyotrophic lateral sclerosis (ALS) is usually an easy diagnosis for a neurologist to make clinically, based on history and exam. Diagnostic consideration frequently begins while listening to the history of progressive weakness that spreads in a predictable pattern. The approximate date and location of onset are the first two key questions to ask. In general, approximately one-third of cases begin in the arms, one-third in the legs, and one-third in the bulbar region. A smaller percentage of cases presents with head drop, respiratory symptoms and signs, or trunk weakness. Only rarely do patients initially present with fasciculations.

The spread of ALS is characteristically predictable. For example, if symptoms begin in the right leg, weakness will almost always appear next in the left leg. When such a case spreads to the arms, the right arm will usually be affected first. Recognizing this predictable pattern of progression increases diagnostic suspicion, and the neurologic examination should be directed toward identifying weakness in regions suggested by the history.

The primary lower motor neuron signs include weakness, atrophy, and fasciculations (Figure 7). Fasciculations may be the most important diagnostic clue, and patients should be undressed and examined in a hospital gown to allow inspection of proximal muscles. Fasciculations frequently occur in proximal arm and leg muscles and may be missed without appropriate examination. Fasciculations are present in nearly all cases of ALS, but their detection requires focused observation.

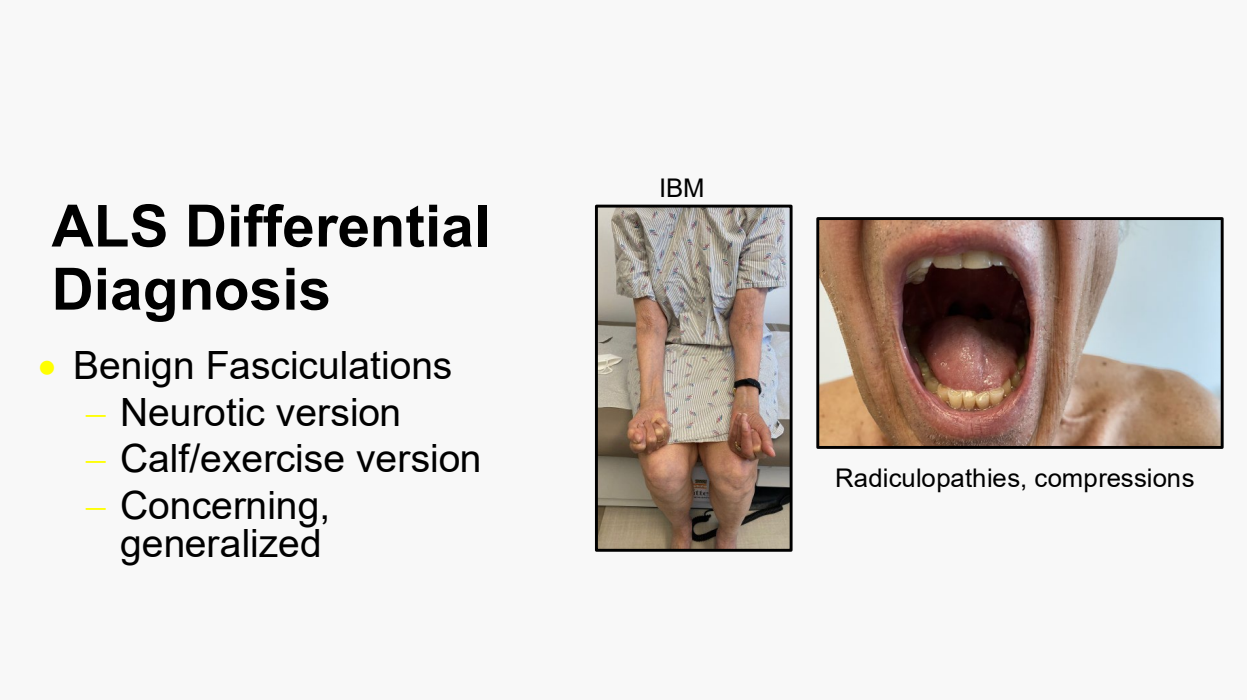
In ALS, upper motor neuron signs are often more subtle than those seen in stroke, multiple sclerosis, or other disorders with predominant corticospinal tract involvement.

Figure 7



Increased tone and Babinski signs are usually absent early in the disease and may never develop in some patients. In contrast, subtle and typically asymmetric findings—such as Hoffman signs, crossed adductor responses or other examples of reflex spread—are often present, making it important for the clinician to actively search for these signs. Asymmetric slowing of finger or foot tapping are other useful indicators of upper or lower motor neuron involvement. Side-to-side comparison of limbs is essential to identify subtle differences.

Differential Diagnosis
Figure 8



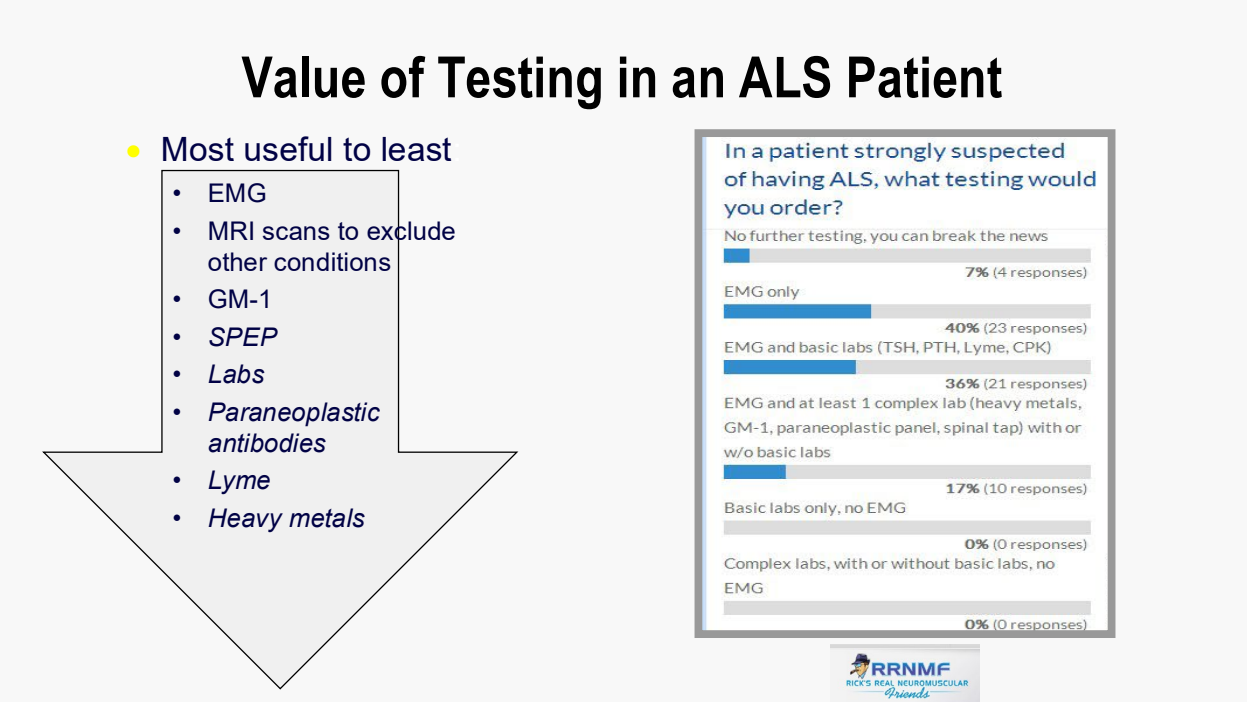
Benign fasciculations are an extremely common complaint and can cause significant anxiety. We recognize three distinct benign fasciculations syndromes. The first involves patients who experience random twitches in facial or extremity muscles. They often become anxious after searching the internet. In these cases, it is important to address anxiety and reassure patients that they do not have an underlying neuromuscular disease. The second category includes patients who experience fasciculations after exercise, most commonly affecting the calf muscles. The third category includes patients with intense, generalized fasciculations that resemble those seen in ALS, but who lack other features of the disease, including weakness or upper motor neuron signs. Although a small number of these patients may later develop ALS, most do not. In such cases, alternative diagnoses such as Isaacs' syndrome should be considered, though a specific cause is often not identified. These patients may require follow-up examinations every few months for a year or longer to ensure that ALS is not evolving.

One condition that can present with focal pure motor weakness and fasciculations is radiation-induced neuropathy. This may involve limb muscles or the tongue. A history of cancer treated with radiation therapy, lack of progression to other regions, and absence of upper motor neuron signs distinguish this condition from ALS.

Myelopathy due to spinal cord compression or other causes can also rarely produce fasciculations that may be mistaken for ALS. Conversely, with limb-onset ALS, patients are often referred to a spine surgeon before seeing a neurologist. As a result, many undergo multiple MRI scans and sometimes surgical

procedures before the correct diagnosis is made. In these cases, symptoms typically progress following surgery, indicating the need to reconsider the original diagnosis.

