Amyotrophic Lateral Sclerosis 2

Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis

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The diagnosis of amyotrophic lateral sclerosis can be challenging due to its heterogeneity in clinical presentation and overlap with other neurological disorders. Diagnosis early in the disease course can improve outcomes as timely interventions can slow disease progression. An evolving awareness of disease genotypes and phenotypes and new diagnostic criteria, such as the recent Gold Coast criteria, could expedite diagnosis. Improved prognosis, such as that achieved with the survival model from the European Network for the Cure of ALS, could inform the patient and their family about disease course and improve end-of-life planning. Novel staging and scoring systems can help monitor disease progression and might potentially serve as clinical trial outcomes. Lastly, new tools, such as fluid biomarkers, imaging modalities, and neuromuscular electrophysiological measurements, might increase diagnostic and prognostic accuracy.

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This is the second in a **Series** of two papers on amyotrophic lateral sclerosis

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Introduction

Amyotrophic lateral sclerosis is a neurodegenerative disease characterised by progressive, painless muscle weakness due to motor neuron death in the brain and spinal cord.[1] Weakness begins in facial, tongue, and pharyngeal muscles in individuals with bulbar-onset disease, producing dysarthria and then dysphagia, or in distal upper-limb or lower-limb muscles in people with spinal-onset disease. Most patients with spinal-onset amyotrophic lateral sclerosis present with weakness in one body region that spreads over time to the same region on the contralateral side, as well as to regions rostral and caudal to the initial region of onset. Amyotrophic lateral sclerosis is now understood as a systems disease and there is substantial variation in clinical presentation, including of non-motor symptoms, behavioural changes, and cognitive decline (eg, frontotemporal dementia). Death generally occurs within 2–4 years of diagnosis from respiratory failure, although more slowly progressive forms of the illness occur in a small proportion of patients.

Diagnosis can be challenging, and the process has remained essentially unchanged in clinical practice in the past decade. No test or tool has replaced clinical history and examination for confirming diagnosis, even with the increased adoption of genetic testing. The typical median time between initial symptoms and a definitive diagnosis is 10–16 months,[2] due to the rarity of the disease, incomplete recognition of symptoms, and lack of early and appropriate specialist involvement.[3] Additionally, prognosis remains suboptimal because the determinants of disease progression are not fully known.

To facilitate earlier diagnosis and improve prognosis, research is ongoing into new diagnostic criteria and scoring systems, as well as emerging diagnostic and prognostic fluid biomarkers, imaging modalities, and electrophysiological measurements. This Series paper will highlight these emerging discoveries and focus on the most recent advances in diagnosis and prognosis within the past 5 years. This paper is accompanied by a research-focused Series paper,[4] which provides an update on the complex genetics, pathophysiology, therapeutic development, and exposome science of amyotrophic lateral sclerosis.

Epidemiology

Amyotrophic lateral sclerosis incidence and prevalence varies across the globe, and estimates are based on different data sources. The availability of registries in some countries enables more accurate calculations of incidence and prevalence, advocating for the need of population-based registries worldwide (panel 1). A recent meta-analysis of 110 incidence studies and 58 prevalence studies estimated an average global incidence of 1·59 (95% CI 1·39–1·81) and a prevalence of 4·42 (3·92–4·96) per 100 000 individuals.[11] Ancestral background and biological sex are linked to amyotrophic lateral sclerosis rates in an age-dependent manner.[12] Despite male predominance, heritability is greater in women, with the highest concordance in female–female parent–offspring pairs.[9] Male carriers of the *C9orf72* repeat expansion develop amyotrophic lateral sclerosis at an earlier age (by about 2 years) than female carriers do.[13] Thus, an intricate interplay between age, sex, and complex genetics drives the risk of amyotrophic lateral sclerosis.[12] These sex-dependent differences urge consideration of sex in preclinical and clinical research (to understand the basis of these effects), and in clinical trials for developing therapeutics.

Clinical presentation

Amyotrophic lateral sclerosis was historically considered a fairly uniform disease of progressive, painless weakness of voluntary muscles.[1] However, studies have redefined it as a complex disorder with considerable heterogeneity in clinical presentation, site of disease onset, and distribution of upper and lower motor neuron signs (figure A, table 1). Recognition of these multiple heterogeneous presentations can facilitate early diagnosis and inform prognosis.[16] The Australian National Motor Neuron Disease (1677 patients with amyotrophic lateral sclerosis)[14] and Italian Piemonte and Valle d'Aosta registries (2839 patients with amyotrophic lateral sclerosis)[12,15] have documented this heterogeneity in presentations, which also correlate with median survival (figure B). Patients with bulbar-onset disease are at a greater risk of frontotemporal dementia than are patients with other presentations.[12] Additionally, less common presentations exist (eg, hemiplegic; table 1).[17] Furthermore, presentations can correlate with the timing of some treatments. In the Australian registry, feeding tube placement secondary to dysphagia occurs earlier in patients with bulbar-onset disease than in those with spinal-onset disease,[14] as was also reported in a European tertiary care cohort of people with amyotrophic lateral sclerosis.[18]

Panel 1: Global incidence

Standardised incidence

The standardised incidence of amyotrophic lateral sclerosis is similar among European populations (1·89 per 100 000 in Northern Europe, 1·71 per 100 000 in Western Europe, and 1·75 per 100 000 Southern Europe), and is higher than the standardised incidence in South American populations (1·59 per 100 000) and Asian populations (0·83 per 100 000 in East Asia, 0·94 per 100 000 in West Asia, and 0·73 per 100 000 in South Asia).[5] Standardised rates are highest in Oceanian populations (2·56 per 100 000) and north African populations (2·03 per 100 000).[5] There are no data on incidence for sub-Saharan Africa. Standardised incidence in North American populations is 1·79 per 100 000.[5]

Incidence by age

Incidence peaks between the ages of 60 and 75 years.[6] In the USA, the National ALS Registry, which is coordinated by the Centers for Disease Control and Prevention, reports a peak prevalence between the ages of 60 and 79 years.[7] Although global burden of amyotrophic lateral sclerosis is anticipated to increase due to the ageing of populations,[8] the Irish ALS Register did not observe a rise in incidence between 1995 and 2017.[9]

Incidence by sex

Sex plays a part in amyotrophic lateral sclerosis incidence and prevalence. In the Southeast England ALS Registry, the male-to-female ratio in incidence at younger ages (25–34 years) was 3·7, which narrows to 1·2 in the 65–74-year age group, but then grows slightly to 1·4 for those aged 75 years or older.[10] Sex differences in the prevalence of amyotrophic lateral sclerosis are present in the US National ALS Registry, which reports that 60% of people living with amyotrophic lateral sclerosis are male.[7] The Irish ALS Register reports a lifetime risk of 1:347 for males and 1:436 for females.[9]

