Amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis is a fatal CNS neurodegenerative disease. Despite intensive research, current management of amyotrophic lateral sclerosis remains suboptimal from diagnosis to prognosis. Recognition of the phenotypic heterogeneity of amyotrophic lateral sclerosis, global CNS dysfunction, genetic architecture, and development of novel diagnostic criteria is clarifying the spectrum of clinical presentation and facilitating diagnosis. Insights into the pathophysiology of amyotrophic lateral sclerosis, identification of disease biomarkers and modifiable risks, along with new predictive models, scales, and scoring systems, and a clinical trial pipeline of mechanism-based therapies, are changing the prognostic landscape. Although most recent advances have yet to translate into patient benefit, the idea of amyotrophic lateral sclerosis as a complex syndrome is already having tangible effects in the clinic. This Seminar will outline these insights and discuss the status of the management of amyotrophic lateral sclerosis for the general neurologist, along with future prospects that could improve care and outcomes for patients with amyotrophic lateral sclerosis.

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Introduction

Amyotrophic lateral sclerosis, a fatal CNS neurodegenerative disease, can be difficult to recognise, especially in the early stages. The disease is rare, and more common illnesses are frequently considered before amyotrophic lateral sclerosis, delaying diagnosis. However, the lifetime risk of the disease is approximately one in 350 people, although low life expectancy reduces the prevalence.[1] Recognition of phenotypic heterogeneity, and amyotrophic lateral sclerosis as a complex syndrome that frequently includes behavioural deficits, could help physicians better recognise it earlier in the disease course. Development of new diagnostic criteria and identification of genetic risk factors could also expedite the diagnostic process.[2] Regarding prognosis, a clearer understanding of the multisystem nature of amyotrophic lateral sclerosis, including cognitive dysfunction and behavioural changes, has important ramifications for caregiving support and end-of-life decision making. Moreover, newly developed predictive models, scales, and scoring systems can give patients with amyotrophic lateral sclerosis and their physicians a clearer idea of their disease course.[2] Advances in our understanding of disease pathophysiology are leading to mechanism-based and potentially disease-modifying therapies, currently in clinical trials. This Seminar will outline these topics and current clinical practice for amyotrophic lateral sclerosis, along with research advances, which could facilitate future improvements in diagnosis and prognosis for patients with amyotrophic lateral sclerosis.

Epidemiology

Incidence of amyotrophic lateral sclerosis rises with age and is highest between 60 years and 79 years,[3,4] although variation can occur by ancestral background.[5] Some studies show stable incidence over the past two or three decades,[1] whereas others report a possible increase.[6,7] Changes in perceived incidence could arise from improved diagnosis or changes in reporting standards over time, advocating the construction of well curated population registries. Whether the incidence of amyotrophic lateral sclerosis has changed in the past couple of decades is unclear, although it is anticipated to increase with an ageing population.[8] Prevalence of amyotrophic lateral sclerosis is also expected to increase due to an ageing population, in addition to improved management, which supports increased life expectancy.[8,9] However, it remains a relatively rare disease. Standardised global incidence of amyotrophic lateral sclerosis by meta-analysis is only 1·68 per 100 000 person-years of follow-up, but varies by region.[10] In populations of predominantly European descent, such as in Europe and North America, incidence is slightly higher than the global average, ranging from 1·71 per 100 000 to 1·89 per 100 000, and could even be higher within population-based studies.[11] Asian populations have lower incidences, varying from 0·73 per 100 000 in south Asia to 0·94 per 100 000 in west Asia, whereas Oceania

Search strategy and selection criteria

We searched PubMed for English language articles from Sept 15, 2021, to Oct 5, 2021, and then again in January, 2022, with the terms, in addition to "amyotrophic lateral sclerosis": "epidemiology"; "phenotype"; "diagnostic", "diagnosis", "cognition", and "cognitive"; "GWAS", "genetic", "risk", "oligogenic", "polygenic", and "heritability"; "mimic" and "GWAS" combined with every amyotrophic lateral sclerosis gene in turn; "pathophysiology", "mechanism", "nucleocytoplasmic transport", "cell-to-cell transmission", "immune system", "exposure", "environment", "pollutant", "toxin", "metals", and "traffic"; "prognosis", "scoring", "scaling", and "staging"; "multidisciplinary care", "riluzole", "edaravone", "non-invasive ventilation", and "gastrostomy"; and "gene therapy", "antisense oligonucleotide", "antibody", "immune", "clinical trial", "neurofilaments", "imaging", "PET", "connectome", "EEG", and "hyperexcitability". The search focused on articles published from Jan 1, 2017, to Jan 31, 2022, although older seminal articles were also considered. We also included articles from the authors' personal reference lists. Articles were selected on the basis of relevance to this Seminar. Additionally, we searched ClinicalTrials.gov for "amyotrophic lateral sclerosis".

***Panel 1*: Definitions of amyotrophic lateral sclerosis motor signs and phenotypes**

Lower motor neurons (LMN)
- Brainstem cranial motor nerve nuclei or anterior horn cells
- LMN dysfunction is characterised by muscle weakness, atrophy, and fasciculations

Upper motor neurons (UMN)
- Betz cells in layer V of the primary motor cortex
- UMN dysfunction is characterised by increased and pathological reflexes (including Hoffmann's sign, Babinski, and snout), pathological spread of reflexes, preserved reflexes in a weak limb, and spasticity

Bulbar amyotrophic lateral sclerosis
- Phenotype presents with weakness starting in the muscles controlling speaking and swallowing
- Both LMN and UMN signs are present

Pseudobulbar palsy
- A non-classical subset of bulbar onset, characterised by prominent bulbar features, predominantly from UMN signs, which slowly spread to limbs

Pseudobulbar affect
- Uncontrollable emotional outbursts, including laughing, crying, and excessive yawning

Classical amyotrophic lateral sclerosis
- Phenotype presents with muscle weakness starting in the limbs; both LMN and UMN signs are present

Cervical-onset amyotrophic lateral sclerosis
- A subset of classical amyotrophic lateral sclerosis with weakness commencing in the upper limbs, especially hand weakness

Lumbar-onset amyotrophic lateral sclerosis
- A subset of classical amyotrophic lateral sclerosis with weakness commencing in the lower limbs, especially foot drop

Flail arm
- Prominent LMN dysfunction initially causing proximal muscle weakness greater than distal muscle weakness in the arms
- Unlike progressive muscular atrophy, patients with flail arm do manifest progressive UMN dysfunction; this entity can also be referred to as brachial amyotrophic diplegia

Flail leg:
- LMN dysfunction causing muscle weakness in the legs; unlike progressive muscular atrophy, this phenotype does not generalise or generalises very slowly

Primary lateral sclerosis*:
- UMN dysfunction causing weakness in muscles controlling limbs, swallowing, and speaking
- Less commonly causes respiratory dysfunction

Pyramidal:
- Like primary lateral sclerosis but additionally eventually exhibiting LMN signs

Progressive muscular atrophy*:
- LMN dysfunction causing weakness in muscles controlling limbs, swallowing, speaking, and respiratory function

Respiratory onset
- LMN and UMN dysfunction causing weakness commencing in the respiratory muscles

Hemiplegic
- Predominantly UMN dysfunction causing muscle weakness in one side of the body

Cachexia
- Unexplained weight and muscle loss

*This Seminar considers primary lateral sclerosis and progressive muscular atrophy on the spectra of amyotrophic lateral sclerosis phenotypes, although they can also be considered as separate clinical entities.

universally has the highest incidence (2·25 per 100 000).[7,10] Incidence also varies by sex, with an overall standardised male-to-female ratio of 1·35, which is affected by age of onset.[12] Genetics also has a role; heritability is higher in mother–daughter pairs,[1] whereas the most common known amyotrophic lateral sclerosis risk gene, *C9orf72*, lowers onset age in men versus women.[13] Thus, amyotrophic lateral sclerosis arises from complex interrelationships between age, sex, and genetics,[14] which has implications for preclinical and clinical research, and clinical trials.

Clinical presentation

Phenotypic heterogeneity

Amyotrophic lateral sclerosis presents as a combination of upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction, affecting the bulbar, cervical, thoracic, or lumbar segments.[2] This dysfunction leads to progressive weakness of voluntary skeletal muscles involved in limb movement, swallowing (dysphagia), speaking (dysarthria), and respiratory function, with different clinical presentations (panel 1). Sphincter and extraocular muscles are classically spared, although autonomic dysfunction in amyotrophic lateral sclerosis is increasingly recognised (eg, urinary urgency and incontinence).[15] Clinical weakness spreads contralaterally, rostrally, and caudally, most often in an anatomically contiguous manner. A 2018 survey of 470 patients with amyotrophic lateral sclerosis found that 85% had focal onset in one body segment, which progressed to the contralateral side and then to adjacent anatomical segments.[16] Spread of disease to non-contiguous segments was less common.