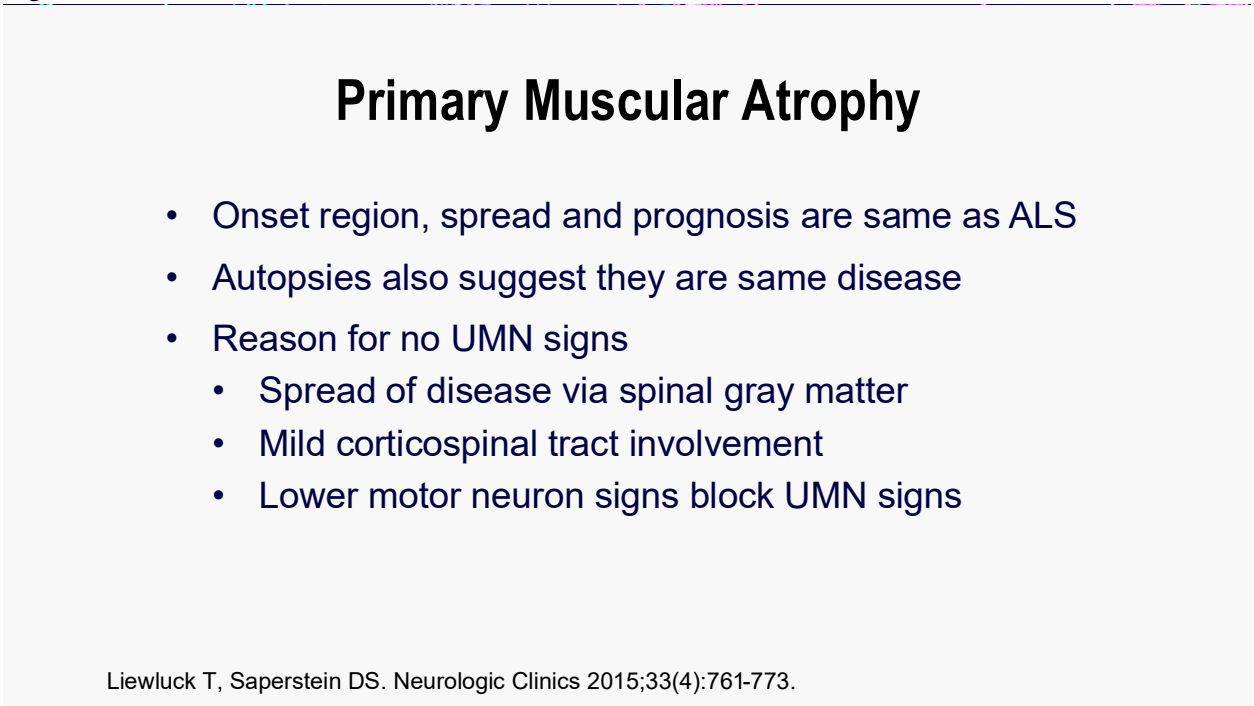
The Value of Testing in ALS
Figure 9



In our experience, clinicians can often be confident in the diagnosis of ALS without electromyography (EMG); however, this rarely occurs in current neurology practice. Laboratory testing is likely to have limited value once the physician recognizes ALS from the history and physical examination. Many patients with ALS have a mildly elevated creatine kinase (CK), but this is non-specific. We believe there is an over-reliance on EMG to make the diagnosis of ALS. EMG is done in most patients during the evaluation, but the diagnosis should be clear from the history and physical examination. In a small number of cases, demonstrating denervation in limb muscles that are not weak can help the clinician increase their diagnostic confidence about the diagnosis of ALS. If weakness in a muscle is detected on examination, demonstrating denervation potentials—fibrillations and often fasciculations—actually adds little to the diagnosis. On the other hand, EMG can also be useful for identifying denervation in thoracic paraspinous muscles, which cannot be examined for weakness in the same way as limb muscles. Very few other conditions produce denervation in thoracic paraspinous muscles.

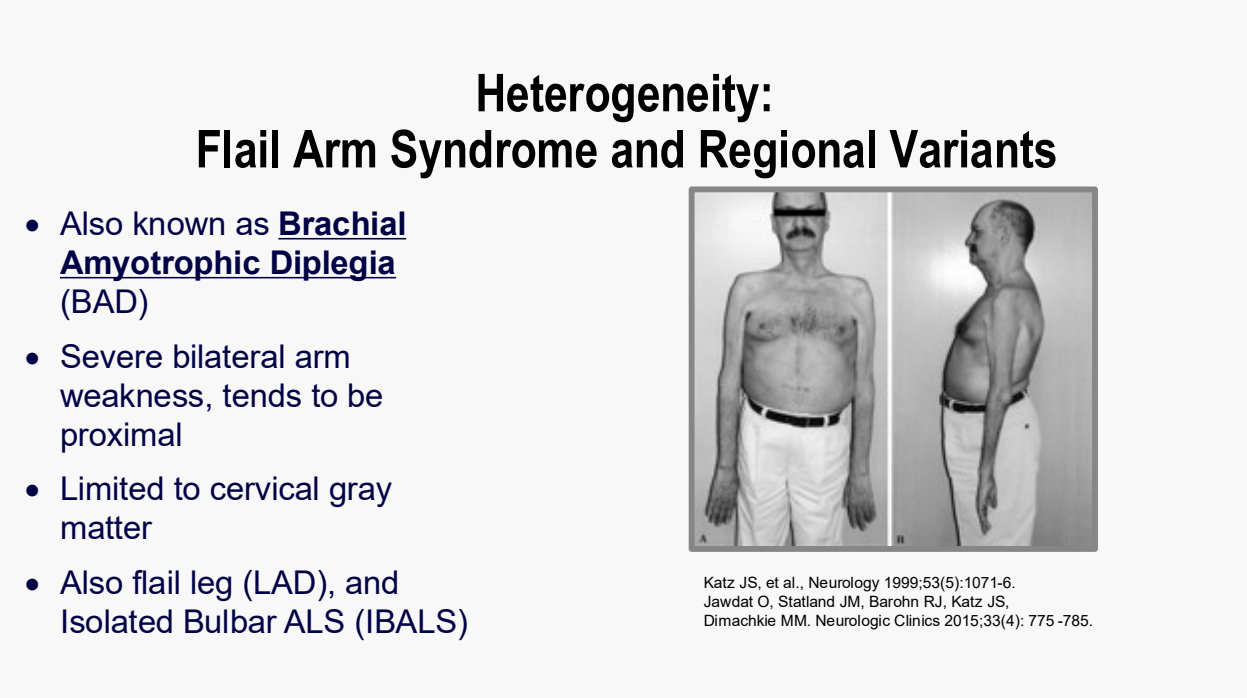
Similar to EMG, we believe magnetic resonance imaging (MRI) is over-utilized in typical cases of ALS. MRI is not necessary when ALS affects multiple regions (bulbar and limb) but can be useful when the clinical findings have a specific localization. For example, if a patient has a focal anatomical pattern such as lower motor neuron signs in the arms and upper motor neuron findings in the legs, without bulbar symptoms or signs, a cervical spine MRI may be helpful.

Figure 10



Primary muscular atrophy (PMA) is the lower motor neuron variant of ALS. We consider PMA to be essentially the same disease as ALS, but without upper motor neuron findings on physical examination. The regions of onset (one-third arm, one-third leg, one-third bulbar) and the pattern of spread are identical to those seen in typical ALS. Although the implication of a PMA diagnosis is that only gray matter is pathologically involved, autopsy studies often reveal abnormalities in the corticospinal and corticobulbar upper motor neuron tracts. Potential explanations that may account for the absence of upper motor neuron signs on examination include that upper motor neuron tracts are not degenerating rapidly or severely enough to produce clinical signs. Additionally, if lower motor neuron involvement occurs first and is marked by significant atrophy, weakness, and reduced movement, upper motor neuron signs may be difficult or impossible to detect on examination.

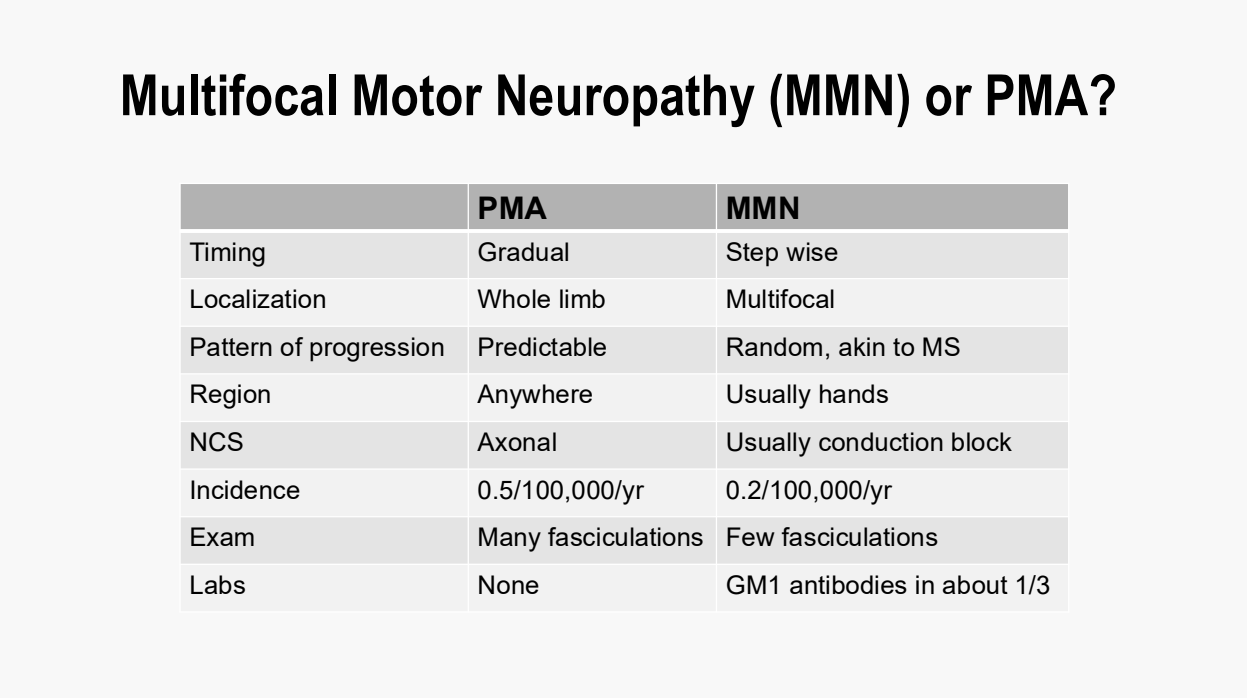
Regional Lower Motor Neuron Variants of PMA
Figure 11



A subset of patients have pure lower motor neuron involvement that begins in one arm and spreads to the contralateral arm without involvement of the legs, neck, or bulbar muscles. We have termed this condition brachial amyotrophic diplegia (BAD), while a British group has referred to it as flail arm syndrome. The general consensus is that a patient can be categorized as having BAD only after there has been no progression to the legs or bulbar muscles for at least two years, at which point the prognosis may be more favorable than that of typical PMA or ALS. Most patients with BAD eventually do show involvement in other regions. Overall survival can be five to ten years, or even longer.