Thus, classification is based on clinical criteria, such as site of disease onset and distribution of upper and lower motor neuron signs.[16] Additional relevant clinical variables, such as age, sex, family history, progression rate, genetic profile, and presence of cognitive impairment and other non-motor symptoms, aid disease classification and can provide prognostic guidance.[19]

Non-motor symptoms

The concept of amyotrophic lateral sclerosis as a pure motor disease is now abandoned. In fact, it has been known for decades that executive dysfunction occurs in 50% and frontotemporal dementia in 15% of patients. Executive dysfunction is evaluated by a suite of neuropsychological tests (table 2),[20] and frontotemporal dementia in patients with amyotrophic lateral sclerosis is diagnosed by the revised Strong criteria.[25] The most characteristic cognitive changes in amyotrophic lateral sclerosis include impaired language function[22] and executive function deficits involving working memory, inhibition, set shifting, and fluency, whereas memory and spatial function are typically spared.[23] Patients also experience cognitive decline and neuropsychiatric symptoms, including apathy, disinhibition, irritability, loss of sympathy or empathy, perseveration, reduced concern for hygiene, and changes in eating habits. Similar clinical patterns are present in patients with frontotemporal dementia.[23] Additionally, many patients with amyotrophic lateral sclerosis have anxiety, depression, and sleep disorders.[26]

***Figure:* Heterogeneity in initial presentation and staging of amyotrophic lateral sclerosis**

(A) Involvement of motor neuron dysfunction at initial presentation in different presentations. Spinal-onset amyotrophic lateral sclerosis involves variable motor neuron dysfunction in a combination of limbs. Bulbar-onset amyotrophic lateral sclerosis involves motor neuron dysfunction in bulbar muscles (eg, facial, tongue, and pharyngeal). Flail-arm amyotrophic lateral sclerosis involves lower motor neuron dysfunction in the arms, although mild dysfunction of the upper motor neurons can occur in the legs too. Flail-leg amyotrophic lateral sclerosis often involves asymmetric lower motor neuron dysfunction in the legs. Primary lateral sclerosis mainly involves upper motor neuron dysfunction in the arms and legs or bulbar region, although restricted dysfunction of lower motor neurons can develop in the later disease stages or become more widespread if it transitions to amyotrophic lateral sclerosis, often within 4·5 years of symptom onset. (B) Distribution of amyotrophic lateral sclerosis presentations in the Australian National Motor Neuron Disease Registry (N=1677; each human figure represents one percentage point)[14] and distribution of amyotrophic lateral sclerosis presentations in the Italian Piemonte and Valle d'Aosta Registry (N=1332; each human figure represents one percentage point);[12,15] median survival in years is presented under each presentation. Note that the two registries use slightly different classification systems. (C) King's staging with four stages indicated (1, 2A/B, 3, 4A/B; blue); time to progress to stages and median survival at each stage (in months) for both bulbar-onset and limb-onset forms are also annotated. (D) ALS-MiToS staging with six stages indicated (0, 1, 2, 3, 4, 5; orange); staging is based on four functional domains from the ALSFRS-R: (i) movement (walking or self-care; ALSFRS-R question 6 or 8); (ii) swallowing (ALSFRS-R question 3); (iii) communicating (ALSFRS-R questions 1 and 4), and (iv) breathing (ALSFRS-R question 10 or 12). Intensifying colour indicates progression along stages for both King's and ALS-MiToS. ALS-MiToS=Amyotrophic Lateral Sclerosis Milano-Torino Staging. ALSFRS-R=amyotrophic lateral sclerosis functional rating score–revised.

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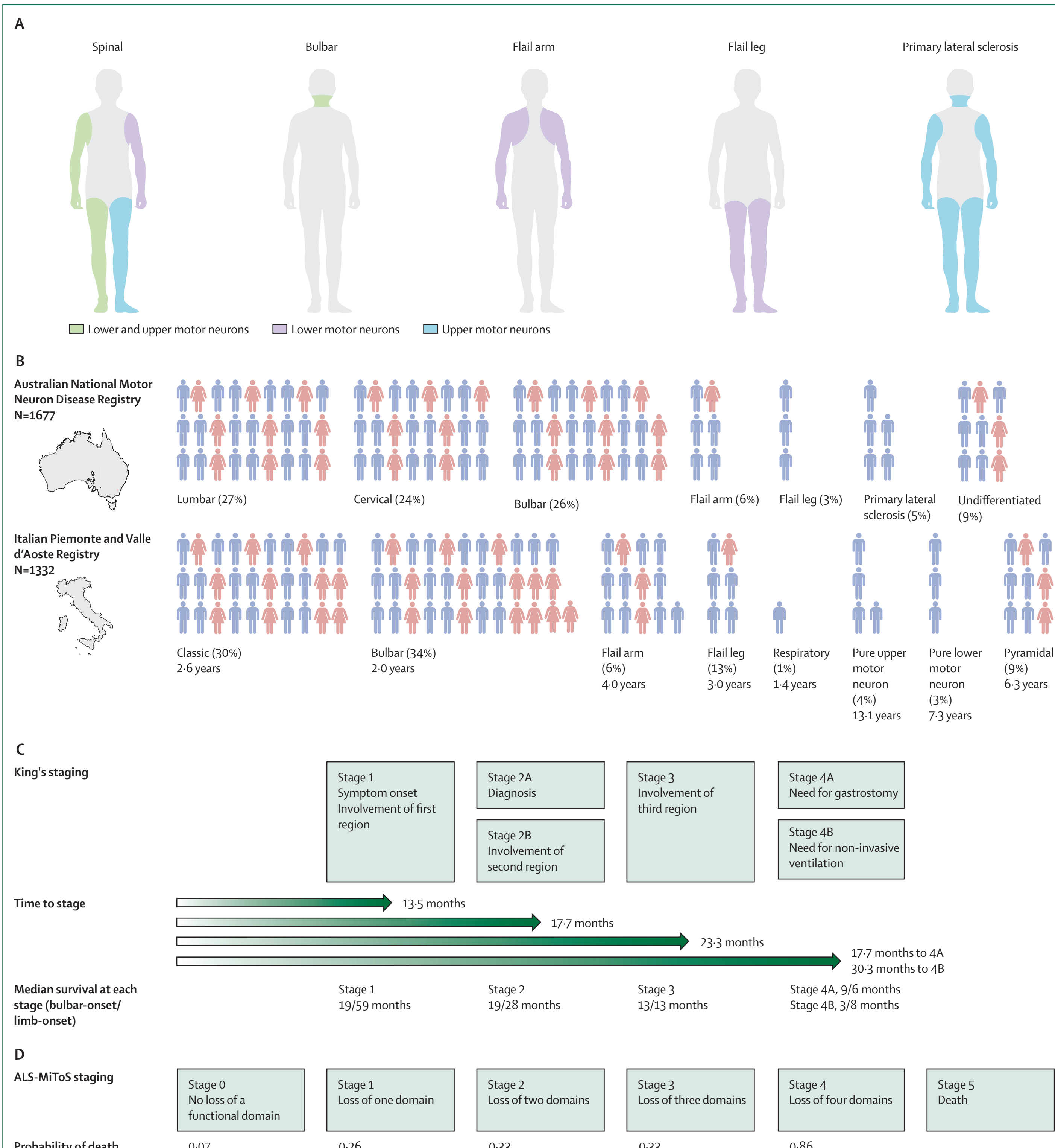
Executive dysfunction is a negative prognostic indicator and, if present, tends to worsen over time.[27] Cognitive impairment can later manifest even in patients who seem to be cognitively spared at diagnosis[27] and might be partly related to the worsening of motor function.[23] Thus, there is a growing need to incorporate an evaluation of cognitive