Amyotrophic lateral sclerosis presents as multiple phenotypes (figure 1A–B; appendix pp 4–6). Bulbar-onset and spinal-onset (cervical and lumbar) amyotrophic lateral sclerosis are the most common presentations, each constituting about a quarter of the cases. Less frequently, patients present flail arm and leg, primary lateral sclerosis, progressive muscular atrophy, respiratory onset, or hemiplegia.[12,13] This Seminar considers primary lateral sclerosis and progressive muscular atrophy on the spectra of amyotrophic lateral sclerosis phenotypes, although they could also be considered as separate clinical entities. Age, sex, and genetics also contribute to amyotrophic lateral sclerosis phenotypes. Women aged 60 years or older more commonly develop bulbar-onset amyotrophic lateral sclerosis, whereas men aged less than 60 years present with the classical phenotype. Pure UMN variants are more commonly seen in men and women aged less than 60 years. Flail arm, leg, and respiratory onset primarily develop in men, irrespective of age.[14] Specific genetic mutations favour certain phenotypes. One study of German and Chinese registries suggests that phenotypes could vary globally.[18] German patients with amyotrophic lateral sclerosis have an older onset age (66·6 years), a larger proportion of bulbar onset (35·9%), and a smaller male-to-female ratio (1·33) than do Chinese patients (53·2 years onset age; 22·8% bulbar; 1·51 male-to-female ratio).[18] Consensus phenotyping between registries would advance our knowledge of age, sex, genetics, racial, and ethnic contributions to phenotypes.

Cognitive and behavioural changes

Classically, amyotrophic lateral sclerosis was predominantly considered a disease of motor dysfunction (eg, dysarthria, dysphagia, and weakness of upper and lower limb muscles). However, cognitive and behavioural changes, which can occur early in the disease course,[19,20] are now recognised to occur in 35–50% of patients with amyotrophic lateral sclerosis.[21,22] Individuals with amyotrophic lateral sclerosis have loss of normal language and executive function (ie, poor working memory, inhibition, and fluency). Typically, more long-term memory and spatial domains remain intact.[21] Other behavioural changes include apathy, irritability, disregard for hygiene, and eating habit changes. Approximately 15% of patients with amyotrophic lateral sclerosis meet the diagnostic criteria for frontotemporal dementia.[20,23] Furthermore, depression, anxiety, and sleep disruptions occur in amyotrophic lateral sclerosis[24] along with pseudobulbar affect, which causes emotional lability.[16]

These cognitive and behavioural changes support the concept that amyotrophic lateral sclerosis is a global neurodegenerative disease along the same continuum as frontotemporal dementia (figure 1C). Transactive response DNA-binding protein 43 kDa (TDP43) proteinopathy, an almost universal finding in amyotrophic lateral sclerosis, is present in around 97% of patients and around 50% of patients with frontotemporal dementia. Mild deficits in executive function, language, and fluency have 100% specificity for TDP-43 pathology in non-motor brain regions corresponding to these domains.[25] Some patient characteristics, such as *C9orf72* status[26,27] and bulbar onset,[27] are strong determinants of cognitive impairment and could help the physician and patient to

See **Online** for appendix

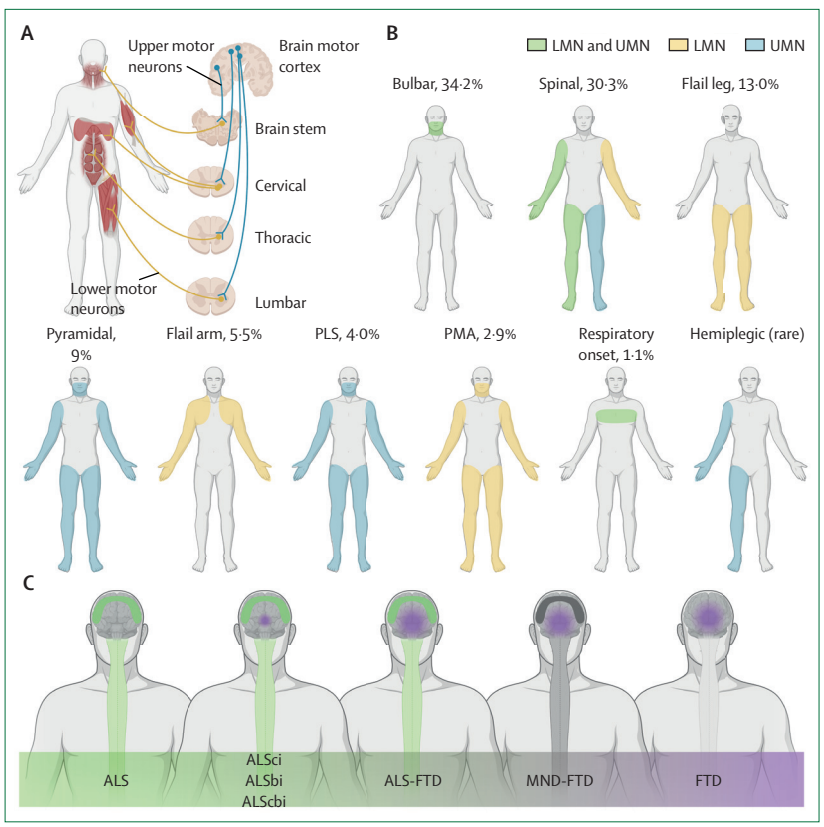


Figure 1: **Amyotrophic lateral sclerosis phenotypic variation and spectrum with frontotemporal dementia**
(A) Schematic showing UMNs (blue), which relay signals from the motor cortex to the LMNs (yellow; ie, cranial motor nerve nuclei in the brainstem and anterior horn cells in the spinal cord), which relay signals to the muscles. Motor neurons connecting within the brain stem innervate, among other muscles, cranial muscles. Initial UMN and LMN degeneration in the brain stem are linked to bulbar-onset amyotrophic lateral sclerosis. Motor neurons connecting within the cervical region of the spinal cord innervate, among other muscles, upper limb and respiratory muscles. Motor neurons connecting within the thoracic and lumbar regions of the spinal cord innervate, among other muscles, accessory respiratory, abdominal, and lower limb muscles. Initial UMN and LMN degeneration in the cervical and lumbar regions are linked to spinal-onset amyotrophic lateral sclerosis. (B) Patients with amyotrophic lateral sclerosis can present with signs of UMN (blue), LMN (yellow), and combined UMN and LMN (green) dysfunction. Most common amyotrophic lateral sclerosis phenotypic presentations are bulbar and classical spinal limb onset (cervical and lumbar). Less common amyotrophic lateral sclerosis phenotypic presentations are flail leg, pyramidal, flail arm, PLS, PMA, respiratory onset, and hemiplegic. Proportion of amyotrophic lateral sclerosis phenotypes shown in the figure as the percentage of a total representative amyotrophic lateral sclerosis population.[14,17] Pyramidal is predominantly UMN, but still exhibits some LMN signs, differentiating it from PLS (appendix pp 4–6). (C) Amyotrophic lateral sclerosis occurs on a continuum with frontotemporal dementia. Amyotrophic lateral sclerosis is on one end of the spectrum and presents with pure motor signs from UMN and LMN neurodegeneration. Frontotemporal dementia is on the other end of the spectrum and presents with behavioural and cognitive deficits from frontotemporal neurodegeneration. After pure amyotrophic lateral sclerosis are patients with amyotrophic lateral sclerosis not meeting frontotemporal dementia criteria, defined as ALSci, ALSbi, and ALScbi, followed by patients meeting frontotemporal dementia criteria (ALS–FTD). Patients on the remainder of the continuum have frontotemporal dementia but do not meet the criteria for amyotrophic lateral sclerosis. Some patients still have evidence of MND with frontotemporal dementia and patients with no MND signs have frontotemporal dementia. ALS=amyotrophic lateral sclerosis. ALSbi=amyotrophic lateral sclerosis behavioural impairment. ALSci=amyotrophic lateral sclerosis cognitive impairment. ALScbi=amyotrophic lateral sclerosis cognitive and behavioural impairment. FTD=frontotemporal dementia. LMN=lower motor neurons. MND=motor neuron disease. PLS=primary lateral sclerosis. PMA=progressive muscular atrophy. UMN=upper motor neurons.