We have also described a comparable regional variant that remains confined to the legs for at least two years, which we have termed leg amyotrophic diplegia (LAD); this is referred to as flail leg syndrome by British authors (Dimachkie et al., 2013; Jawdat et al., 2015). Rarely, we have observed patients in whom the disease remains confined to the arms or legs for decades without spreading to other regions.

Differentiating PMA from Multifocal Motor Neuropathy (MMN)
Figure 12



In contrast to ALS, PMA must be distinguished from multifocal motor neuropathy (MMN) due to the shared features of weakness and lack of upper motor neuron signs. PMA tends to demonstrate a very predictable and gradual pattern of spread, as discussed above. In contrast, MMN often progresses in a stepwise fashion, involving distal extremity muscles, in which a particular muscle group may become affected relatively quickly without further weakness developing in the remainder of the limb (Dimachkie et al., 2013; Saperstein et al., 1999; Stino et al., 2025). MMN also shows a degree of randomness in its involvement of nerves and the muscles they innervate. For example, left hand weakness may be followed by right foot weakness. A discerning clinician may note selective muscle sparing in MMN, such as ulnar nerve involvement without median nerve involvement in the same limb. MMN almost always affects the hands initially, may never progress to the legs, and does not involve bulbar muscles. Finally, PMA is far more common than MMN.

Nerve conduction studies should also differentiate these two conditions. MMN typically demonstrates demyelinating features on motor nerve conduction studies, which may include partial conduction block, temporal dispersion, or slowed conduction velocities. In rare cases, a very proximal lesion in MMN may result in only downstream axonal damage being evident, making electrophysiologic evidence of demyelination difficult to identify. We have referred to cases with no clear evidence of focal demyelination—many of which ultimately respond to immunoglobulin therapy—as multifocal acquired motor axonopathy (MAMA).

Respiratory Presentation of ALS
Figure 13

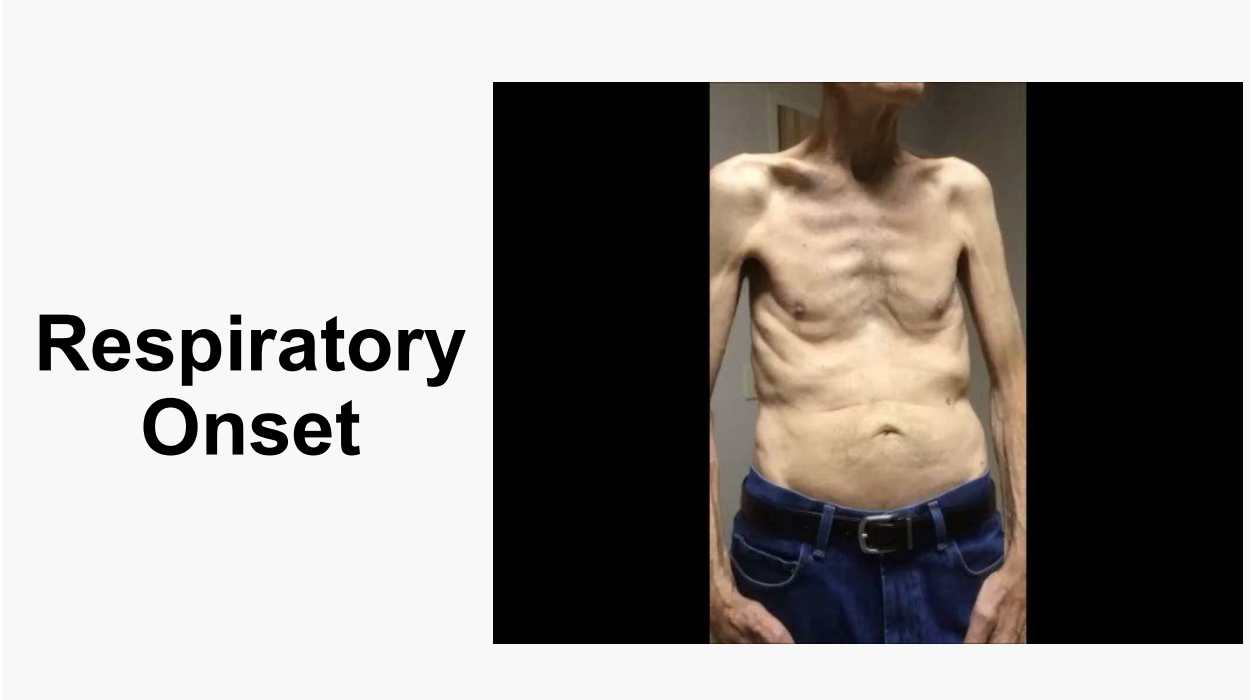
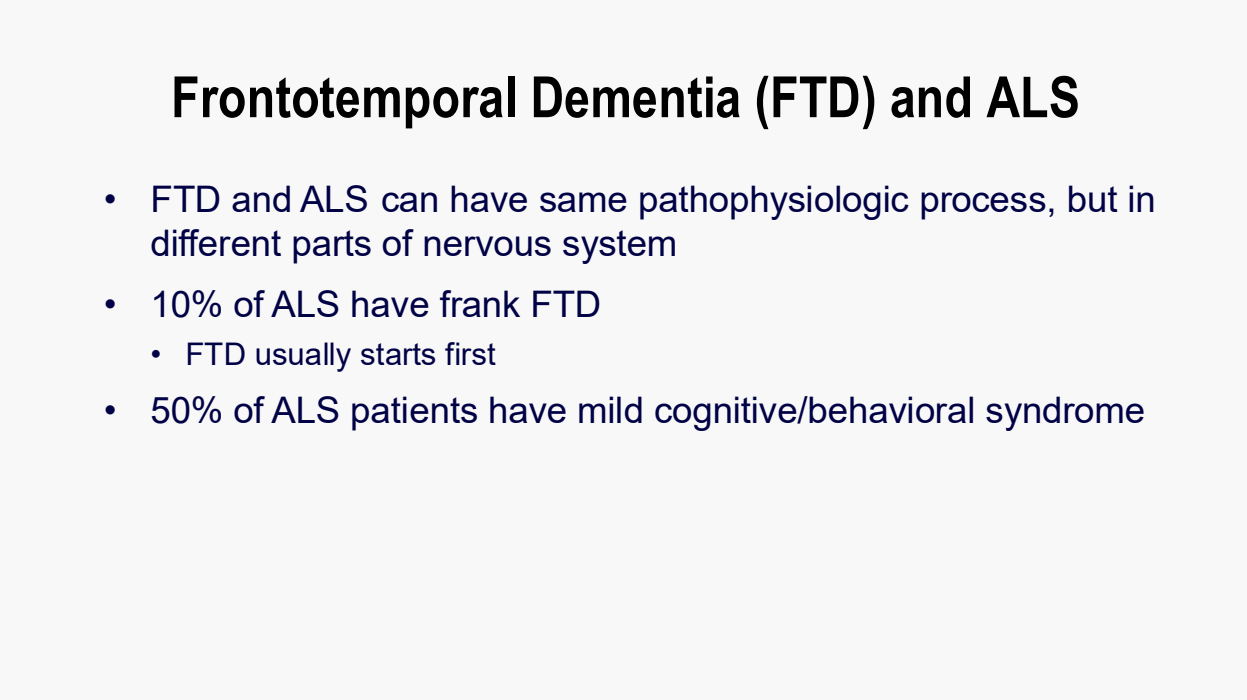


Figure 13 illustrates respiratory-onset ALS, showing atrophied intercostal muscles with relative sparing of the limbs. The respiratory presentation also indicates that there is diaphragmatic muscle weakness. Fasciculations are evident in the chest wall but not in the arms. These patients have a characteristic clinical presentation that often does not initially include neurological complaints. The first symptom is usually weight loss, likely due to inefficient breathing and loss of appetite. Because patients often present to their physicians for evaluation of weight loss, they may undergo extensive cancer and malnutrition workups before it is recognized that they have a respiratory problem. Weight loss and decreased appetite frequently begin before the forced vital capacity (FVC) has declined substantially.

Other symptoms may include frequent nighttime awakenings related to respiratory compromise from the combination of diaphragmatic weakness and REM sleep, during which accessory breathing muscles become paralyzed. Patients sometimes think they are awakening due to urinary frequency, which mistakenly raises the question of urologic problems. The variability of these symptoms can result in multiple referrals over several months before the patient is evaluated by a neurologist. Not surprisingly, some patients progress to advanced respiratory failure and admission to intensive care units before ALS is recognized.

ALS with Cognition Changes
Figure 14



Frontotemporal dementia (FTD) and ALS represent the same disease process affecting different regions of the nervous system (Woolley & Strong, 2015). Both disorders have pathology with misfolded aggregated TDP-43 protein in neurons and glia. Approximately 10% of ALS patients have frank FTD. FTD may begin in the right hemisphere with behavioral abnormalities or in the left hemisphere with aphasia. A key historical clue is that the spouse does most of the talking while the patient appears inattentive due to disinhibition or language problems. The patient may frequently stand up, walk around the room, or behave inappropriately. Other times, it may appear that the patient does not understand what is being said, and in some cases, the patient is frankly aphasic.

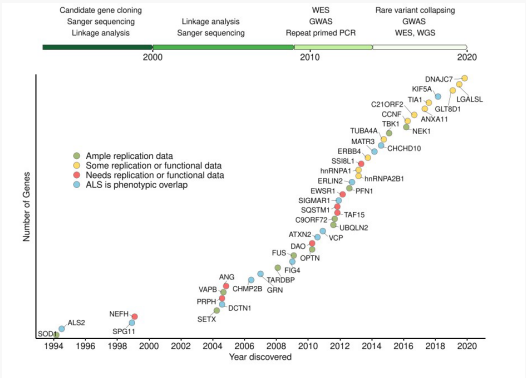
ALS patients with FTD may also develop apraxia of the mouth and oral musculature and be unable to speak, even though facial and tongue strength appear normal on examination. In addition, another 40% of ALS patients have some degree of cognitive impairment that can be diagnosed by neuropsychological testing but do not have any overt cognitive symptoms. Recognizing FTD in ALS patients is critical because it is associated with a poor prognosis and significantly alters how spouses and caregivers must manage the disease.