	Affected motor neurons	Progression	Additional features
Classic bulbar onset	Upper and lower motor neurons	Begins with dysarthria, then dysphagia, then spreads to the limbs	Might have unexplained weight loss; typically will benefit from earlier feeding tube placement *vs* those with limb-onset disease
Pseudobulbar palsy	Upper motor neurons	Prominent bulbar features that slowly spread to the limbs	Affects more females than males; longer survival than for other phenotypes; pseudobulbar effect
Progressive bulbar palsy	Lower motor neurons	Prominent bulbar features, which spread to limbs	Patients progress to ALS, although median survival can be longer than for those with classic bulbar-onset disease
Classic cervical onset	Upper and lower motor neurons	Typically, hand weakness that spreads to bulbar and lumbar regions	Trouble with hand dexterity or grip; split hand a prominent symptom
Classic lumbar onset	Upper and lower motor neurons	Typically, foot drop with weakness spreading to cervical and bulbar regions	Trouble with gait and a tendency to trip
Flail arm	Lower motor neurons in upper extremities; upper motor neurons in lower extremities	Symmetrical weakness in proximal upper limb (more so than in distal upper limb) that eventually spreads	Slower progression than for other presentations; affects more males than females
Flail leg	Lower motor neurons in lower extremities	Symmetrical lower-limb weakness	Lower motor neuron weakness usually, but upper motor neuron signs will often develop
Primary lateral sclerosis	Upper motor neurons	Might begin in any region and spread over time; if lower motor neuron signs develop within 4·5 years, diagnosis is amyotrophic lateral sclerosis instead	Normal life expectancy; exclude hereditary spastic paraparesis if the disease involves symmetrical lower-limb signs
Progressive muscular atrophy	Lower motor neurons	Might begin in any region and spread over time; if upper motor neuron signs develop within 4·5 years, diagnosis is amyotrophic lateral sclerosis instead	Male predominance; absence of upper motor neuron signs
Respiratory	Upper and lower motor neurons	Limb weakness follows respiratory involvement	Short survival
Hemiplegic	Unilateral upper motor neurons affected more than lower motor neurons	Often begins in leg and spreads to ipsilateral arm	Patients can have protracted disease course
Cachexia	Upper and lower motor neurons	Unexplained weight loss preceding presentation with classic limb-onset amyotrophic lateral sclerosis	Rapidly progressing disease

Classic amyotrophic lateral sclerosis refers to disease with combined upper and lower motor neuron dysfunction in the onset segment, which progressively spreads from region to region. Non-classical or atypical forms refer to phenotypes with predominance of upper or lower motor neuron dysfunction in a segment.

Table 1: **Clinical spectrum of amyotrophic lateral sclerosis**

function into the diagnosis and ongoing management of amyotrophic lateral sclerosis. These behavioural changes can also frustrate family members or caregivers and prevent the patient from accepting medical recommendations, emphasising the importance of addressing care preferences early in the disease.[28] These cognitive and behavioural symptoms can be accompanied by structural changes in extramotor domains of the brain.

The influence of genes on clinical phenotype

The discovery of mutant *SOD1* in a subset of patients with amyotrophic lateral sclerosis in 1993 suggested a potential genetic aetiology, which enhanced our understanding of risk factors and pathophysiology.[29] This possibility was strengthened in 2011 by the discovery of *C9orf72* repeat expansions in a larger proportion of patients, both with and without a family history of amyotrophic lateral sclerosis.[30] The genetic architecture of amyotrophic lateral sclerosis and nuances of familial versus sporadic disease are fully detailed in the accompanying research-focused Series paper.[4] More than 40 genes have been identified to date, which together account for about 15% of cases. Thus, genetic testing is a growing, albeit non-uniform, component of disease management. As the cost of genetic profiling drops, we anticipate earlier and broader adoption. First, detection of known pathogenic variants could complement and bolster diagnoses achieved by diagnostic criteria. Second, although most mutations converge on a typical phenotype, there are important prognostic implications for some mutant genes linked to unique features (table 3). For example, *ALS2*, *DCTN1*, *MATR3*, *OPTN*, and *SETX* mutations are associated with slower clinical trajectories than those in patients with other, more common, types of amyotrophic lateral sclerosis, information that is valuable to patients and their families. Furthermore, routine genetic profiling could move past the inadequate stratification of patients into sporadic or familial disease.

Additionally, genetic profiling promotes precision medicine[33] and clinical trial stratification for targeted therapeutics (eg, gene therapies). Therefore, a genetic profile could potentially facilitate diagnosis, prognosis, and treatment for patients harbouring genetic mutations.

Diagnosis

Diagnostic criteria date back to the original El Escorial and later the revised El Escorial (Airlie House) and Awaji criteria. They rate the degree of diagnostic “certainty by clinical assessment alone” from possible to probable to definite amyotrophic lateral sclerosis, on the basis of the number of affected segments combined with clinical or electrophysiological findings, or both.[34–36] The El Escorial classification provides prognostic information because, for instance, definite amyotrophic lateral sclerosis progresses faster.[19] Although approaches that score the certainty of diagnosis solely by clinical assessment are reasonable (ie, possible amyotrophic lateral sclerosis), they can delay diagnosis and confuse patients, their families, and clinicians, who misinterpret these terms as meaning the diagnosis is improbable or incorrect.[37] In reality, nearly all patients diagnosed as having possible amyotrophic lateral sclerosis progress and ultimately die from the disease.

Emerging diagnostic criteria

To address these limitations, an international consensus group reconsidered criteria to improve the diagnostic process in the early stages of disease when clinical symptoms are minimal.[38] Recognising the broad heterogeneity in presentations, the Gold Coast criteria define amyotrophic lateral sclerosis by: (1) progressive motor impairment, documented by history or repeated clinical assessment, preceded by normal motor function; (2) upper and lower motor neuron dysfunction in at least one body region, or lower motor neuron dysfunction in at least two body regions; and (3) investigative findings that exclude alternative diseases.