***Panel 2*: Amyotrophic lateral sclerosis diagnosis**

Clinical history
- Symptoms (eg, weakness and time course)
- Family history of amyotrophic lateral sclerosis or other neurodegenerative diseases

Neurological examination
- Signs of upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction in bulbar, cervical, thoracic, or lumbosacral segments (eg, hand weakness [split hand] and foot drop)
- Unexplained weight loss, cognition or executive functioning dysfunction, and pseudobulbar affect are additional signs

Electrodiagnostic testing
- Nerve conduction studies and needle electromyography to confirm LMN signs

Laboratory testing
- Serology should be normal except for elevated creatine phosphokinase concentrations, which can also lead to abnormal liver function tests

MRI
- Imaging the spinal cord by MRI is essential to rule out more common differential diagnoses (eg, disc herniation or cord compression)

Criteria
- Most neurologists use the revised El Escorial criteria[32]
- Classifies patients with amyotrophic lateral sclerosis as possible, probable, probable laboratory supported, and definite, on the basis of clinical presentation and electrodiagnostic findings

Revised El Escorial criteria

The presence of:
- LMN signs by clinical, electrodiagnostic testing, or neuropathological examination
- UMN signs by clinical examination
- Progressive symptom or sign spread within a region or to other regions, as determined by history or examination

With the absence of:
- Electrodiagnostic or pathological evidence of other diseases explaining LMN and UMN signs
- Neuroimaging evidence of other diseases explaining the observed clinical and electrodiagnostic signs

El Escorial diagnostic categories

Clinically definite
- Clinical evidence of UMN and LMN signs in the bulbar and two spinal regions, or
- UMN and LMN signs in three spinal regions

Clinically probable
- Clinical evidence of UMN and LMN signs in at least two regions with UMN signs rostral to LMN signs

Clinically probable—laboratory supported
- Clinical evidence of UMN and LMN signs in one region or UMN signs alone in one region, and
- LMN by electrodiagnostic criteria in at least two regions

Clinically possible
- Clinical evidence of UMN and LMN in one region, or
- UMN signs in two or more regions, or
- LMN signs are rostral to UMN signs

anticipate this complication. Furthermore, cognitive dysfunction and behavioural abnormalities might be prognostic of disease stage.[21] In a report of 146 patients with amyotrophic lateral sclerosis, cognition worsened in 30% after 6 months, even among patients that initially presented with normal cognition.[22] The patients who presented with cognitive decline had a more rapid clinical progression and shorter survival than those with normal cognition. Network analyses of brain MRIs show widespread disruption of motor and extramotor networks that correspond with amyotrophic lateral sclerosis phenotypes. Specifically, abnormal structural connectivity correlates with motor impairment, whereas disrupted functional connectivity aligns with changes in cognition and behaviour.[28]

Collectively, this new understanding of amyotrophic lateral sclerosis as a multisystem disorder underscores the importance of managing cognitive decline and neuropsychological problems (eg, depression, dysfunctional sleep, apathy, and irritability).[24] Importantly, when cognitive symptoms emerge, care teams should engage early with patients and their families to inquire about end-of-life care preferences to ensure the patient has an active role in these important conversations.

Diagnosis

Criteria

Patients with amyotrophic lateral sclerosis are unlikely to encounter a neurologist early in the diagnostic journey.[29,30] Therefore, there should be a low threshold for neurological referral when patients present with progressive dysarthria, dysphagia, limb weakness, or neuromuscular respiratory failure. The Amyotrophic Lateral Sclerosis Association's thinkALS tool[31] encourages early neurological referral to avoid unnecessary procedures, starts patients on disease-modifying treatments, and fast-tracks patient enrolment into clinical trials. Additional indications of a diagnosis of amyotrophic lateral sclerosis include unexplained weight loss, pseudobulbar affect, changes in cognition or executive functioning, and a family history of amyotrophic lateral sclerosis or other neurodegenerative

diseases. Clinical features that do not support a diagnosis include prominent sensory, sphincter, and autonomic nervous system dysfunction and anterior visual pathway abnormalities. A detailed neurological examination should identify signs of UMN and LMN dysfunction in bulbar, cervical, thoracic, or lumbosacral segments (panel 2).

Clinical history and neurological examination are accompanied by serological and electrodiagnostic testing. Patients with amyotrophic lateral sclerosis have normal serology, except for elevated creatine phosphokinase concentrations in some cases. Other abnormal serologies call into question an amyotrophic lateral sclerosis diagnosis. Nerve conduction studies exclude sensory nerve involvement and motor nerve conduction block. Needle electromyography can confirm LMN involvement, with the provision that testing of distal muscles, and muscles in the involved clinical segment, have the highest sensitivity.[33,34] Most neurologists still use the revised El Escorial criteria to subclassify amyotrophic lateral sclerosis, which categorises patients as possible, probable, probable laboratory supported, and definite amyotrophic lateral sclerosis, depending on clinical presentation and electromyography findings. The revised El Escorial criteria are most widely used (panel 2).[32]

Regarding advances in diagnostic criteria for amyotrophic lateral sclerosis, the Gold Coast criteria have been proposed to simplify and potentially replace the revised El Escorial and improve inter-rater reliability (appendix pp 7–9).[35] The Gold Coast criteria are primarily based on clinical presentation, although they do not consider cognitive changes, which the authors noted were covered by the 2017 Strong criteria.[36] Gold Coast classifies patients as having or not having amyotrophic lateral sclerosis, streamlining diagnostic certainty and eliminating confusion to patients and their relatives from El Escorial terminology. A comparison of the sensitivity and specificity of the various criteria reveal that Gold Coast criteria are the most sensitive, whereas El Escorial are the most specific (appendix pp 7–9). Additionally, the revised El Escorial criteria provide information that the Gold Coast criteria do not, such as the distribution of clinical segmental involvement, which is important for stratifying disease severity in patients with amyotrophic lateral sclerosis. Although the revised El Escorial criteria remain the mainstay of amyotrophic lateral sclerosis diagnosis, the field could be slowly moving towards simpler criteria, such as the Gold Coast.

Overall, early diagnosis of the disease is important. Educational efforts for physicians most likely to encounter patients with amyotrophic lateral sclerosis during initial symptom onset are essential to support prompt recognition of the disease and timely initiation of treatment. As simplified diagnostic criteria become more universally accepted, we anticipate that more practitioners will recognise and treat amyotrophic lateral sclerosis early in the disease course.

Cognitive assessment

Although not part of formal amyotrophic lateral sclerosis diagnostic criteria, it is essential to evaluate cognition and behaviour in patients with amyotrophic lateral sclerosis, despite potentially further fatiguing individuals undergoing long and complex clinical visits. Assessments of cognitive and behavioural impairment are essential as they relate to prognosis and progression rate, and thus inform clinical management.[21,22] Assessment of cognitive impairment in patients with amyotrophic lateral sclerosis should include multiple cognitive domains (eg, executive and language dysfunction, and social cognition).[37] Behavioural impairment (eg, apathy, disinhibition, loss of empathy, and compulsive behaviour) also affects the wellbeing of patients and family members and requires evaluation.

Some patients are diagnosed with frontotemporal dementia (amyotrophic lateral sclerosis–frontotemporal dementia, known as ALS–FTD), as defined by the criteria set by Neary and colleagues[38] or Rascovsky and colleagues.[39] For patients not meeting formal frontotemporal dementia criteria, the revised Strong criteria define patients with amyotrophic lateral sclerosis with cognitive dysfunction as amyotrophic lateral sclerosis cognitive impairment, with behavioural problems as amyotrophic lateral sclerosis behavioural impairment, or with both, as amyotrophic lateral sclerosis combined cognitive behavioural deficits (appendix p 10).[36] Several assessment batteries can classify these changes. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS) is a validated, multidomain, assessment tool developed for patients with amyotrophic lateral sclerosis, which can be administered by neuropsychological and non-neuropsychological professionals.[37] ECAS, available in 23 languages, covers the largest number of amyotrophic lateral sclerosis-specific cognitive or behavioural assessment scales. Incorporating ECAS into management of amyotrophic lateral sclerosis has a positive effect on the quality of care by stimulating end-of-life care discussions, referrals to other services, and identifying caregiver support needs.[40]

The Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen, available in three languages, can also identify cognitive and behavioural impairment and frontotemporal dementia in patients with amyotrophic lateral sclerosis.[37] The ALS–FTD questionnaire, completed by health-care professionals or caregivers to assess behavioural changes in patients with amyotrophic lateral sclerosis, is translated into nine languages and able to identify patients with behavioural variant frontotemporal dementia.[37] The Beaumont Behavioural Inventory is a screening tool developed in 2017 for evaluating behavioural impairment in patients with amyotrophic lateral sclerosis and might be more sensitive than the ALS–FTD questionnaire.[37]

Overall, cognitive symptoms should be recognised as a manifestation of amyotrophic lateral sclerosis, and