Genetics of ALS

Figure 15

ALS Genetics

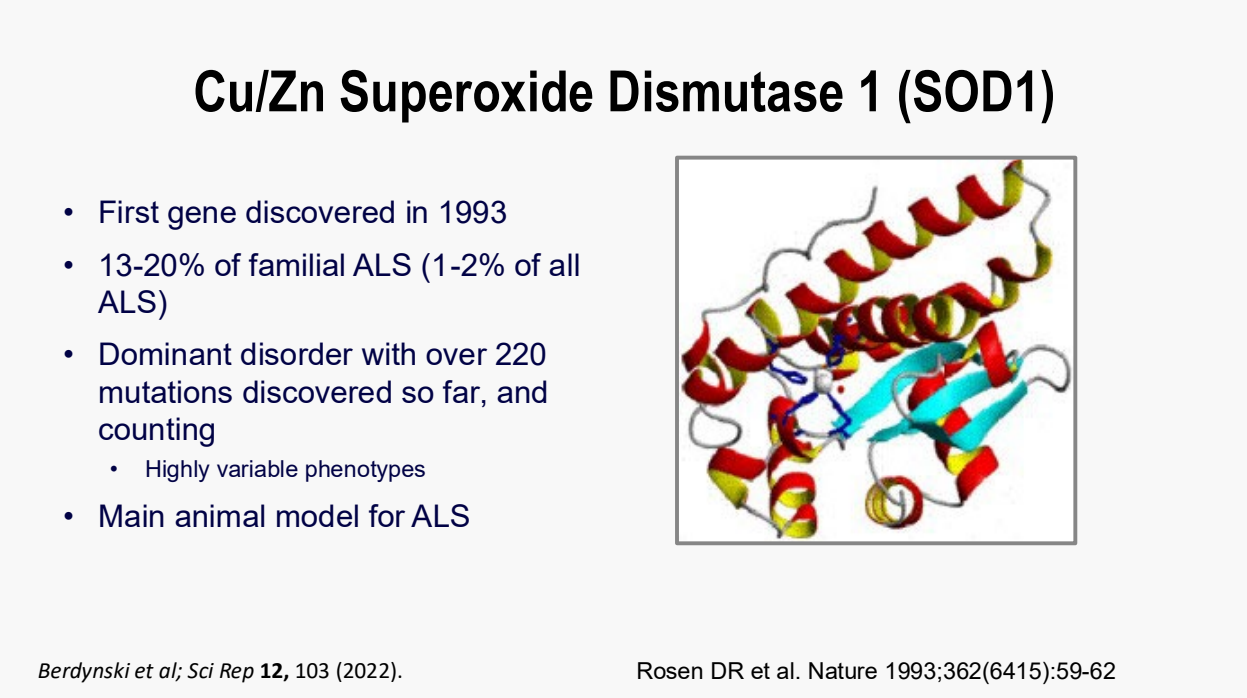
- More than 40 associated genes today
  - Risk factor for developing sporadic ALS
  - Direct cause of pathology
  - Modifier of disease course
- FUS
  - Early onset, severe
  - Antisense proving beneficial
- TARDBP
  - Produces TDP-43 protein aggregates



Gregory et al. Current Genetic Medicine Reports (2020) 8:121–131

Approximately 30-40 causal or risk-modifying gene mutations have been identified in ALS. The two most common mutations are in the SOD1 gene and the C9ORF72 gene SOD1 mutations account for the majority of familial autosomal dominant ALS cases (Boylan, 2015; DeJesus-Hernandez et al., 2011; Rosen et al., 1993).

Figure 16



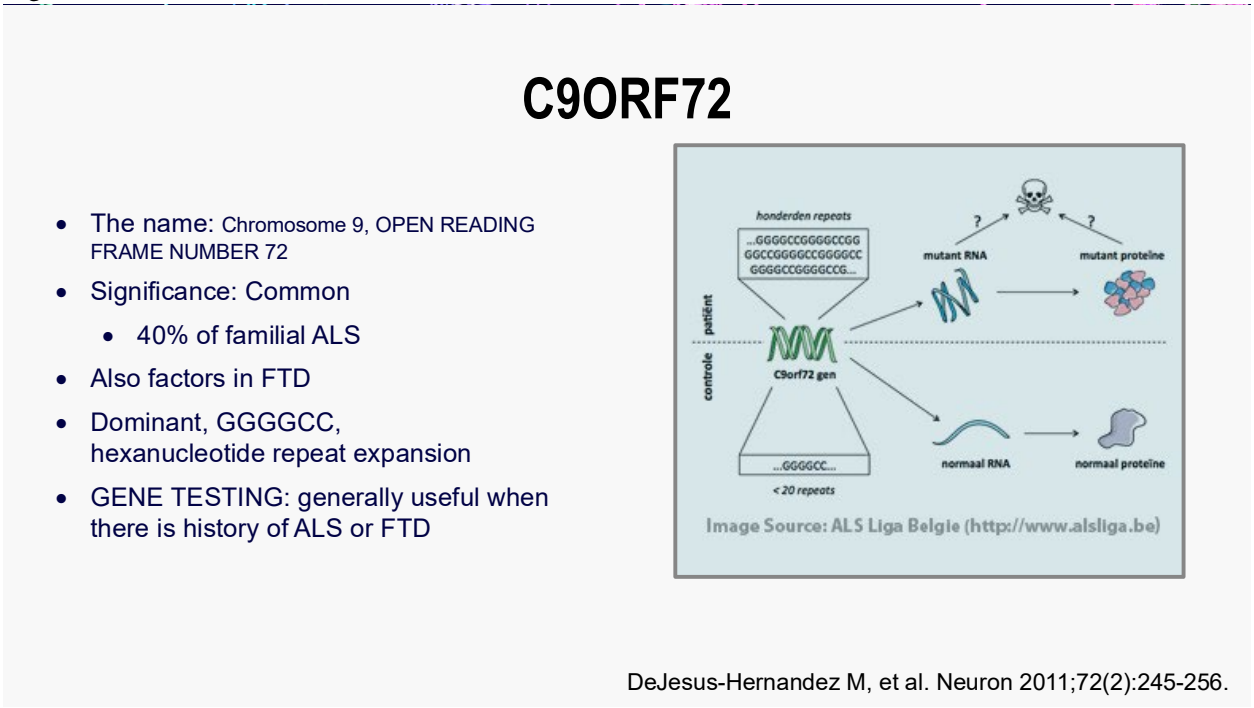
Approximately 10% of all ALS patients have familial autosomal dominant disease and up to 20% of these patients have SOD1 mutations. Therefore roughly 2% of all ALS patients harbor a SOD1 mutation.

SOD1 mutations were the first genetic abnormalities identified in ALS in 1993 (Rosen et al., 1993). More than 200 mutations in the SOD1 gene have been described, most of which are missense variants. Some mutations are associated with aggressive disease, while others produce a relatively mild phenotype. The A4V mutation is notable for being both common and associated with a rapidly progressive form of ALS.

The principal animal model used in ALS research is based on SOD1 mutations. However, patients with SOD1 mutations develop misfolded SOD1 protein aggregates, whereas other genetic and sporadic forms of ALS typically demonstrate aggregates of TDP-43. Notably, many therapeutic agents that have shown efficacy in SOD1 mouse models have not been effective in human ALS. An exception is the drug tofersen (See below). This discrepancy suggests that the SOD1 mouse model may not be an ideal preclinical model for studying potential treatments for human ALS.

Another gene of major importance is the C9ORF72 gene, located on chromosome 9 (chromosome 9 open reading frame 72).

Figure 17



DeJesus-Hernandez M, et al. Neuron 2011;72(2):245-256.

This mutation represents the most common genetic cause of ALS, occurring in approximately 50% of familial ALS cases and about 7% of all ALS cases. The disorder is caused by a hexanucleotide repeat expansion on chromosome 9. Frontotemporal dementia (FTD) is also caused by mutations in the same gene, and both degenerative disorders share TDP-43 pathology.

Families in which some members have FTD and others have ALS are highly likely to harbor a C9ORF72 mutation. For example, we have observed identical twin brothers where one presented with FTD and the other with ALS within the same year.