Adoption of these simplified criteria abandons the previous diagnostic categories of possible, probable, and definite. The advent of these new criteria facilitates early and definitive diagnosis. An Australian study found that the diagnostic sensitivity of Gold Coast criteria (92%) was maintained irrespective of functional status, disease duration, or onset site, and was generally similar to that of the revised El Escorial (88·6%) and Awaji criteria (90·3%); however, the Gold Coast criteria were more sensitive and specific for identifying progressive muscular atrophy and for ruling out primary lateral sclerosis as a form of ALS, the latter of which meets the definition of possible amyotrophic lateral sclerosis in the revised El Escorial and Awaji criteria.[39] This finding was validated in a five-centre European study, which found consistent and improved sensitivity of the Gold Coast criteria, due to greater sensitivity for identifying progressive muscular atrophy.[40] Lastly, a Chinese study corroborated the greater sensitivity of the Gold Coast against the revised El Escorial and Awaji criteria,[41] suggesting that its diagnostic utility would be maintained in racially diverse populations. Importantly, the Gold Coast criteria were marginally less specific, which clinicians should bear in mind as they monitor their patients’ disease course. However, overall, we anticipate that the new Gold Coast criteria will facilitate diagnosis and dispel uncertainty and confusion for patients and their families.

	Signs and symptoms	Neuropsychological tests
Executive function		
Working memory	Unable to temporarily process, store, and use information with conscious awareness[20]	Digit span subtest (Wechsler Adult Intelligence Scale, fourth edition); Corsi block-tapping test or spatial span (Wechsler Memory Scale, third edition)
Inhibition	Inability to ignore stimuli, which can result in impulsive behaviour	Flanker task, continuous performance test, antisaccade task (NIH EXAMINER); Stroop test (Delis-Kaplan Executive Function System)
Set shifting	Inability to change attention and behaviour for different circumstances and demands,[20] causing rigid thinking and impairments in multitasking	Trail-making test (Delis-Kaplan Executive Function System); Wisconsin card sorting; set shifting test (NIH EXAMINER)
Fluency	Disorganised thoughts or inability to initiate tasks	Verbal and design fluency tests; category fluency
Language function		
Language impairment	Impairment in word naming, spelling, and grammatical processing	Psycholinguistic Assessments of Language Processing in Aphasia
Behaviour		
Apathy	Passivity and low levels of spontaneity and initiative, loss of interest and motivation for previously rewarding activities, and diminished social interest[21]	Beaumont Behavioural Inventory
Disinhibition	Impulsivity, low self-restraint, socially inappropriate behaviours, irritability, verbal or physical aggression, disinhibited emotional display, changes in sexual behaviour, and decline in personal hygiene[21]	Beaumont Behavioural Inventory
Loss of sympathy or empathy	Diminished response and understanding of the needs and feelings of others, reduced inter-relatedness and personal warmth, and emotional detachment[21]	Beaumont Behavioural Inventory
Perseveration and stereotyped or obsessive–compulsive behaviours	Simple repetitive movements, more complex ritualistic behaviours, and stereotypy of speech[21]	Beaumont Behavioural Inventory
Eating behaviours	Changed food preferences, and increased smoking, binge eating, hyperorality, and oral exploration of inedible items[21]	Beaumont Behavioural Inventory

Changes are shown along with associated symptoms and testing strategies.[20–24] NIH=National Institutes of Health.

Table 2: **Cognitive impairment and psychiatric comorbidities in patients with amyotrophic lateral sclerosis**

Clinical overlap with other neurodegenerative disorders

Amyotrophic lateral sclerosis is a multifaceted disease with remarkable heterogeneity of motor and non-motor features. This complexity contributes, in part, to the difficulty of diagnosing the disease, which is rendered more challenging by its clinical overlap with other more common neurological and neuromuscular diseases (table 3). Additionally, *C9orf72* repeat expansions, the most

	Inheritance pattern	Proportion of familial cases	Proportion of sporadic cases	Associated clinical phenotype	Overlap with other diseases
ALS2	Autosomal recessive	<1%	<1%	Slowly progressive; infantile and juvenile forms mainly affect upper motor neurons; primary lateral sclerosis	Hereditary spastic paraparesis
ANG	Autosomal dominant; presence is a risk factor	<1%	<1%	Typical; bulbar-onset tendency; frontotemporal dementia	No overlap
ANXA11	Autosomal dominant	~1%	~1·7%	Not determined	Autoimmune diseases, sarcoidosis
ATXN2	Autosomal dominant; presence is a risk factor	<1%	<1%	Typical; early onset; phenotype modifer	Spinocerebellar ataxia
C9orf72	Autosomal dominant	40%	7%	Typical; frontotemporal dementia	Huntington's disease phenocopy, parkinsonism, essential tremor, myoclonus
C21orf2	Not determined	<1%	<1%	Typical; frontotemporal dementia	No overlap
CCNF	Autosomal dominant	~1·0–3·3%	<1%	Typical; frontotemporal dementia; primary lateral sclerosis	No overlap
CHCHD10	Autosomal dominant	<1%	<1%	Typical; frontotemporal dementia	Cerebellar ataxia, myopathy
CHMP2B	Autosomal dominant	<1%	<1%	Typical; progressive muscular atrophy	Frontotemporal dementia
DCTN1	Autosomal dominant; presence is a risk factor	<1%	<1%	Slowly progressive; juvenile	Perry syndrome (parkinsonism)
DNAJC7	Not determined	<1%	<1%	Not determined	No overlap
ELP3	Allelic	<1%	<1%	Typical	No overlap
FUS	Autosomal dominant or recessive, depending on variant; de novo	4%	1%	Typical or atypical; frontotemporal dementia; dementia; juvenile or adult onset	Essential tremor*
GLT8D1	Autosomal dominant	<1%	<1%	Typical; shorter or longer survival than typical ALS, depending on variant	Schizophrenia
GRN	Autosomal dominant; modifier	<1%	<1%	Earlier onset; shorter survival than typical ALS	Frontotemporal dementia, frontotemporal lobar degeneration, dementia with Lewy bodies*
HNRNPA1	Autosomal dominant; de novo; presence is a risk factor	<1%	<1%	Typical; cognitive impairment	Inclusion body myopathy
HNRNPA2B1	Autosomal dominant; presence is a risk factor	<1%	<1%	Typical; cognitive impairment	Inclusion body myopathy
KIF5A	Autosomal dominant	~0·5–3%	<1%	Early onset; longer survival than typical ALS	Charcot-Marie-Tooth disease type 2, primary progressive multiple sclerosis phenocopy,* hereditary spastic paraplegia