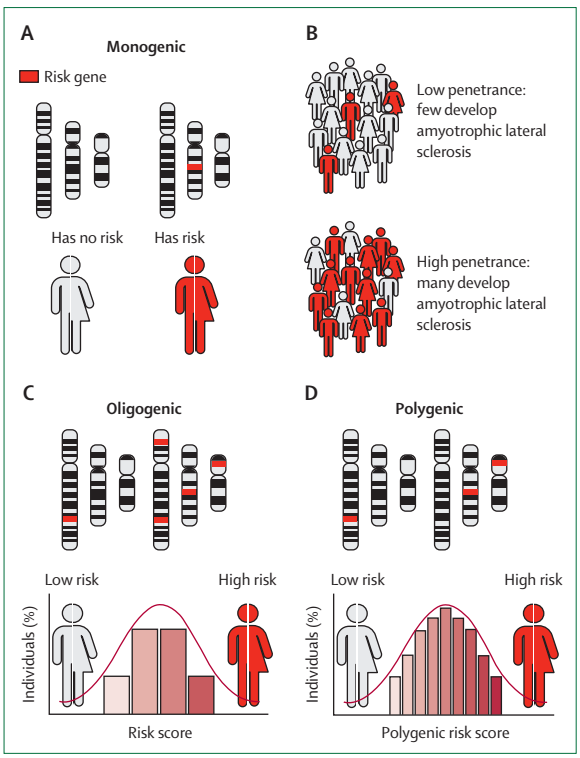


Figure 2: **Amyotrophic lateral sclerosis genetic architecture**
Adapted from Goutman et al.[2] Amyotrophic lateral sclerosis genetics is characterised by monogenic, oligogenic, and polygenic risk; figure featuring only three representative chromosomes (within each panel, chromosomes on the left for a person without the disease, on the right for a person with the disease). (A) Monogenic inheritance is characterised by inheritance of a single gene. (B) amyotrophic lateral sclerosis genes are not fully penetrant and pathogenicity of certain variants is uncertain. (C) Oligogenic inheritance is characterised by inheritance of several genes (four shown in the figure). (D) Polygenic inheritance is characterised by inheritance of many genes (nine shown in the figure).

properly identifying these symptoms improves disease management, counselling, and prognostication. Since cognitive symptoms can change with disease progression, regularly assessing them is crucial to best care for the patient. Future directions include standardising cognitive assessments for in-clinic screening, determining whether neuropsychologists should become part of the regular multidisciplinary team, and developing evidence-based treatments for cognitive impairment in amyotrophic lateral sclerosis.

Genetic architecture

Amyotrophic lateral sclerosis is currently classified as either familial or sporadic. Familial amyotrophic lateral sclerosis, which constitutes 10–15% of cases, is inherited from family members with amyotrophic lateral sclerosis and associated syndromes (eg, frontotemporal dementia).[41] About 70% of familial cases have mutations within known amyotrophic lateral sclerosis genes. Sporadic amyotrophic lateral sclerosis, which constitutes approximately 85% of the remaining cases, arises in patients without a family history of amyotrophic lateral sclerosis. About 15% of patients with sporadic amyotrophic lateral sclerosis harbour private pathogenic mutations (mutations limited to a single individual) to known amyotrophic lateral sclerosis genes, hence, they are without a family history of amyotrophic lateral sclerosis.[41] There is no known cause in the remaining 85% of sporadic cases of amyotrophic lateral sclerosis. Sporadic cases harbouring low penetrant mutations and belonging to small families, or having incomplete or poor knowledge of family history, could in fact be familial amyotrophic lateral sclerosis. Thus, familial amyotrophic lateral sclerosis might be under-reported and represent closer to 20% of cases.[42,43] As genetic testing becomes more widely implemented, and potential candidate therapies more targeted, it might become useful to drop the familial versus sporadic dichotomy of amyotrophic lateral sclerosis, in favour of genetically confirmed versus non-genetically confirmed amyotrophic lateral sclerosis (ie, presence versus absence of an amyotrophic lateral sclerosis mutation underpinning the molecular subclassification of the disease).

Genetic architecture of amyotrophic lateral sclerosis is highly complex and largely based on monogenic inheritance of rare variants (single disease-causing genes; figure 2A).[44] More than 40 amyotrophic lateral sclerosis-associated genes have been identified,[45,46] which vary in frequency, mode of inheritance (mostly dominant, rarely recessive), and penetrance (figure 2B; appendix pp 11–14). The most common and penetrant mutations are *C9orf72*, *TARDBP*, *SOD1*, and *FUS*,[45] although the frequency of genetic subtypes varies by population ancestry.[47] Some amyotrophic lateral sclerosis genes are not necessarily disease-inducing, but rather confer an increased risk of developing amyotrophic lateral sclerosis (*ANG*, *ATXN2*, and *DCTN1*).[45] Importantly, uncertainty remains on the relevance of some identified genes, which require further confirmation and replication efforts.[48] Consortia of amyotrophic lateral sclerosis genetics experts can curate and maintain an up-to-date list of amyotrophic lateral sclerosis genes as evidence emerges,[49] facilitating clinical translation for genetic testing. Since amyotrophic lateral sclerosis genetic architecture is complex, it is advisable that specialist amyotrophic lateral sclerosis centres perform genetic testing to avoid overdiagnosing or missing genetic amyotrophic lateral sclerosis. Of note, genetic testing in amyotrophic lateral sclerosis might not identify rare pathogenic variants (ie, allele frequency less than 1%).

In addition to primary monogenic inheritance in amyotrophic lateral sclerosis, interest in the effect on oligogenic and polygenic inheritance on disease risk has also gained traction. Several studies highlight that oligogenic inheritance, meaning a trait or disease controlled by inheritance of several genes, might have a role in amyotrophic lateral sclerosis risk and disease progression (figure 2C).[50,51] Genetic screening identified a subset of patients with sporadic amyotrophic lateral sclerosis harbouring two or more variants in amyotrophic

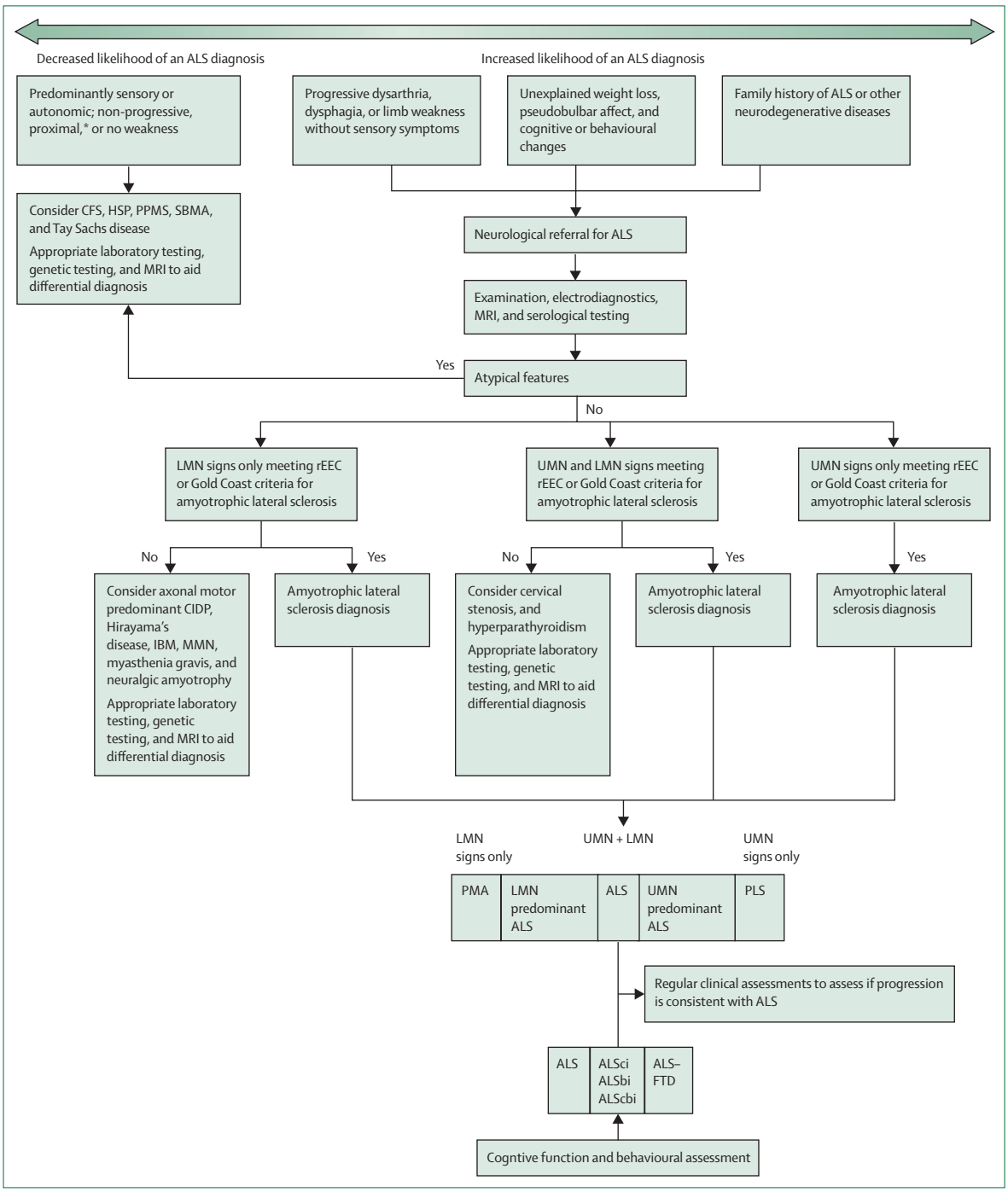


Figure 3: **Amyotrophic lateral sclerosis differential diagnosis**
Differential diagnosis, represented here by a flowchart for the classical process by use of symptoms and signs, is central to the diagnostic process in amyotrophic lateral sclerosis. At minimum, individuals suspected of the disease will undergo physical and neurological examinations, electrodiagnostic assessment, MRI of involved regions, and relevant serological testing. This figure is based on a summary of potential differential diagnoses for diseases more common or as common as amyotrophic lateral sclerosis (appendix p 10). Overlap of known amyotrophic lateral sclerosis genes with other diseases and syndromes also occurs (appendix pp 11–13). ALS=amyotrophic lateral sclerosis. CFS=cramp-fasciculation syndrome. CIDP=chronic inflammatory demyelinating polyneuropathy. HSP=hereditary spastic paraparesis. IBM=inclusion body myositis. LMN=lower motor neuron. MMN=multifocal motor neuropathy. MG=myasthenia gravis. PPMS=primary progressive multiple sclerosis. rEEC=revised El Escorial criteria. SBMA=spinobulbar muscular atrophy. UMN=upper motor neuron. *Several potential differential diagnoses present with proximal weakness and should be considered along with flail arm amyotrophic lateral sclerosis, which also presents with proximal greater than distal upper extremity weakness. Thus, check for increased proximal reflexes on examination and neurogenic motor unit action potentials on electromyography.