Caring for the Patient with ALS
Figure 18

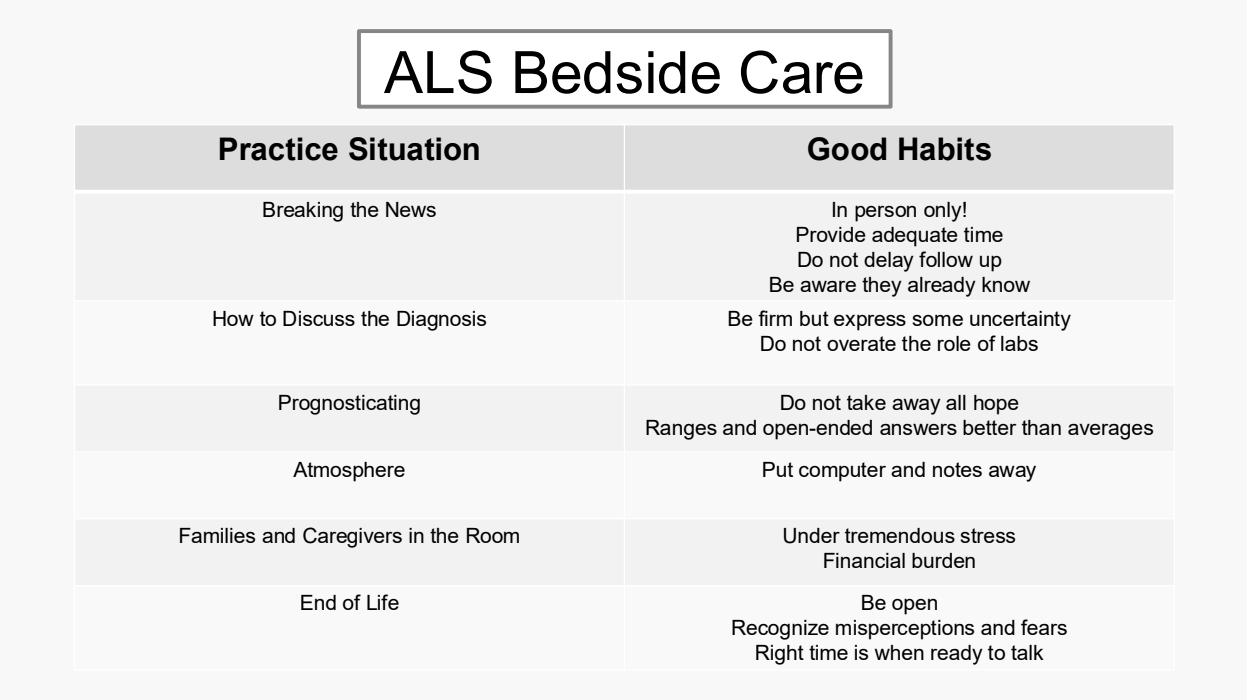


Figure 18 highlights practical considerations regarding communication with patients and families at the time of an ALS diagnosis. It is important that sufficient time is allocated when first informing the patient and family of the diagnosis. The clinician should clearly explain why ALS is the correct diagnosis and avoid overemphasizing the role of prior or future laboratory testing. Instead, patients and families should understand that the diagnosis is based predominantly on symptoms and physical examination findings, and that only ALS produces this specific constellation of features.

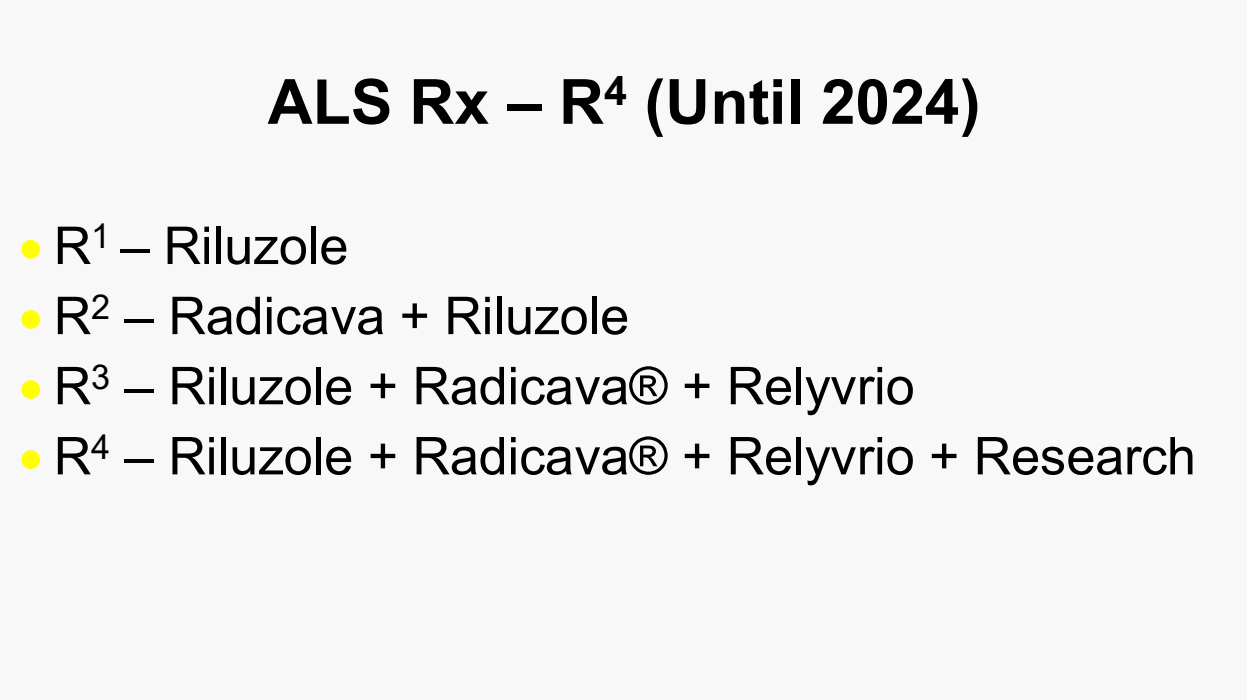
With regard to prognosis, we explain that although approximately half of patients die from the disease within three to five years, some will live longer and a few will live much longer. We stress that the prognosis in an individual patient cannot be determined at the time of diagnosis and often requires an additional six to twelve months of follow-up. Thus, while receiving the diagnosis of ALS is ominous for the patient and family, they can benefit from having hope that perhaps they will have a slower-than-typical course. The multidisciplinary teams that make up ALS clinics often serve to support patients and families as they gradually come to terms with the implication of the diagnosis.

Although it is ultimately important to discuss end-of-life issues, including advance directives and decisions regarding do-not-resuscitate and do-not-intubate orders, these topics should not be addressed during the initial visits. However, it is the responsibility of the ALS physician to ensure that these discussions occur at the appropriate time as the disease progresses, which in some cases may be years after the initial diagnosis (Jackson et al., 2015).

Approach to the Management and Treatment of ALS

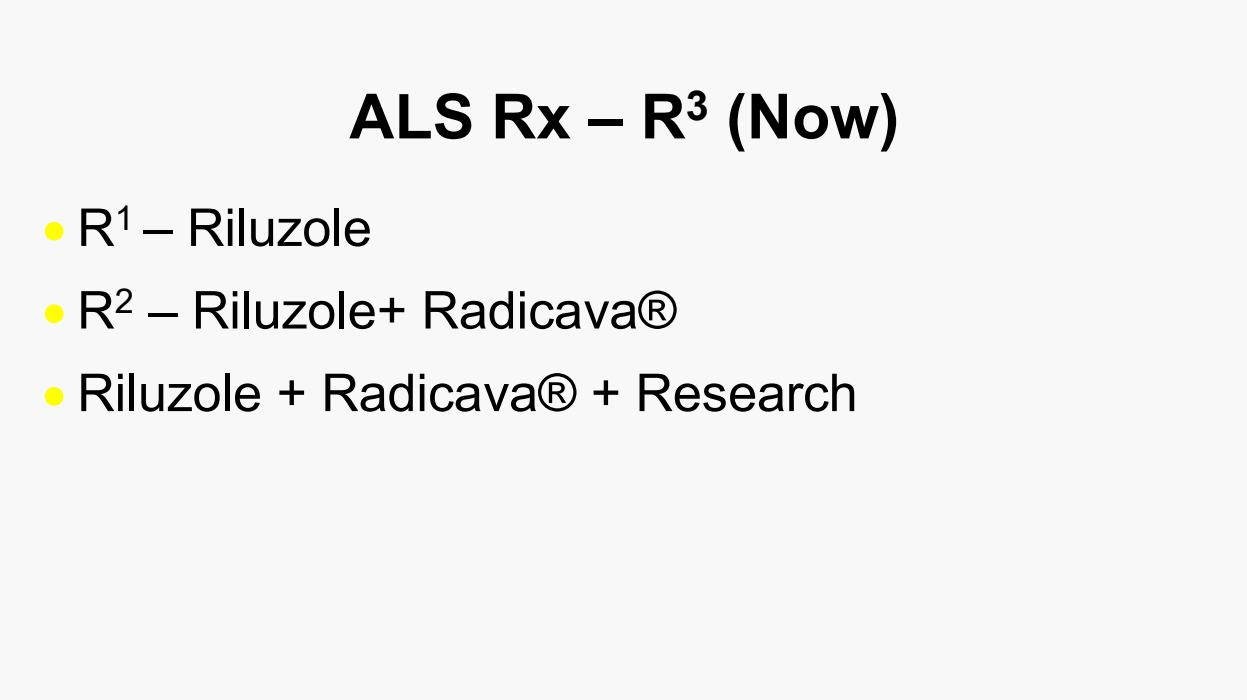
Until 2024, we used the R^4 approach to ALS management. This stands for Riluzole, Radicava, Relyvrio, and Research (Figure 19).

Figure 19



However, in 2024, the FDA withdrew its approval of Relyvrio, and we have since returned to the R^3 approach (Figure 20). The Relyvrio story will be discussed near the end of this treatment section.

Figure 20



Riluzole (trade name Rilutek), a glutamate inhibitor, was the first medication approved for the treatment of ALS (Figure 21) (Lacomblez et al., 1996). It received FDA approval in the 1990s after studies demonstrated that patients taking riluzole had longer survival compared with those receiving placebo. Riluzole is taken twice daily and, very rarely, can affect liver enzyme levels.

Figure 21

Riluzole
Effect on Survival

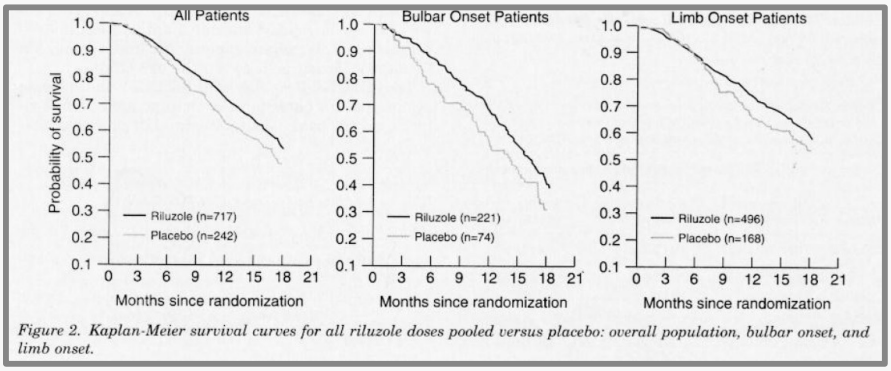


Figure 2. Kaplan-Meier survival curves for all riluzole doses pooled versus placebo: overall population, bulbar onset, and limb onset.