(Table 3 continues on next page)

common mutations associated with amyotrophic lateral sclerosis in populations of European descent, are among the strongest determinants of frontotemporal dementia. However, the clinical phenotypes present as a continuum from amyotrophic lateral sclerosis, to amyotrophic lateral sclerosis–frontotemporal dementia, to frontotemporal dementia, sometimes even within the same pedigree. Further complicating the situation, *C9orf72* repeat expansions are associated with movement disorders such as parkinsonism, essential tremor, and myoclonus,[42] in addition to cognitive impairment. The disease might present as atypical amyotrophic lateral sclerosis, which could contribute to a more difficult and lengthy diagnosis process. Therefore, awareness of additional manifestations of an amyotrophic lateral sclerosis mutation could facilitate early diagnosis. Additionally, *C9orf72* repeat expansions are the most frequent cause of Huntington's disease phenocopies (patients with the classic Huntington's disease phenotype but lacking characteristic *HTT* repeat expansions and inclusions).[43] Conversely, patients with amyotrophic lateral sclerosis might harbour *HTT* repeat expansions simultaneously with TDP-43 inclusions,[44] underscoring the complexity of genotype–phenotype associations. Understanding the spectrum of clinical presentations and overlap arising from mutations will expedite diagnosis. Finally, amyotrophic lateral sclerosis aggregates with neuropsychiatric illnesses, such as psychosis and suicidal ideation.[45] Amyotrophic lateral sclerosis and schizophrenia share a risk gene, *GLT8D1*,[46] as well as polygenic risk.[47] Therefore, in the family history of a patient with amyotrophic lateral sclerosis, it is not uncommon to find

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	Inheritance pattern	Proportion of familial cases	Proportion of sporadic cases	Associated clinical phenotype	Overlap with other diseases
(Continued from previous page)					
LGALSL	Not determined	<1%	<1%	Early onset; typical	
MATR3	Autosomal dominant	<1%	<1%	Slowly progressive; typical or atypical; frontotemporal dementia; myopathy	Distal myopathy
NEFH	Autosomal dominant; presence is a risk factor	<1%	<1%	Typical	Charcot-Marie-Tooth disease type 2*
NEK1	Not determined	~1–2%	<1%	Not determined	No overlap
OPTN	Autosomal dominant or recessive, depending on variant	<1%	<1%	Slowly progressive; atypical	Open-angle glaucoma, Paget's disease
PFN1	Autosomal dominant	<1%	<1%	Typical	No overlap
SETX	Autosomal dominant	<1%	<1%	Slowly progressive; juvenile	Spinocerebellar ataxia, progressive motor neuropathy
SPG11	Autosomal recessive	<1%	<1%	Slowly progressive; juvenile, mainly affects upper motor neurons	Hereditary spastic paraparesis
SOD1	Autosomal dominant or recessive, depending on variant; de novo	12%	1–2%	Prominent lower motor neurons; cognitive impairment very rare	No overlap
SQSTM1	Autosomal dominant	~1%	<1%	Typical	Paget's disease, frontotemporal dementia, dementia with Lewy bodies*
TARDBP	Autosomal dominant or recessive, depending on variant; de novo	4%	1%	Typical; frontotemporal dementia	Supranuclear gaze palsy
TBK1	Autosomal dominant; de novo	~3%	<1%	Typical; frontotemporal dementia	Frontotemporal lobar degeneration, dementia with Lewy bodies*
TIA1	Autosomal dominant	~2·2%	<1%	Frontotemporal dementia	Dementia with Lewy bodies*
TUBA4A	Autosomal dominant	<1%	<1%	Typical; frontotemporal dementia	No overlap
UBQLN2	X-linked; autosomal dominant	<1%	<1%	Typical; juvenile or adult onset; frontotemporal dementia	Frontotemporal dementia*
VAPB	Autosomal dominant	<1%	<1%	Typical or atypical	Spinal muscular atrophy, essential tremor
VCP	Autosomal dominant; de novo	1%	1%	Typical; frontotemporal dementia	Inclusion body myositis with Paget's disease, parkinsonism, scapuloperoneal muscular dystrophy, dropped head syndrome

Adapted, with modifications, from Goutman et al (2018)[31] and Chia et al (2018).[32] Typical phenotype refers to the classic motor phenotype. ALS=amyotrophic lateral sclerosis. *Findings limited to few patients.

Table 3: **Summary of genotype–phenotype correlations and their overlap with other diseases in people carrying genetic mutations associated with ALS**

members with other neurodegenerative or psychiatric diseases.

Prognosis

Nearly every patient with amyotrophic lateral sclerosis asks a series of questions, including on the amount of time the patient has left to live. Access to reliable prognostic methods allows clinicians to give patients and their families evidence-based answers. Despite important limitations,[48] clinicians and researchers currently rely on the revised functional rating score for amyotrophic lateral sclerosis (ALSFRS-R),[49] a scoring system that monitors the rate of disease progression. ALSFRS-R changes do not necessarily reflect improvement in disease; for instance, symptom management (eg, treating sialorrhoea) or medical decisions (eg, discontinuing non-invasive ventilation) affect the ALSFRS-R, even though there is no change in the patient's underlying disease. The multidimensionality of the ALSFRS-R limits its clinical usefulness, especially in clinical trials,[50] as well as its low responsiveness during plateau periods, which makes it hard to discern treatment effects in trials.[51] Clinicians also derive prognostic value from respiratory tests, such as forced vital capacity;[52] indeed, forced vital capacity is a predictive parameter in the European Network for the Cure of Amyotrophic Lateral Sclerosis (ENCALS) model.

Emerging prognostic methods

Scoring systems

The self-reported Rasch-Built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) was developed to overcome ALSFRS-R limitations by ensuring that symptom management or medical decisions do not ameliorate the disease score, which instead reflects true changes in disease progression.[53] Compared with the ALSFRS-R, the 28-question ROADS better captures functional changes because it accounts for function at the upper and lower ranges of disability. Additionally, the scale has high test–retest reliability and is designed for a 1-point change to represent the same change in function across the whole score spectrum. This new scale is not used in clinical practice as it requires validation; thus, whether ROADS will supplant or complement the ALSFRS-R requires further study.