lateral sclerosis genes; these patients were more likely to have earlier onset disease versus patients with one or no variants.[50,51] Polygenic inheritance, arising from inheritance of multiple genetic variants, is also a component of amyotrophic lateral sclerosis genetic architecture (figure 2D).[52,53] Analysis of the genetic profiles identified shared polygenic risk of amyotrophic lateral sclerosis with traits and single nucleotide polymorphisms correlated with smoking status, physical activity, cognitive performance, and educational attainment,[52] as well as obesity-related traits, [52,53] particularly hyperlipidaemia. Our growing knowledge of the genetic architecture is due, in great part, to large collaborative projects, which are driving discovery in this relatively rare disease, such as the Amyotrophic Lateral Sclerosis Sequencing Consortium,[54] International Amyotrophic Lateral Sclerosis Genomics Consortium,[55] Genomic Translation for Amyotrophic Lateral Sclerosis Care Consortium,[54] Answer Amyotrophic Lateral Sclerosis Foundation,[54] and Project MinE.[54] We anticipate that these consortia will continue to deliver results and foster further investigation.

Importantly, amyotrophic lateral sclerosis is also characterised by incomplete heritability, meaning genetics does not fully account for all disease burden. Estimates vary, but most studies report heritability of 45–50% in amyotrophic lateral sclerosis parent–child dyads, driven largely by rare genetic variants.[1] However, heritability estimates can be as high as 66% in some dyad comparisons and as low as 37% in patients without a known genetic risk.[1] Several additional factors can account for missing heritability in amyotrophic lateral sclerosis,[56] such as alterations in the non-coding genome, structural variants,[57] epigenetic changes,[58] and environmental factors.[59] The contribution of the environment has led to the gene–time–environment hypothesis of amyotrophic lateral sclerosis,[60] which proposes that an interaction of genes and environment over time causes amyotrophic lateral sclerosis through a multistep process.[61] Evolving evidence shows that the environment effects amyotrophic lateral sclerosis risk and progression in a gene-dependent manner.

As therapeutics that target some genetic forms of amyotrophic lateral sclerosis become a possibility, genetic testing for all patients with amyotrophic lateral sclerosis will probably become standard practice. Future genetic treatments will increase the need for classifying and assessing genetic variants in amyotrophic lateral sclerosis. Additionally, partnership with genetic counsellors will expand to facilitate discussions of these complex results with patients and their families.[62]

Differential diagnosis and overlap syndromes

General physicians, and even specialist neurologists, might not initially recognise a diagnosis of amyotrophic lateral sclerosis in a patient with symptoms due to overlap of disease presentation with other conditions. Thus, classical differential diagnosis on the basis of clinical presentation is an important element of the diagnostic process in amyotrophic lateral sclerosis (figure 3; appendix pp 14–15).

Diseases more common than amyotrophic lateral sclerosis are often considered and thoroughly evaluated first, which ultimately delays an amyotrophic lateral sclerosis diagnosis. Conditions that most commonly mimic amyotrophic lateral sclerosis include multifocal motor neuropathy with conduction block, axonal motor-predominant chronic inflammatory demyelinating polyneuropathy, spinobulbar muscular atrophy, and inclusion body myositis.[63] Simultaneous cervical nerve root and spinal cord compression by disc herniations, tumours, or malformations might cause combined LMN symptoms in the arms and UMN symptoms in the legs, and be misdiagnosed as classical amyotrophic lateral sclerosis.[63] UMN-dominant amyotrophic lateral sclerosis or primary lateral sclerosis can be confused with hereditary spastic paraplegias or primary progressive multiple sclerosis. Additional, but rare, differential diagnoses include hyperparathyroidism and hexosaminidase A deficiency.[63] Since some of these disorders are treatable, these possibilities should be ruled out.

In conjunction with clinical presentation, genetic testing is increasingly used to explain disease cause and predict family risk. Risk amyotrophic lateral sclerosis genes can cause other syndromes or phenocopy alternative neurodegenerative diseases (appendix pp 11–13). *C9orf72* expansions, the most common amyotrophic lateral sclerosis gene, are linked to movement disorders[64,65] and phenocopy Huntington's disease in patients without huntingtin (*HTT*) expansions.[66] Conversely, patients with amyotrophic lateral sclerosis can have *HTT* repeat expansions simultaneously with TDP-43 inclusions.[67] Thus, patients could present with atypical amyotrophic lateral sclerosis, delaying diagnosis. Additional amyotrophic lateral sclerosis genes overlap with other syndromes and an improved understanding of the complexity of genotype–phenotype relationships will expedite the diagnosis of amyotrophic lateral sclerosis. Finally, the disease is associated with neuropsychiatric illnesses, such as psychosis and suicidal ideation,[68,69] thus, clinicians should obtain comprehensive detailed family history, not just of amyotrophic lateral sclerosis, but of neurodegenerative and neuropsychiatric illnesses.

Risk, progression, and pathophysiology

Identifying factors that increase amyotrophic lateral sclerosis risk and progression is central to patient diagnosis and care. Genetics are a major risk factor for amyotrophic lateral sclerosis (appendix pp 11–14). For instance, *C9orf72* expansions are penetrant and confer high risk, and are also associated with bulbar onset[14] and a decreased survival[70] in some studies. However, there are genetic mutations that confer risk but do not affect progression; therefore, risk and progression can be independent processes, and factors influencing either, or both, are an active area of research.[71]

A patient's cumulative environmental lifetime exposures, known as the exposome, is also increasingly recognised to confer amyotrophic lateral sclerosis risk and could accelerate disease progression.[72] Independent of whether risk is secondary to genetics or the exposome, a knowledge of amyotrophic lateral sclerosis pathophysiology will promote the development of novel treatment and prevention strategies, such as genetic therapies for asymptomatic carriers of highly penetrant pathogenic mutations.[73]

Molecular pathomechanisms

In amyotrophic lateral sclerosis, pathological processes arise from toxic gain-of-function or loss-of-function mutations to the approximately 40 known amyotrophic lateral sclerosis genes. Toxicity also occurs from aggregates of both wild-type and mutant proteins, which is a universal pathological feature in sporadic and familial amyotrophic lateral sclerosis.[74] Pathophysiological processes broadly fall into four major categories: impaired RNA metabolism, altered proteostasis or autophagy, cytoskeletal or trafficking defects, and mitochondrial dysfunction.[75] Several amyotrophic lateral sclerosis genes, including *C9orf72*, *TARDBP*, and *FUS*, impair RNA metabolism. Aggregation of the DNA and RNA binding proteins, TDP-43 and FUS, into inclusions impairs their normal function, causing broad changes to transcription and RNA processing. *TDP-43*, among several other amyotrophic lateral sclerosis genes, also dysregulates proteostasis and autophagy by preventing the clearance of damaged proteins. Multiple mutant amyotrophic lateral sclerosis genes, such as tubulin alpha 4a (*TUBA4A*) and profilin 1 (*PFN1*), induce cytoskeletal and tubulin defects, blocking axonal trafficking. Mitochondrial dysfunction, as triggered by *SOD1*, is a central characteristic for amyotrophic lateral sclerosis, which also increases oxidative stress.