Lacomblez L et al, Lancet 1996 May 25;347(9013):1425-31

Radicava was the next drug approved for ALS (Figure 22) (Writing Group on Behalf of the Edaravone ALS 19 Study Group, 2017). The generic name for Radicava is edaravone.

Figure 22

Radicava® (edaravone)

- A free radical scavenger used in stroke since early 2000s
  - IV infusion: 10 of 14 days on/ 14 days off
- Two trials:
  - Initial trial found trends of efficacy over six months
    - Result was not significant due to slow progressors
  - Pivotal trial in more than 130 patients using very specific criteria found significant result

Edaravone is a free radical scavenger that has been used intravenously in Japan for many years in the treatment of acute ischemic stroke. The initial trial of edaravone in ALS showed a trend toward efficacy but did not reach statistical significance. Based on a subgroup analysis, the investigators hypothesized that the study had failed because it included too many slow progressors for a six-month trial duration. A second trial was designed using very specific inclusion criteria to exclude slow progressors and found that edaravone reduced the rate of functional decline by approximately 33% compared with placebo (Figure 23). The FDA approved edaravone for the treatment of ALS based on the results of the second trial (Figure 24). Notably, this is believed to be the first instance in which the FDA approved a drug without any trial participants from the United States.

Figure 23

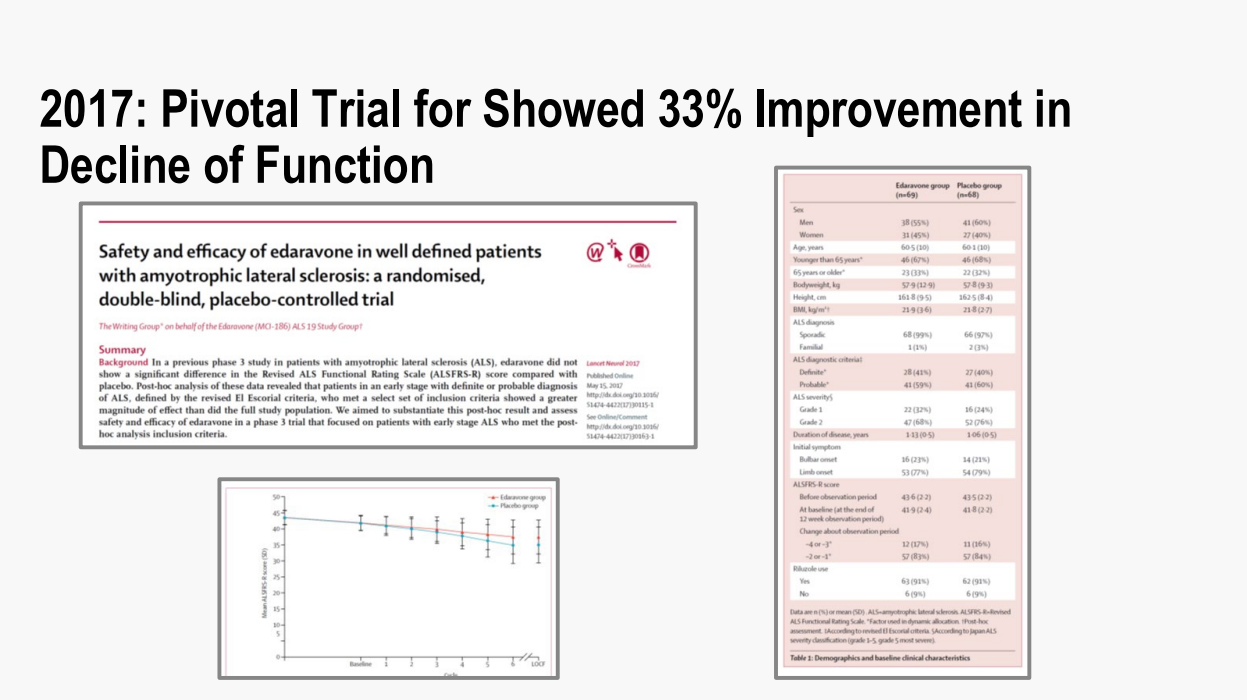
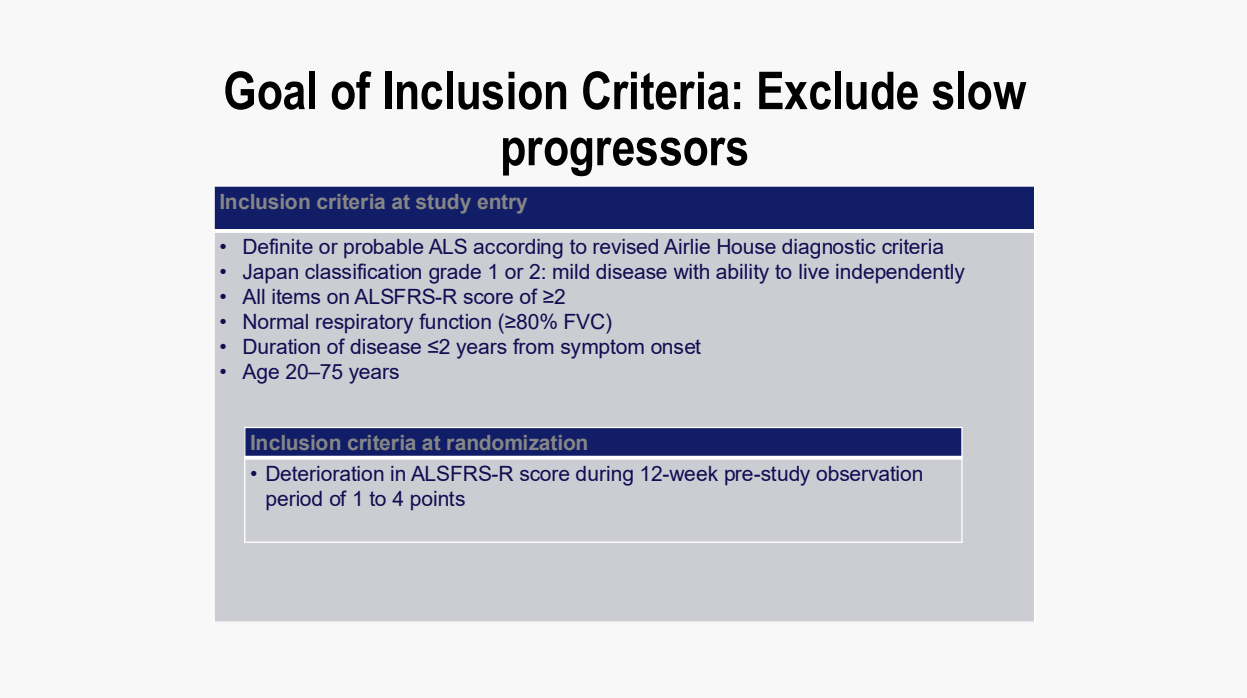


Figure 24



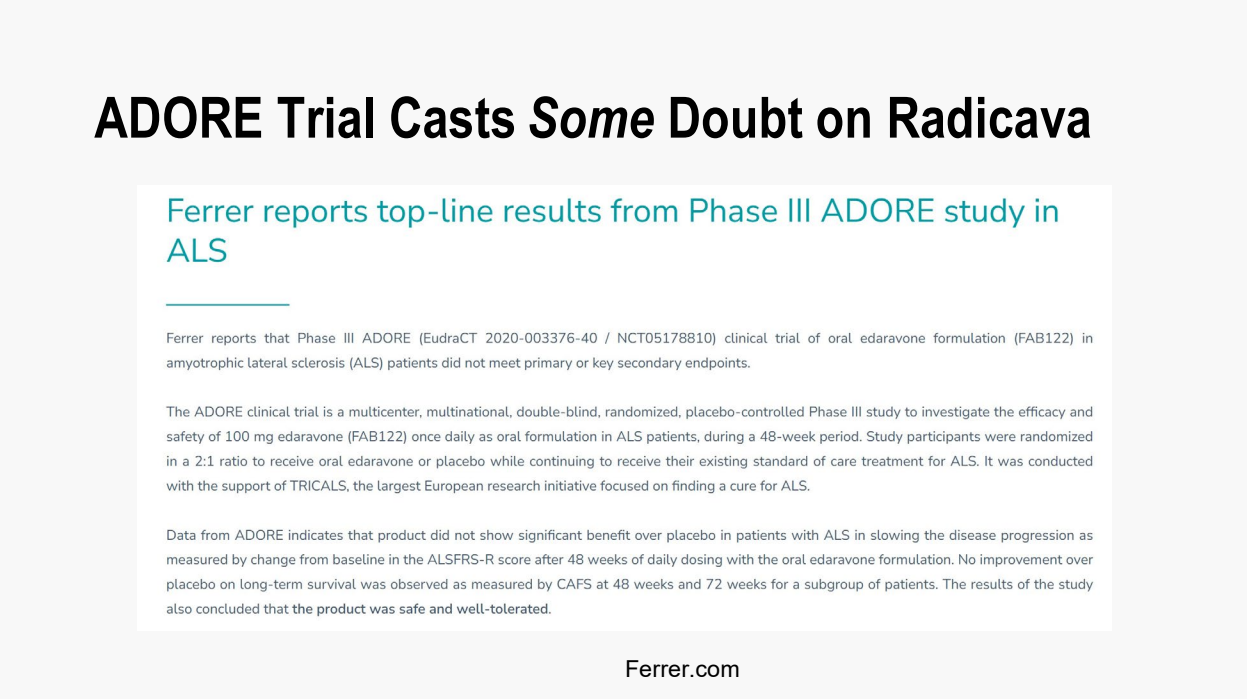
Patients enrolled in the edaravone trials were already receiving riluzole, suggesting that the benefit of edaravone may be additive when used in combination with riluzole. The original trials used an intravenous formulation. Subsequently, the manufacturer developed an oral formulation and demonstrated that the oral preparation had pharmacodynamic properties similar to the intravenous formulation. As a result, edaravone is now administered as an oral suspension, taken 10 out of every 28 days, following the same dosing schedule as the original intravenous trials.