Staging systems

A staging system identifies where an individual is in the disease course, thereby improving counselling and resource allocation. Staging systems are also useful in clinical trials to establish whether an intervention reduces advancement from less-severe to more-severe disease stages. The King's staging defines four progressive stages linked to survival (figure C) and can help in prognostication.[18] King's staging shows the different progression of patients as well. For instance, patients with bulbar onset require gastrostomy (stage 4A) before non-invasive ventilation (stage 4B), whereas non-invasive ventilation is usually needed before gastrostomy in patients with limb-onset disease. The Milano-Torino Staging for Amyotrophic Lateral Sclerosis (ALS-MiToS) places patients at one of six stages on the basis of select ALSFRS-R responses in four functional domains.[54] In ALS-MiToS, staging depends on the number of functional domains lost (figure D); stage 0 is no loss, a patient at stage 1 will have lost one functional domain, a patient at stage 2 will have lost two functional domains, and so on, with stage 5 representing death. Patients probably progress from stage to stage, as opposed to skipping stages, with increasing probability of death with each stage. The King's and ALS-MiToS systems are complementary; the King's staging system is superior for staging earlier in the disease course, whereas ALS-MiToS outperforms later in the disease course.[55] Although none of these instruments is used in clinical practice, both staging systems describe progression and survival, albeit with limitations,[56] and could be useful in clinical trials.[57]

ENCALS survival model

The ENCALS survival model is a recently developed approach for predicting survival in patients with amyotrophic lateral sclerosis, with non-survival defined as time to non-invasive ventilation for more than 23 h per day, tracheostomy, or death.[19] The model used data from 11 475 patients with amyotrophic lateral sclerosis from 14 centres at several European sites, and included 16 clinical predictors, of which only eight reached statistical significance (p<0·001), including age at onset, 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. These predictors define five survival groups: very short (predicted median survival 17·7 months); short (25·3 months); intermediate (32·2 months); long (43·7 months); and very long (91·0 months). The ENCALS survival model unlocks the potential for personalised prognosis, which is essential for a disease of such heterogeneity. The model accurately estimated the life expectancy of Stephen Hawking,[58] in stark contrast to the 2-year expectancy he was given at diagnosis.

Emerging diagnostic and prognostic biomarkers

Currently, the diagnosis of amyotrophic lateral sclerosis relies on an integrative approach, which leverages clinical history (eg, presenting illness and symptom evolution), physical examination (eg, testing strength and reflexes), and confirmatory tests (eg, electromyography).[59] Genetic testing is gaining traction but is not without caveats (table 3). Electromyography and nerve conduction studies are the mainstay of electrodiagnostic tests, although additional methods are available (panel 2). Although diagnosis remains suboptimal, there is an expanding toolbox of available methods and novel biomarkers. Presently, most of these approaches are only used in the research setting and have not been validated for clinical use.

Neurofilaments

Neurofilaments are neuronal cytoskeletal proteins that control neuron shape. Two markers are being developed: phosphorylated neurofilament heavy chain (NfH) in CSF and neurofilament light chain (NfL) in plasma, serum, or CSF. Phosphorylated NfH concentrations and NfL concentrations are elevated in individuals with amyotrophic lateral sclerosis compared with healthy controls.[71] NfL concentrations also rise 1 year before phenoconversion in presymptomatic individuals harbouring an amyotrophic lateral sclerosis gene.[72] Higher NfL and phosphorylated NfH concentrations correlate with more aggressive disease and shorter survival, but are of low prognostic value.[71,73] Because baseline NfL concentrations are predictive of ALSFRS-R trajectory, incorporating them into mixed-effects models of ALSFRS-R slopes might lower the number of participants needed in clinical trials.[82] However, increased neurofilament concentrations are characteristic of neurodegenerative diseases generally,[83] although they might still be fairly diagnostic of amyotrophic lateral sclerosis;[73] thus, overall, neurofilaments remain of uncertain diagnostic and prognostic use alone, but could add value when combined with other methods.

Brain and spinal cord imaging

Functional and structural brain imaging is a rapidly growing field,[67] with considerable progress after the advent of multisite imaging protocols,[84] studies indicating feasibility for early diagnosis[68] and possibility

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Panel 2: Diagnostic and prognostic biomarkers for amyotrophic lateral sclerosis

Diagnostic methods in clinical use

Criteria: the most frequently used are the revised El Escorial[34] (ie, Airlie House)[36] and Awaji[35] criteria; these criteria rate the degree of diagnostic certainty (possible to probable to definite) on clinical assessment, on the basis of the number of affected segments or electrophysiological findings, or both.

Electrodiagnostic: needle electromyography recordings are used to confirm the presence and extent of lower motor neuron involvement.[59]

Ultrasound: lower motor neuron fasciculations are often an early sign[60] (method is not very specific, so differential diagnosis might be needed); ultrasound can also be used to localise specific muscle groups during needle electromyography.

MRI: can be used to exclude cerebral and spinal amyotrophic lateral sclerosis mimics.[59]

Genetic testing: around 40 genes associated with disease are currently known; genetic testing is burgeoning, but with caveats.

Diagnostic methods in the research setting

Criteria: Gold Coast criteria are simplified criteria to define amyotrophic lateral sclerosis, particularly in the early stages.[38]

Electrodiagnostic: the number of functioning lower motor neuron units can be quantified using various methods,[61] whereas upper motor neuron involvement can be assessed by cortical hyperexcitability through transcranial magnetic stimulation with some diagnostic utility (and also by spectral EEG mapping and magnetoencephalography, which are both novel techniques);[62–66] these techniques will be useful as adjuncts to existing methods, but require further research to evaluate their integration in clinical practice and to establish their sensitivity and specificity.

MRI and PET: advanced brain and spinal cord imaging offer some diagnostic insight;[67–69] these techniques will be useful as adjuncts to existing methods but require additional research to evaluate their integration in clinical practice and their sensitivity and specificity.

Fluid biomarkers: the focus is on neurofilaments, but other biomarkers have been reviewed[70] (neurofilaments have uncertain diagnostic utility);[71–73] such biomarkers could serve as adjuncts to other methods.

Prognostic methods in clinical use

Scoring: the revised functional rating score for amyotrophic lateral sclerosis (ALSFRS-R) is an established scoring system to monitor the rate of disease progression.[48,49]

Spirometry: respiratory tests, such as forced vital capacity, generate prognostic value.[52]

Prognostic methods in the research setting

Scales and scoring: the self-reported Rasch-Built Overall ALS Disability Scale captures functional changes at upper and lower disability ranges,[53] but requires validation.

Staging: the four-stage King's staging[18] and six-stage Milano-Torino Staging[54] systems are not used in clinical practice but might be useful in clinical trials;[57] patients progress across stages over the disease course and median survival drops from stage to stage.

Prediction models: the ENCALS model can predict individual patient survival by leveraging eight characteristics;[19] it is not in clinical use but could be useful for providing additional information to patients and their families.

Electrodiagnostic: hyperexcitability by transcranial magnetic stimulation has some prognostic utility;[62–66] it might be useful as an adjunct to existing methods but requires further research to evaluate its integration into clinical care.[74–76]

MRI and PET: advanced brain and spinal cord imaging offer some prognostic insight;[67,77–79] neuroimaging will be useful as an adjunct to existing methods but requires additional research to evaluate its integration in clinical practice.