Although much progress has been made, the full molecular underpinnings of the pathophysiology are incompletely understood. In addition to the major processes previously mentioned, TDP-43 and SOD1 aggregates also transfer from cell to cell in prion-like transmission,[76,77] which would propagate the pathology. *TARDBP*, *FUS*, and several other genes are linked to dysfunctional DNA repair in amyotrophic lateral sclerosis. For instance, loss of nuclear TDP-43 induces accumulation of double-stranded DNA breaks,[78] which would compromise genome stability. TDP-43 aggregates,[79] mutant *FUS*,[80] and *C9orf72* repeat expansions[81] also impair nucleocytoplasmic transport, the shuttling of cargo between the nucleus and cytoplasm.[79] Dipeptide repeat proteins derived from mistranslated *C9orf72* expansion transcripts are neurotoxic and might promote heterochromatin anomalies[82] and TDP-43 aggregation.[83]

Central and peripheral inflammatory mechanisms are important contributors to amyotrophic lateral sclerosis,[84] both in the context of specific genetic mutations[85–87] and probably as a consequence of the general disease process in sporadic disease.[88,89] In amyotrophic lateral sclerosis, changes occur in specific immune cell populations,[88,89] their activation state,[88] and cytokine production.[86,87] Immune system involvement in amyotrophic lateral sclerosis is double-edged; a protective initial response is overcome by a destructive cytotoxic phase.[84] Hypermetabolism is also a broad characteristic,[90] both dependent and independent of mutations in amyotrophic lateral sclerosis, and metabolomics investigations[91] could provide information on the specific molecular changes that underscore disease progression. Pathways related to amyotrophic lateral sclerosis genes, inflammation, hypermetabolism, and other continued insights into the pathological mechanisms underlying the disease provide an essential knowledge base for therapeutic development and prevention strategies.

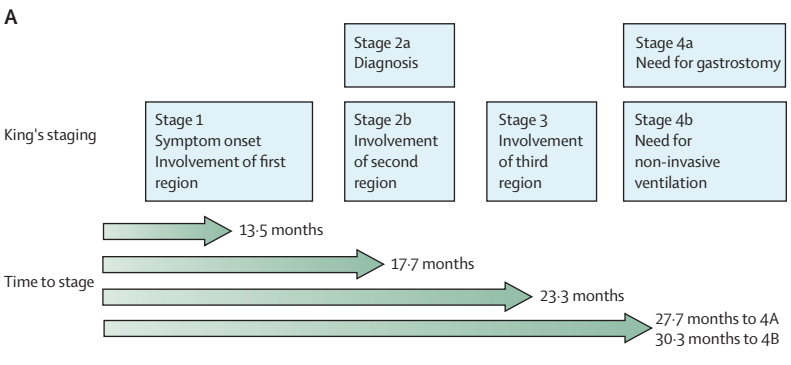
Environmental exposure

The gene–time–environment hypothesis of amyotrophic lateral sclerosis suggests that genetic susceptibility, age-related cellular damage, and a burden of environmental exposures combine to trigger amyotrophic lateral sclerosis.[60] Several lines of evidence support this model. First, genetic variants do not fully account for the disease.[92] Second, population-based modelling of amyotrophic lateral sclerosis indicates that disease occurs in a multistep process,[61] even in patients with highly penetrant monogenic mutations (eg, mutant *SOD1*).[93] Finally, a growing body of research supports the association of environmental exposures with disease risk, with a new focus on the amyotrophic lateral sclerosis exposome.[59]

The amyotrophic lateral sclerosis exposome is defined as the cumulative lifetime effect of environmental exposures, including lifestyle factors. Since the exposome involves exposures throughout a patient's lifespan, multiple study designs are needed to interrogate its role in amyotrophic lateral sclerosis. Many case-control studies have explored the relationship between occupational, residential, and avocational environmental risk factors on the risk of amyotrophic lateral sclerosis. Although studies leveraging population-based registries would provide a higher level of evidence, studies based on retrospective cohorts show reassuringly consistent results (appendix pp 16–17).

Of exposures with documented relevance to amyotrophic lateral sclerosis, plasma-persistent organic pollutants[94] and blood metals[95,96] correlate with disease risk and shortened survival.[72] Lifestyle factors associated with risk of amyotrophic lateral sclerosis include high cigarette pack-years, a low current BMI, and lifetime alcohol consumption.[97] Some relationships are dependent on *C9orf72* status,[97] showing an interaction between genes and environment. Physical activity as a risk is supported by several studies,[97,98] including analysis of the National Football League players.[99] Military service is also a recurring theme in risk assessments for amyotrophic lateral sclerosis.[100]

A

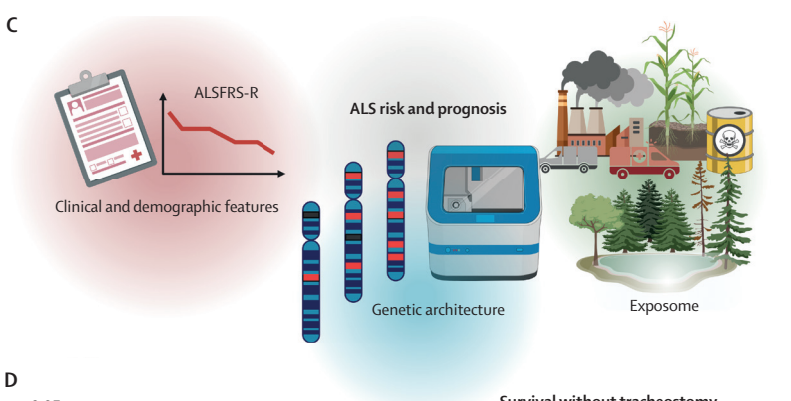


	Stage 1	Stage 2	Stage 3	Stage 4A
Median survival at each stage (bulbar or limb)	19 months for bulbar, 59 months for limb	19 months for bulbar, 28 months for limb	13 months for bulbar and limb	9 months for bulbar, 6 months for limb Stage 4B, 3 months for bulbar, 8 months for limb

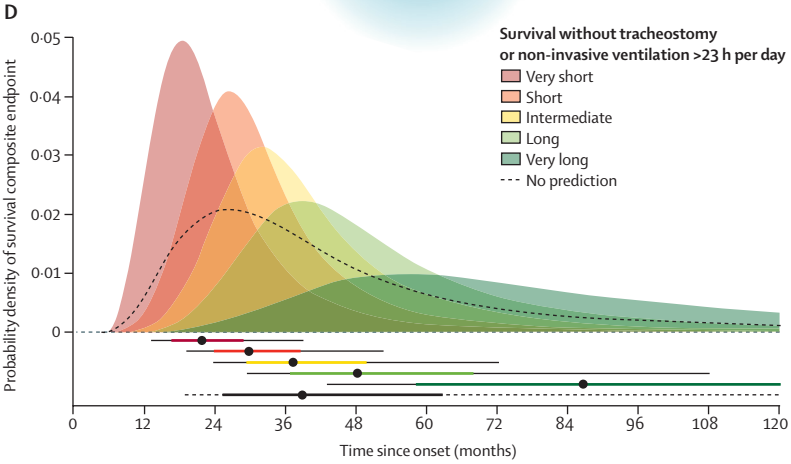
B

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
ALS-MiToS staging	No loss of a functional domain	Loss of 1 domain	Loss of 2 domains	Loss of 3 domains	Loss of 4 domains	Death
Probability of death at each stage	0·07	0·26	0·33	0·33	0·86	

C



D



There are some important unanswered questions relating to the amyotrophic lateral sclerosis exposome. Are there periods of greater susceptibility to exposure throughout life, which increase the risk of amyotrophic lateral sclerosis? Will it be possible to adopt a preventative approach to the disease if modifiable risks are identified? Prospective studies using well curated population registries and biorepositories can help answer these questions and are a future goal of the field.[59]

Prognosis

Prognosis of amyotrophic lateral sclerosis is dependent on disease progression. Currently, clinicians monitor disease progression using the Amyotrophic Lateral Sclerosis Functional Rating Score-Revised (ALSFRS-R), a multidomain assessment that also serves as the gold standard for primary efficacy outcomes in clinical trials.[101] Respiratory function, which is a domain of the ALSFRS-R, provides prognostic information.[102] One shortcoming of the ALSFRS-R is that some subscores increase with symptom improvement despite continued underlying disease progression.[101,103] The Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale was designed to specifically capture functional decline arising from the underlying disease course,[103] thereby overcoming the limitations of the ALSFRS-R. The Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale awaits clinical validation before widespread adoption.