The definitive edaravone study focused on a very narrow population of ALS patients in their effort to exclude slow progressors. The goal was to enroll patients who were likely to demonstrate measurable progression over a six-month period. To accomplish this, investigators designed entry criteria to avoid both floor and ceiling effects (Figure 24). To avoid floor effects, patients were required to retain a significant degree of function across all muscle groups as defined by changes on the ALS Functional Rating Scale (ALSFRS). To avoid ceiling effects, patients had to demonstrate involvement in at least three or four regions according to the El Escorial criteria for ALS.

While this approach allowed for a successful clinical trial, it had the unintended consequence of insurance companies later using these narrow criteria to deny coverage to patients who did not meet them. We believe that although restrictive criteria were necessary to demonstrate drug efficacy in a clinical trial setting, they should not be used to exclude patients in real-world practice who may have progressed beyond the narrow enrollment window or who have not yet developed significant weakness.

Subsequent to the FDA approval, some doubt has been raised regarding the effectiveness of edaravone (Figure 25). The ADORE clinical trial was a multicenter, international, randomized, double-blind, placebo-controlled phase III study (Ferrer, 2024; Maia, 2024). This trial, which was conducted after edaravone had already received FDA approval, did not demonstrate superiority of edaravone over placebo when ALSFRS decline or survival were used as endpoints. However, this study did not apply the same narrow inclusion criteria and employed a different dosing protocol with daily administration. Interestingly, this study has not been published.

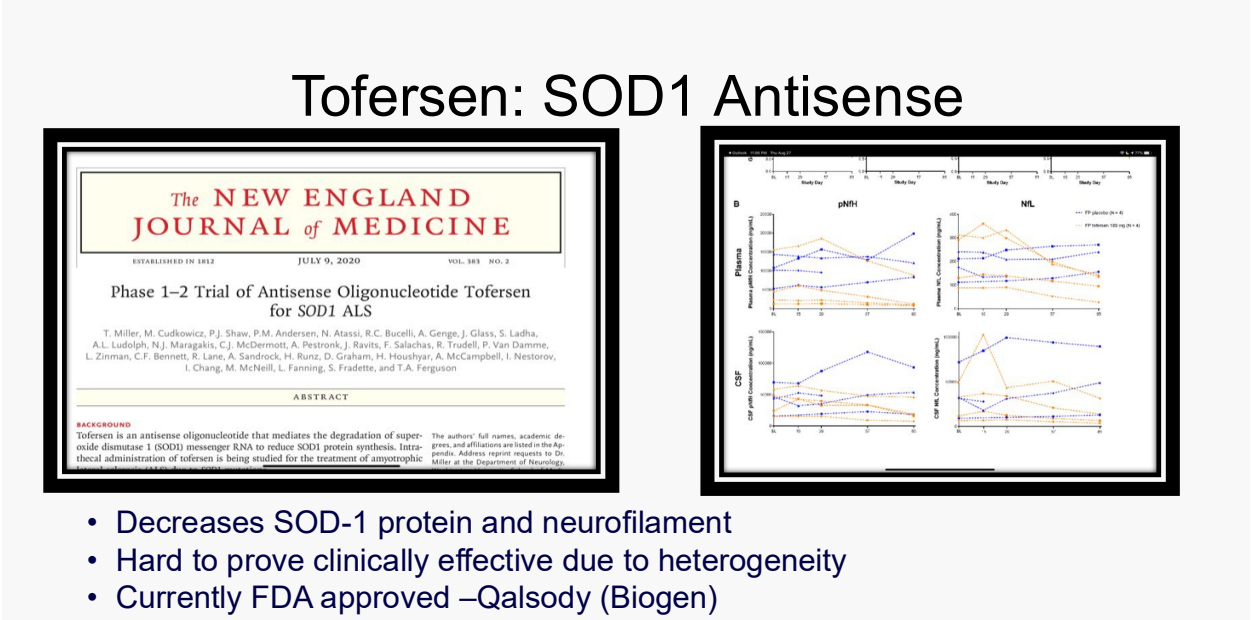
Figure 25



The most recent drug approved for the treatment of ALS is tofersen (named after former Biogen employee Toby Ferguson), an antisense oligonucleotide administered intrathecally that blocks the synthesis of SOD1 protein. This treatment is used in patients with SOD1 mutations and lowers levels of both mutant and wild-type SOD1 protein, theoretically preventing the protein aggregation that contributes to disease pathogenesis.

Initial studies demonstrated that tofersen reduced SOD1 and neurofilament levels but did not show that patients receiving the drug experienced a slowing of disease progression. Nevertheless, the FDA approved treatment for patients with autosomal dominant ALS associated with SOD1 mutations. Subsequent studies show that tofersen extends survival and slows disease progression, particularly when administered early in the disease course (Miller et al., 2025).

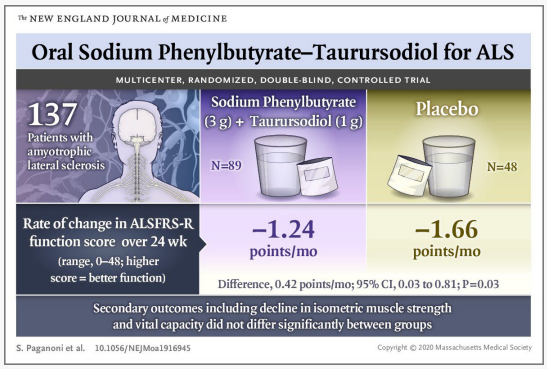
Figure 26



A company called Amylyx conducted a study of a combination therapy consisting of tauroursodeoxycholic acid (TUDCA) and phenylbutyrate. In 2020, a phase II trial demonstrated improved survival and slower disease progression compared with placebo (Paganoni et al., 2020, 2021). Based on these results, the FDA approved the drug but required that a planned phase III trial be completed. The drug was marketed as Relyvrio. Part of the rationale for approval after a phase II study was pressure from patient advocacy groups, who felt it was unfair to deny patients access to the drug while awaiting results from the pivotal phase III trial.

Figure 27

Recent Developments

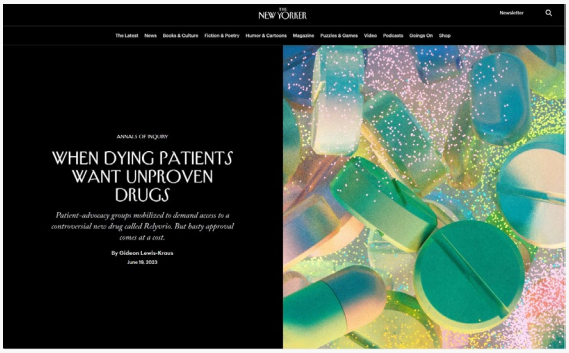


- Amylyx
  - Sodium phenylbutyrate is a histone deacetylase inhibitor
  - Taurursodiol
  - First trial completed in 2019
    - Improved function and survival
  - FDA approved as of September 2022

After Relyvrio entered the market and was widely used by ALS patients in the United States, results from the phase III trial demonstrated that the drug was not superior to placebo (Johnson, 2024). Despite several publications showing positive results from the phase II trial, the negative findings in the phase III trial, termed “The Phoenix Trial”, were never formally published. Consequently, Relyvrio was withdrawn from the market and is no longer a treatment option for ALS. The pressure placed on the FDA to approve the drug early prompted discussion in the lay press regarding the risks and benefits of approving therapies based on early-stage studies (Figure 28).

Figure 28

Relyvrio (2024 – Ineffective in Larger Trial)



- Autopsy suggests:
  - First trial relatively small
  - Tested limits of what FDA allowed for registration
  - Pressures from various groups

BrainStorm funded and conducted a stem cell trial for ALS in which stem cells were harvested from patients' own bone marrow, modified by the company, and then reintroduced via intrathecal injection into the cerebrospinal fluid.

Figure 29

Stem Cells

- BrainStorm
  - Trial of about 200 patients
  - Stem cells from own bone marrow
    - Altered and then returned to CSF
  - Earlier work suggested some patients improved transiently, but not seen in trial
  - Trial shows interesting results, but not significant
    - Still under FDA review

Clinicaltrials.gov

The BrainStorm trial did not demonstrate a statistically significant slowing of disease progression in the treatment group compared with placebo, although trends toward benefit were reported in patients earlier in the disease course (Figure 30) (Cudkowicz et al., 2022). One potential limitation of the study was that baseline ALS Functional Rating Scale (ALSFRS) scores were lower than those in prior ALS trials due to the specific enrollment criteria used (Figure 31) (Lindborg et al., 2024). This raised the possibility that the trial failed because of floor effects in patients with more advanced disease.