Fluid biomarkers: the current focus is on neurofilaments, but various markers have been reviewed[70] (neurofilaments have some prognostic utility but it is generally low[71,80]); another new biomarker is neutrophil-to-lymphocyte ratio,[81] which positively correlates with shorter survival.

of prognosis,[77,78] and for insight into pathogenesis—eg, quantifying brain atrophy and connectomics (ie, connections between brain regions). Spinal cord MRI is widely used to rule out diagnostic considerations other than amyotrophic lateral sclerosis,[59] but more advanced diagnostic[69] and prognostic[79] applications are emerging.[85]

MRI assesses tissue appearance, brain structure volumes, and diffusivity, among other factors (appendix). Routine MRI does not identify people with amyotrophic lateral sclerosis; findings, if present, might be higher corticospinal tract and corpus callosum intensity in patients with amyotrophic lateral sclerosis than in healthy controls.[86] A hypo-intensity of the cortical band along the precentral gyrus, called the motor band sign, might be characteristic of amyotrophic lateral sclerosis and can be detected by routine susceptibility-weighted images.[87] However, advanced MRI analyses generate deeper insights using post-image processing (eg, assessing brain volumes by mapping brain regions *vs* established clinical standards). Advanced MRI of patients with amyotrophic lateral sclerosis indicates, to variable degrees, atrophy in the precentral gyri, posterior cingulate cortex, thalamus, caudate, pallidum, putamen, hippocampus, and amygdala.[88] Additional MRI techniques include diffusion tensor imaging (DTI) and diffusion weighted imaging (DWI), which focus on white matter tracts. Studies consistently report changes to the corticospinal tract, corticopontine tract, corticorubral

See **Online** for appendix

tract, corticostriatal pathway, and corpus callosum.[88,89] Diffusion kurtosis, a DTI adjunct, is a newer, more sensitive neuroimaging technique of white matter abnormalities, which might more accurately identify patients with amyotrophic lateral sclerosis than DTI without kurtosis.[90] White matter changes are usually the earliest findings, followed by grey matter changes.[91] Spinal cord findings suggest a drop in corticospinal tract magnetisation transfer ratio and potential DTI changes, although progressive atrophy and cross-sectional area might be the most accurate biomarkers.[85]

The complexity of amyotrophic lateral sclerosis pathology advocates for multimodal MRI, which combines multiple MRI techniques. Multimodal MRI of both brain volume and white matter integrity has 85·7% sensitivity and 78·4% accuracy for discriminating scans from people with amyotrophic lateral sclerosis and healthy controls.[92] A multisite Italian study evaluated global and lobar connectivity in patients with amyotrophic lateral sclerosis using DTI, fractional anisotropy (a white matter tract integrity measure), and resting-state functional MRI.[93] The study found widespread connectomics dysfunction, with early degeneration of brain motor regions followed by a breakdown in functional connections, leading to cognitive decline.[93] Multimodal longitudinal MRI can monitor spatiotemporal spread via the brain connectome and potentially serve as a disease biomarker.[89] Finally, quantitative susceptibility mapping MRI measures iron accumulation in the motor cortex,[94] which can be coupled with white matter assessments (ie, DTI, DWI, or diffusion kurtosis) to identify early tract changes associated with metal toxicity in individuals with amyotrophic lateral sclerosis. Similarly, multimodal MRI of the spinal cord has leveraged fractional anisotropy, magnetisation transfer ratio, and cross-sectional area to build a survival prediction model.[79]

PET imaging is another modality that might facilitate diagnosis and prognosis (appendix pp 3–8). By use of [^{18}F]-fluorodeoxyglucose (FDG) PET, a two-site study reported hypometabolism in the frontal cortex and hypermetabolism in the temporal cortex, cerebellum, and brainstem in patients with amyotrophic lateral sclerosis.[95] [^{11}C]-peripheral-type benzodiazepine receptor (PBR28) PET brain uptake, a surrogate of microglial activation, is increased in the bilateral precentral and paracentral gyri of patients with amyotrophic lateral sclerosis compared with healthy controls, and colocalises with cortical thinning (as assessed by integrated MRI imaging)[96] but might not correlate with clinical progression.[96] Integrating the spinal cord with the brain in [^{18}F]-FDG PET allows differentiation of amyotrophic lateral sclerosis from mimics of the disease.[97]

Overall, tremendous progress has been made in advanced brain MRI and PET along with advanced spinal cord imaging, which could improve diagnosis[68,69] and prognosis.[77–79] Although we anticipate that imaging will be useful as an adjunct to existing methods, additional research is required to evaluate how to integrate imaging into clinical care. Furthermore, most imaging studies focused on individuals with amyotrophic lateral sclerosis versus healthy controls; however, future studies will need to include patients with mimic disorders to better evaluate sensitivity and specificity.[68,97]

Spectral EEG mapping and magnetoencephalography

Electrophysiological techniques are used to assess brain networks. High-density spectral EEG mapping measures the coherence of several frequency bands between brain regions, generating a functional measure of brain connectivity.[98,99] EEG changes occur to brain connectivity in both motor and non-motor systems, confirming that amyotrophic lateral sclerosis is not a pure motor disease, in agreement with MRI connectomics findings.[99] Magnetoencephalography shows that brain networks become increasingly connected during disease progression, indicating a dysfunctional, modified brain topology.[100] These findings are important because reorganisation of brain connections could potentially predict disease spread.[89] Connectomics studies are needed that combine multimodal MRI, high-density spectral EEG, and magnetoencephalography to further understand how brain structural changes and corresponding connectivity changes associate with the symptomatology and disease course. EEG and magnetoencephalography connectomics are novel techniques not presently in clinical use and their potential as diagnostic and prognostic tools is unknown.

Hyperexcitability

Excessive cortical excitability (ie, hyperexcitability) is increasingly recognised as a pathophysiological mechanism of the neurodegenerative cascade.[101] Clinically, hyperexcitability manifests as fasciculations combined with upper motor neuron features of increased tone and hyperreflexia.[102] Hyperexcitability is linked to excitotoxicity from excessive glutamate receptor activity at the synaptic cleft, leading to motor neuron death.[33,103] Cortical motor neuronal hyperexcitability can be captured by transcranial magnetic stimulation (TMS).[104] A TMS coil is placed over the motor cortex and responses are recorded from the contralateral hand in the abductor pollicis brevis muscle. TMS extracts measures of short-interval intracortical inhibition and facilitation that represent interneuron function.