New staging examples have also been developed to inform prognosis. Patients assessed with the King's staging system[104] and Amyotrophic Lateral Sclerosis Milano-Torino Staging (ALS-MiToS)[105] system consistently

Figure 4: **Amyotrophic lateral sclerosis risk and prognosis**
(A) King's staging with four stages indicated (blue); time to progress to stages and median survival at each stage in months. (B) ALS-MiToS staging with six stages indicated (orange); staging based on four functional domains from the ALSFRS-R: (1) movement (walking and self-care; ALSFRS-R question 6 or 8); (2) swallowing (ALSFRS-R question 3); (3) communicating (ALSFRS-R questions 1 and 4); and (4) breathing (ALSFRS-R question 10 or 12). Intensifying colour indicates progression along stages for both King's and ALS-MiToS. (C) Schematic overview of factors that affect amyotrophic lateral sclerosis risk (onset) and prognosis, which include clinical and demographic features, genetic architecture (eg, rapidly progressive *SOD1*^{A5V} and slowly progressive *DCTN1* mutations), and exposome (eg, environmental exposures). (D) ENCALS prediction model of amyotrophic lateral sclerosis prognosis. Reproduced from Westeneng and colleagues,[70] with permission from Elsevier. The model defines five survival groups: very short (red; predicted median survival 17·7 months), short (orange; predicted median survival 25·3 months), intermediate (light orange; predicted median survival 32·2 months), long (light green; predicted median survival 43·7 months), and very long (green; predicted median survival 91·0 months). The dashed black line represents median survival without the use of the ENCALS prediction model, which is overly optimistic for patients with amyotrophic lateral sclerosis classified to the very short and short survival groups (ie, they end up with less time), and overly pessimistic for patients classified to long and very long groups (ie, they end up with more time). Horizontal bars have dots to represent median times to composite outcome, thick lines to represent probability IQR, and thin lines to represent 10–90% probability intervals to composite outcome. ALS=amyotrophic lateral sclerosis. ALS-MiToS=ALS Milano-Torino Staging. ALSFRS-R=ALS Functional Rating Score-Revised.

progress along stages that are associated with decreasing median survival (figure 4A, B). The King's staging system is more sensitive early in the disease course; the ALS-MiToS later in the disease course.[106,107] Neither staging system is yet in widespread clinical use.

Although median survival for amyotrophic lateral sclerosis is only 2–4 years, there is a broad distribution of individual patient survival, affecting both the clinician's ability to discuss and the patient's ability to understand disease prognosis. This variability is attributable to various factors that influence survival in amyotrophic lateral sclerosis (figure 4C), such as clinical and demographic features (eg, age at onset, site of onset, and presence of frontotemporal dementia), genetic architecture (eg, rapidly progressive *SOD1*^{A5V} and slowly progressive *DCTN1* mutations; appendix pp 14–15), and the exposome (eg, environmental exposures). The European Network for the Cure of Amyotrophic Lateral Sclerosis model was created to predict personalised survival (defined as survival without tracheostomy or non-invasive ventilation >23 h/day) based on eight parameters: onset age, time to diagnosis, ALSFRS-R progression rate, forced vital capacity, bulbar onset, definite amyotrophic lateral sclerosis by revised El Escorial criteria, frontotemporal dementia, and *C9orf72* repeat expansion (figure 4D).[70] Although not in routine clinical use, the European Network for the Cure of Amyotrophic Lateral Sclerosis prediction tool can potentially benefit patients by giving them a more accurate perspective of life expectancy.

Overall, accurate prognostication of the clinical course of the disease remains in its infancy since even predictions by the best models retain uncertainty. Thus, clinical care teams should advise patients and their families on the anticipated disease course and range of expected symptoms, with the caveat that these predictions can vary with each patient. Variation of disease phenotypes, even within the same family, attests to this unpredictability. Although clinical staging methods provide useful metrics for comparing participant stages in clinical research populations, their use in the clinic remains to be established.

Treatment

As amyotrophic lateral sclerosis remains incurable, treatment is focused on the use of disease-modifying therapies and maximising quality of life. The American Academy of Neurology, the European Federation of Neurological Societies, the UK National Institute for Health and Care Excellence,[108] and Amyotrophic Lateral Sclerosis Canada[109] have published evidence-based and expert consensus guidelines for managing amyotrophic lateral sclerosis, and supportive multidisciplinary care improves survival and quality-of-life for patients with amyotrophic lateral sclerosis (table 1).[110] The two medications with approval in some countries for slowing progression of amyotrophic lateral sclerosis are riluzole and edaravone. Riluzole, an antiglutamate agent, improves patient survival in clinical trials and postmarketing analyses, but whether this prolongation occurs at all stages of amyotrophic lateral sclerosis or just at advanced disease stages remains a topic of debate.[116,117] The antioxidant edaravone, given for 6 months, showed some efficacy in post-hoc analysis of the first phase 3 trial for participants, meeting the criteria of definite or probable amyotrophic lateral sclerosis (El Escorial and revised Airlie House diagnostic criteria), disease duration less than 24 months, forced vital capacity (lung function test) of more than 80%, and ALSFRS-R subscale scores all more than 2.[121] The trial was repeated prospectively with this defined patient population,[118,122] and again reported that edaravone slowed disease progression. However, this trial design could lack generalisability to the broader population of patients with amyotrophic lateral sclerosis and postmarketing analyses raise questions about edaravone's safety and benefits.[119,120] Thus, use of edaravone remains controversial and has not obtained worldwide approval. A combination of dextromethorphan and quinidine is approved in the USA for managing symptoms of pseudobulbar affect.[123] This drug is not marketed in all countries and alternative and more cost-effective treatments are available. Non-invasive ventilation also improves amyotrophic lateral sclerosis survival and quality of life.[124] For this reason, patients with amyotrophic lateral sclerosis should be regularly monitored for respiratory symptoms and undergo the appropriate respiratory assessments, such as overnight oximetry or measures for blood gas partial pressure of CO_2, blood bicarbonate concentrations, vital capacity, or maximum inspiratory pressure to confirm whether they qualify for non-invasive ventilation.[125]

Gastrostomy is also an effective therapy for supporting nutrition and is probably of greater benefit when established earlier in the disease course. Gastrostomy tubes can be inserted with percutaneous endoscopic gastrostomy, radiologically inserted gastrostomy, and per-oral image-guided gastrostomy placement with similar mortality.[126] Factors that are associated with a poor outcome after gastrostomy include use of non-invasive ventilation for more than 16 h/day, older age, BMI less than 20 kg/m², and recurrent accumulation of airway secretions.[127] High calorie nutrition has also been investigated for treating amyotrophic lateral sclerosis[90] and post-hoc analysis of a phase 3 trial suggests that it might be helpful for rapidly progressing patients,[128] although confirmatory trials are needed.

Several additional treatments are available (panel 3). Patients with amyotrophic lateral sclerosis might also contemplate alternative and off-label treatments, often found on the internet. Amyotrophic Lateral Sclerosis Untangled was conceived to provide a systematic review of unproven treatments. Care guidelines for amyotrophic lateral sclerosis encourage providers to have an open

For more on **Amyotrophic Lateral Sclerosis Untangled** see https://www.alsuntangled.com/

***Panel 3*: Treatments and interventions for management of amyotrophic lateral sclerosis**

Disease-modifying treatments

Disease progression

Only two drugs with regulatory approval are available, riluzole and edaravone. They are of marginal efficacy and only in select populations, and merely lengthen survival by a few months.[116–118] However, even within select populations, the efficacy of edaravone is contested.[119,120]

Symptomatic management

Comprehensive care

A multidisciplinary clinic plans the comprehensive, multidisciplinary care needed to manage symptoms in patients with amyotrophic lateral sclerosis. Care spans the management of respiration and oral symptoms (speech and swallowing); nutrition and gastrointestinal symptoms; pain and symptoms secondary to muscle loss; and cognition, mood, and behavioural changes.

Respiratory and oral symptoms

Bronchial secretions

Stop any provoking medications. Administer mucolytics if the patient exhibits sufficient cough flow, including N-acetylcysteine, anticholinergic bronchodilator, β-receptor antagonist and nebulised saline, furosemide, and guaifenesin. Mechanical or non-pharmacological approaches are also available, including manual assisted cough, mechanical insufflator–exsufflator, portable home suction device, and room humidifier. Additionally, patients are encouraged to remain hydrated or drink pineapple or papaya juice to break up secretions.

Dysarthria

Evaluate speech and language regularly and identify language impairments. Provide assistive communication tools, such as electronic writing, voice banking, and voice amplification devices.

Dyspnoea

Options include elevating the head of the bed, use of a hospital bed for elevation, non-invasive ventilation, and invasive tracheostomy ventilation.

Sialorrhea

Administer anticholinergics, such as amitriptyline, atropine ophthalmic drops, glycopyrrolate, and scopolamine patch. If sialorrhea is refractory to anticholinergics, botulinum toxin injections, external beam radiation therapy, and surgery can be considered. A portable suction device is a less aggressive approach. Dark grape juice and ginger tea are reported to decrease saliva production.

Nutrition and gastrointestinal symptoms

Constipation

Increase fluid and fibre intake or adjust enteral nutrition. Administer an osmotic or stimulant laxative. Increase physical activity.

Sources

EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis,[62] the American Academy of Neurology,[111–113] the UK National Institute for Health and Care Excellence (NICE),[108] Amyotrophic Lateral Sclerosis Canada[109] and other Canadian guidelines,[114] and Bradley and Daroff's Neurology in Clinical Practice.[115] These therapies, in most cases, represent good clinical practice as few clinical trials involving patients with amyotrophic lateral sclerosis exist to provide a robust evidence base for these interventions.

dialogue about the use and risks of these treatments, especially as some can carry medical or financial risk.

Emerging directions in amyotrophic lateral sclerosis

Novel treatment approaches

Recognition of heterogeneity, genetics, and a deeper understanding of pathophysiology in amyotrophic lateral sclerosis brings new treatment approaches to the amyotrophic lateral sclerosis community. This recognition promotes new trial designs to address heterogeneity, genetic therapies, immune-targeting agents against inflammation, and stem cells to enrich the CNS environment.