Figure 30

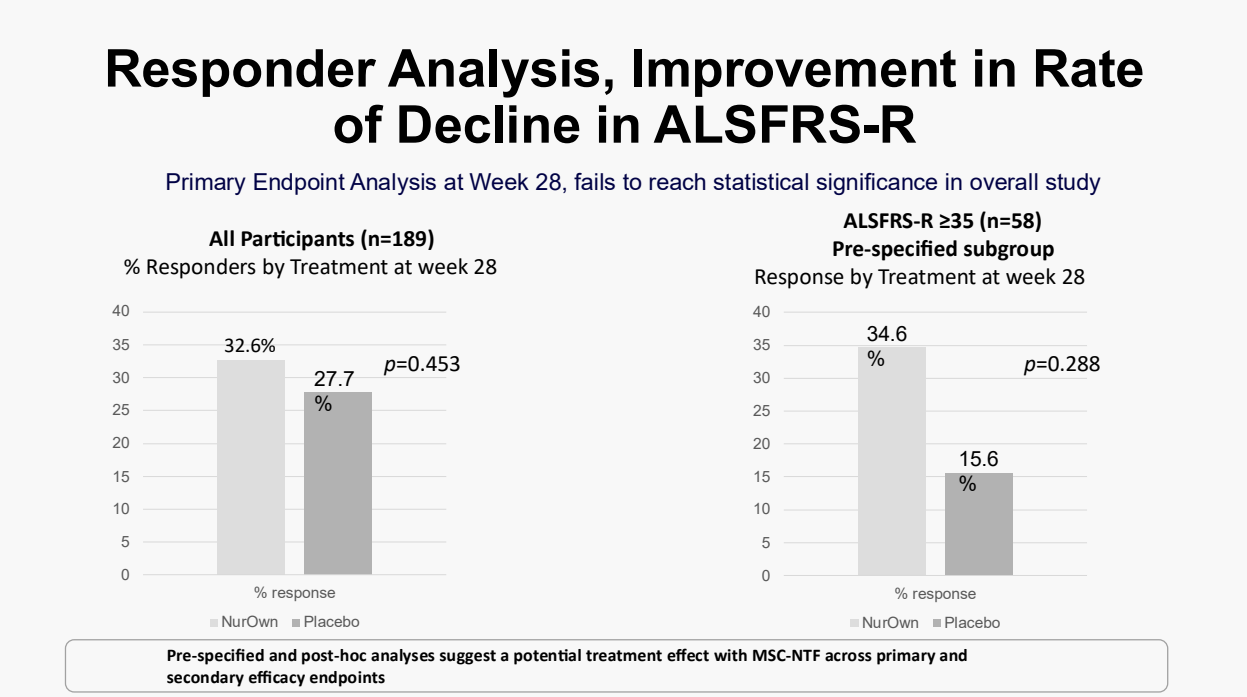
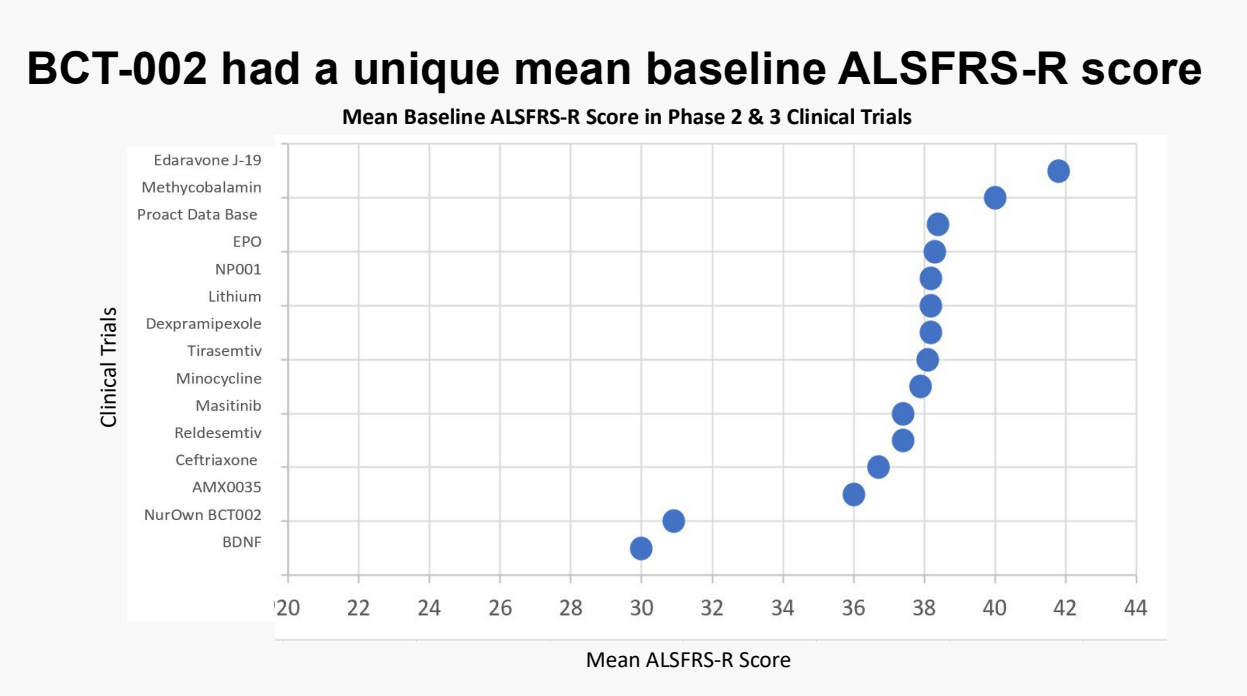


Figure 31



There have been numerous ALS clinical trials since the BrainStorm and Relyvrio development programs in which investigational drugs have failed to demonstrate clinical efficacy. It is common for sponsors to search for signals of benefit within patient subgroups after results from relatively small trials are reported. As a result, the field continues to face a dilemma regarding which therapies should advance to large phase III trials. It remains unclear whether these failures reflect shortcomings in trial design or whether ALS is an inherently complex disease with pathophysiology that is still poorly understood, limiting our ability to develop effective therapies.

The Platform Trial is a study based at Massachusetts General Hospital. In a platform trial, multiple drugs are evaluated simultaneously using a single shared placebo group. This design reduces the number of patients assigned to placebo while allowing randomization across several active treatment arms. The advantages include improved efficiency, shared protocols and infrastructure, a single institutional review board, and reduced overall costs. This approach creates an economy of scale and allows sponsors to de-risk financial investments by identifying potentially effective therapies before committing to large and expensive phase III trials.

Figure 32

Platform Trial and a Word on ALS Trial Philosophy

- Platform Trial (MGH)
  - Many drugs in pipeline, human data
  - Study several drugs at same time
  - Now on Protocol G
  - Five ineffective trials thus far
- Creative Destruction
  - Study a lot of drugs
  - Don't miss a winner
  - Don't push ineffective treatments

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

Roger J. Lewis, MD, PhD
Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC, Austin, Texas.

The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and combinations of treatments, in heterogeneous patient populations, with the capability to add new treatments

benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The **Table** summarizes the general differences between a traditional clinical trial and a platform trial.

During a platform trial, accumulating outcome data

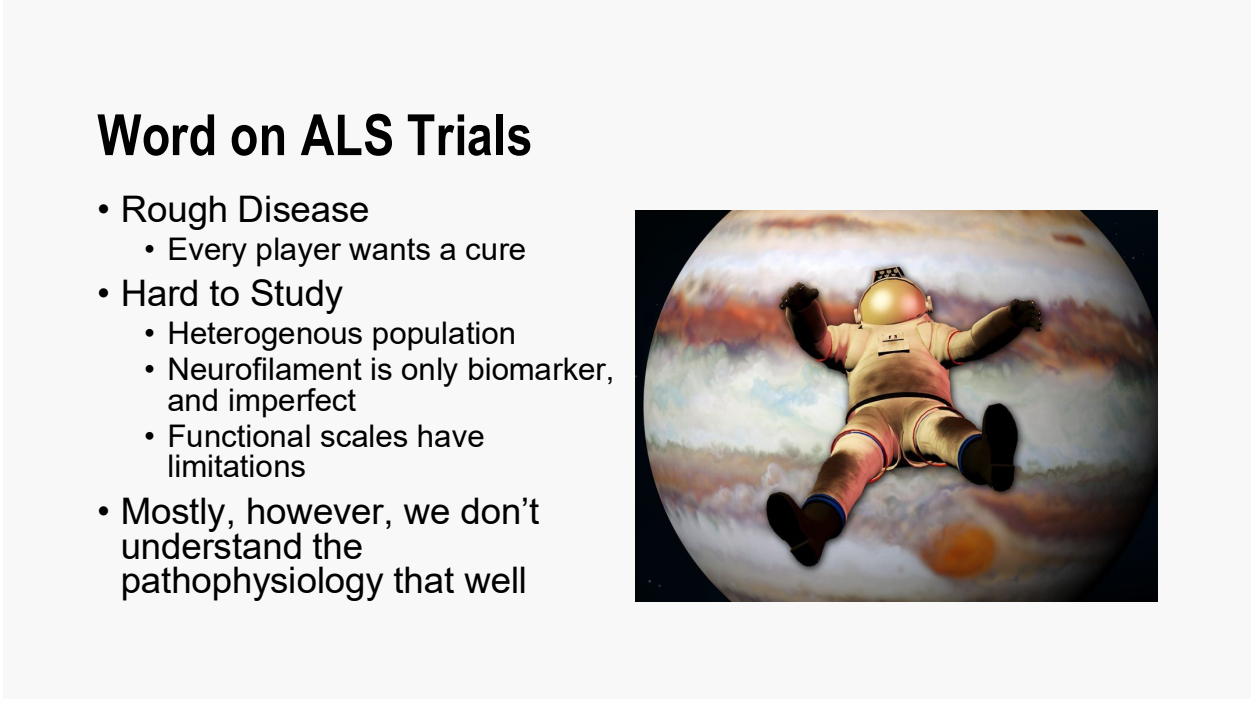
JAMA Published online March 23, 2015 Opinion
Berry, et al. JAMA. 2015;313(16):1619-1620.

In reality, ALS remains an exceptionally challenging disease in which it is difficult to achieve meaningful progress through clinical trials. Figure 33 depicts a man attempting to reach Jupiter. We are often asked why, if humans can land on the moon, we cannot find an effective treatment for ALS. One answer is that developing a treatment for ALS is far more complex than landing on the moon and may be more comparable to placing a human on Mars—or even Jupiter.

The ALS clinical trial population is highly heterogeneous, with patients enrolling at different stages of disease and exhibiting widely variable rates of progression. This heterogeneity necessitates large sample sizes to minimize random effects that can lead to misleadingly positive or negative outcomes. Current biomarkers for ALS include serum and cerebrospinal fluid neurofilament light chains; however, reliance on these markers remains somewhat theoretical, as there have been too few successful trials to validate their predictive value fully.

Ultimately, the major challenge in ALS clinical trials is our incomplete understanding of disease pathophysiology. Until significant advances are made in elucidating the underlying mechanisms of ALS, it will remain difficult to make rational decisions about which therapeutic targets to pursue. Nonetheless, these trials are conducted with the understanding that scientific knowledge continues to advance and with the hope that we will eventually cross a threshold leading to clearly effective treatments in the near future. Of course, a little luck would also help.

Figure 33



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