New trial designs

New amyotrophic lateral sclerosis clinical trials can leverage a basket design of targeted agents against participant populations defined by phenotypes or genetics.[129,130] Novel platform trial designs simultaneously evaluate multiple therapies in distinct arms against a single placebo group, lowering the number of required participants and shortening trial duration.[129] Adaptive designs can further shorten trial duration by response-adaptive randomisation, which increases participant allocation to more promising treatment groups.[129] Several major trials with novel compounds and treatment approaches are currently underway (appendix pp 18–23).

Genetic therapies

There is a growing consensus that gene therapy is a promising avenue in amyotrophic lateral sclerosis. One strategy is silencing toxic gain-of-function genes by targeting mRNA and pre-mRNA with antisense oligonucleotides. The first clinical trial of the *SOD1* antisense oligonucleotide, BIIB067, showed safety, evidence of target engagement, and promising trends in exploratory secondary outcome measures.[131] However, the phase 3 clinical trial did not meet its primary efficacy outcome of slowing disease progression as measured by the ALSFRS-R, although cerebrospinal fluid (CSF) SOD1 protein and neurofilament concentrations were significantly decreased.[132] A new approach is earlier

intervention with BIIB067 during the presymptomatic phase of disease in mutant *SOD1* carriers (NCT04856982; appendix p 19). Clinical trials are also underway of antisense oligonucleotides that target other autosomal dominant gain-of-function mutations, including *C9orf72*, *FUS*, and *ATAXN2*.[133]

Antibodies

Monoclonal antibodies against mutant *C9orf72* and *TDP-43* are in preclinical development.[134] Several clinical trials have also been launched, but besides reporting safety, none were effective (eg, tocilizumab and ozanezumab).[134] A few antibody candidates are still in the clinical trial pipeline, including AP-101 against *SOD1* aggregates (NCT05039099), ANX005 against C1q protein (NCT04569435), and AT-1501 against CD40L protein (NCT04322149; appendix pp 18–23).

New anti-inflammatory therapies that target the immune system are also in the clinical pipeline (appendix pp 18–23). Phase 1/2 clinical trial results report that low-dose interleukin-2 is well tolerated and immunologically effective in increasing regulatory T-cell numbers, although its effect on progression of amyotrophic lateral sclerosis is still being evaluated in a phase 2b/3 trial (MIROCALS).[135] Autologous infusion of expanded Treg cells in a small patient cohort slowed disease progression.[136] Masitinib, a tyrosine kinase inhibitor, reduces microglial activation and showed promise in a phase 2/3 trial.[137] These reports underscore the feasibility of immune-targeting drugs as candidate therapies for amyotrophic lateral sclerosis.

Stem cells offer the unique opportunity to simultaneously target multiple dysregulated pathways while providing CNS neurotrophic support.[138] They can derive from diverse sources (eg, mesenchymal stem cells and neural progenitor cells [appendix pp 18–23]), each offering distinct advantages and disadvantages.[138] One meta-analysis concluded that adult stem cells are safe and well tolerated,[139] however, apart from a possible transient positive effect, trials have not shown long-lasting efficacy from stem cells.

Novel diagnostic biomarkers

There is an urgent need for amyotrophic lateral sclerosis biomarkers to expedite diagnosis, particularly in atypical phenotypes, and enable improved prognosis of disease course. Biomarkers can also refine clinical trial participant stratification, facilitate the estimation of progression rates, monitor target engagement, and detect early potential treatment effects.

Neurofilaments

CSF and plasma neurofilaments are well characterised and promising fluid biomarkers. Elevated CSF and plasma neurofilament light chain concentrations correlate with shorter survival, more aggressive disease phenotypes, and presence of *C9orf72* expansion.[140–142] Plasma neurofilaments are also elevated up to 5 years before disease onset in sporadic and familial cases of amyotrophic lateral sclerosis,[143,144] and indicate phenoconversion in clinically asymptomatic mutant *SOD1* carriers.[143] Some 2020 clinical trials support their use as pharmacodynamic markers of amyotrophic lateral sclerosis progression.[131,145]

Regarding brain imaging, although routine MRIs cannot diagnose amyotrophic lateral sclerosis, MRIs with quantitative analysis of fluid-attenuated inversion recovery can identify increased corticospinal tract and corpus callosum intensities in patients with amyotrophic lateral sclerosis.[146] More advanced structural and functional MRI techniques are not yet in routine clinical practice but might provide new diagnostic biomarkers. Examples include diffusion tensor imaging[147,148] and multimodal[147,149] approaches, such as quantitative susceptibility mapping to detect iron-related motor cortex changes, and connectome analyses of motor and non-motor networks. T1-weighted imaging and diffusion tensor imaging detect abnormalities (cortical and subcortical atrophy and white matter changes) already present in presymptomatic *C9orf72* repeat expansion carriers.[150] Although not a disease-specific biomarker, positron emission tomography by use of tracers to quantify brain metabolism ([^{18}F]-fluorodeoxyglucose) or glial activation ([^{11}C]-PBR28) provides new insights into disease mechanisms and could prove useful as pharmacodynamic indices in future clinical trials.[151,152]

Neurophysiological markers

Neurophysiological markers of disease-associated changes are currently available. Spectral electroencephalogram mapping reveals brain connectivity changes in amyotrophic lateral sclerosis, which correlate with MRI findings and could become useful, cost-effective markers of cortical network disruption.[153,154] Magnetoencephalography shows enhanced connectivity during progression of amyotrophic lateral sclerosis.[155]

Cortical motor neuronal hyperexcitability can sometimes be detected by routine transcranial magnetic stimulation (TMS); however, more often, refined techniques such as threshold-tracking TMS measuring short-interval intracortical inhibition and intracortical facilitation are necessary to detect subclinical UMN involvement.[156] Cortical hyperexcitability across phenotypes of amyotrophic lateral sclerosis distinguishes the disease from non-amyotrophic lateral sclerosis disorders, correlates with clinically affected body regions,[157] disease spread,[157] and cognitive dysfunction.[158] TMS might also have a role in prognosis, with increased cortical hyperexcitability associated with longer disease duration[159] and cortical inexcitability with poorer clinical trajectory.[160] Change in short-interval intracortical inhibition was the primary endpoint in a phase 2 amyotrophic lateral sclerosis trial of patients with amyotrophic lateral sclerosis given retigabine, a potassium channel activator, showing the potential of neurophysiological outcome measures as pharmacodynamic disease markers.[161]

LMN degeneration can be quantified by the non-invasive motor unit index, which correlates with the number of functioning motor units.[156] This index detects motor unit decline already in clinically unaffected muscle groups and can monitor motor unit loss over time. When used as an outcome measure in clinical trials, the index requires thorough qualification of the rater to ensure reliability.[162]

Conclusions

Amyotrophic lateral sclerosis remains difficult to diagnose and manage. This difficulty is due to heterogenous presentation and multiple disease phenotypes, and the overlap of symptoms and signs with other illnesses. Early in the diagnostic process, physicians should refer patients presenting with progressive dysarthria, dysphagia, limb weakness, or respiratory failure to a neurologist. This referral aligns with suggestions by advocate groups, as they lobby to help patients seek early treatment and enrol in clinical trials. Unfortunately, there are no effective disease-modifying drugs, and treatment revolves around multidisciplinary care to manage symptoms and aid end-of-life planning.

Research into improved diagnostic and prognostic tools could expedite diagnosis and give patients a better understanding of their disease course. Thus, we anticipate future directions in clinical management of the disease will move towards simpler diagnostic criteria, such as the Gold Coast criteria, and widespread genetic testing. Research will evaluate whether newly developed scoring, staging, and predictive tools will give patients meaningful and accurate insight into their anticipated clinical trajectory. Pathophysiology research and novel trial designs are developing rational, targeted candidates, which are passing through the clinical testing pipeline more efficiently. We anticipate that these research efforts will translate into improved outcomes for current and future patients with amyotrophic lateral sclerosis.

Contributors

All authors contributed to conceptualisation, writing of the original draft, and reviewing and editing it.

Declaration of interests

ELF and SAG have a patent issued (US20200253977A1). SAG reports personal fees from Biogen, ITF Pharma, and Watermark, outside the submitted work. SP reports grants from the German Neuromuscular Society, the German-Israeli Foundation for Scientific Research and Development (GIF), and personal fees from Cytokinetics, Desitin Pharma, Italfarmaco, Biogen, Roche, and Zambon outside the submitted work. PJS reports consultancy and advisory board membership with Biogen, Benevolent AI, QurALIS, Quell, and Aclipse Therapeutics, outside the submitted work. GS reports personal fees from Mitsubishi Tanabe Pharma Corporation, Cyberdyne, Biogen Japan, Takeda Pharmaceutical, Nihon Pharmaceutical, and Teijin Pharma, outside the submitted work. LM and MGS declare no competing interests.

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