There is a decrease in short-interval intracortical inhibition and increase in short-interval intracortical facilitation in presymptomatic individuals with amyotrophic lateral sclerosis.[105] TMS detects cortical hyperexcitability across a range of phenotypes and can differentiate amyotrophic lateral sclerosis from other disorders with high sensitivity (73·21%) and specificity (80·88%) at early disease stages.[62] TMS can also distinguish amyotrophic lateral sclerosis (with cortical hyperexcitability predominance) from primary lateral sclerosis (with cortical inexcitability predominance).[63]

TMS can also investigate pathological spread, using hyperexcitability as a surrogate by recording responses at the tibialis anterior in addition to the abductor pollicis brevis. Analysis of patients with amyotrophic lateral sclerosis shows that there is heterogeneity in cortical dysfunction by body region; cortical hyperexcitability predominates in the upper limbs and cortical inexcitability predominates in the lower limbs when compared with healthy controls.[64] Furthermore, cortical hyperexcitability correlates with the clinically affected body region; patients with amyotrophic lateral sclerosis exhibit focal asymmetry at the onset site early in the disease but widespread hyperexcitability alterations in late stages.[65] Cortical motor hyperexcitability might also detect cognitive dysfunction; cortical resting motor threshold distinguishes amyotrophic lateral sclerosis, amyotrophic lateral sclerosis–frontotemporal dementia, and frontotemporal dementia.[66]

The role of TMS in prognosis is less established than it is in diagnosis. A longitudinal study of participants with suspected amyotrophic lateral sclerosis found cortical hyperexcitability increases with longer disease duration, indicating a potential link to disease progression.[74] Cortical inexcitability might predict a poorer clinical trajectory, with inexcitability in all four limbs correlating with younger age, lower-limb onset, greater extent of functional disability, and more rapid disease progression.[75] Thus, cortical hyperexcitability might improve our ability to predict clinical outcomes. It could also serve as a biomarker for drug activity, such as in clinical trials of retigabine, an activator of voltage-gated potassium channels.[76]

Presently, TMS is not in clinical use, although it does appear to offer some diagnostic and prognostic utility and probably will be informative as an adjunct to pre-existing methods. However, future research will establish the full potential of TMS, and whether this novel electrophysiological assessment will become a fully accepted disease biomarker.

Machine learning

Amyotrophic lateral sclerosis is a highly heterogenous syndrome of genetic and unknown causes with diverse clinical presentations. Machine learning approaches can analyse large datasets (eg, clinical, demographic, electrophysiological, imaging, or morphology) in an agnostic, data-driven manner to develop diagnostic and prognostic models.[106] Tang and colleagues used clinical data encompassing 8000 patients, 3 million records, and 200 clinical features from the Patient Data Pooled Resource Open-Access ALS Clinical Trials database.[107] Their analysis yielded four consistent phenotypes, defined by slope change in ALSFRS-R, with more than 95% diagnostic accuracy on the basis of multivariate features. These investigators used deep learning modelling, a form of machine learning, for prognosis. Their modelling predicted patient survival in this cohort when incorporating TDP-43 aggregation and morphology, and MRI connectivity data with clinical characteristics.[89] Further research will establish whether machine learning can unlock a way forward for diagnosing and prognosticating at the individual level by integrating multidomain information.

Overview of prognostic and diagnostic tests

Overall, most novel diagnostic and prognostic tests for amyotrophic lateral sclerosis are limited to the research setting. Further studies are needed to establish whether these approaches will be useful in a real-world clinical setting. Such evaluation will entail studies enrolling participants with diseases mimicking amyotrophic lateral sclerosis and longitudinal studies against validated prognostic scales to evaluate their potential for improved diagnosis (sensitivity and specificity) and prognosis. Additionally, it will be necessary to identify how to apply findings made from large cohort studies to the diagnosis and prognosis of individual patients. Until more specific and sensitive tests are developed, the diagnosis of amyotrophic lateral sclerosis will remain an integrative and iterative process reliant on clinical history, physical examination, and confirmatory electrodiagnostic tests.

Conclusions and future directions

Although diagnosis and prognosis have remained essentially unchanged in the past decade (except for genetic testing), research is ongoing into new diagnostic and prognostic criteria, and biomarkers (eg, neurofilament, hyperexcitability, and imaging). Even within the realm of genetic testing, questions remain regarding variant pathogenicity, penetrance, and overlap with other neurological disorders. It is anticipated and hoped that advances in these areas will expedite the diagnosis and

Search strategy and selection criteria

Between Aug 3 and Aug 12, 2021, we searched PubMed for English language articles published from Jan 1, 2016, to Oct 12, 2021, using the term “amyotrophic lateral sclerosis”, and the terms “epidemiology”; “phenotype”; “diagnostic”; “cognition” and “cognitive”; “GWAS” plus each amyotrophic lateral sclerosis gene in turn; “neurofilaments”, “Amyotrophic Lateral Sclerosis”[MeSH] AND “magnetic[title] OR mri[title]”, “Amyotrophic Lateral Sclerosis”[MeSH] AND “connectome[title]”, “Amyotrophic Lateral Sclerosis”[MeSH] AND “PET[title] OR positron[title]”, “EEG”, and “hyperexcitability”; and “prognosis”. Additional searches were done during revisions between Nov 15 and Nov 19, 2021, using the terms “amyotrophic lateral sclerosis” and: “spinal cord”, “multimodal MRI”, and “PET”; “machine learning”; “biomarker”, “fluid”, “electrodiagnostic”, and “electrophysiological”. Additionally, authors used articles from their personal files and references from the identified articles. Articles were selected on the basis of relevance to this Series.

prognosis of amyotrophic lateral sclerosis in the future. Faster diagnosis will allow clinicians to initiate care earlier, which might enhance effectiveness or ensure administration within a therapeutic window. Ultimately, insight into the long preclinical phase of amyotrophic lateral sclerosis will be necessary to truly facilitate early diagnosis.[108] Improved prognosis will give patients and their families a better understanding of the disease course, aiding medical decisions and planning. A major advance is the recognition of amyotrophic lateral sclerosis as a disease with both motor and non-motor features, which has implications for diagnosis, management, and prognosis. Importantly, cognitive symptoms are not presently considered in clinical criteria and scales, yet their integration might improve diagnosis and prognosis. We foresee that these and other future advances will lead to better care for patients with this disease.

Contributors

All authors contributed to the conceptualisation, writing of the original draft, and review and editing of the final manuscript.

Declaration of interests

SAG declares consulting fees from Biogen and ITF Pharma, a patent "Methods for treating amyotrophic lateral sclerosis", and participation on a Data Safety Monitoring Board for Watermark. OH declares consulting fees from Novartis, Cytokinetics, Denali Pharma, Stitching Foundation, and La Caixa; payment or honoraria from Biogen; participation on a Data Safety Monitoring Board for Accelsiors and steering committee for Cytokinetics; and is Editor-in-Chief for the journal Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. AA-C declares consulting fees from Mitsubishi Tanabe Pharma, Biogen Idec, Cytokinetics, Wave Pharmaceuticals, Apellis, Amylyx, Novartis, and Eli Lilly. AC declares grants from Biogen to his institution, payments or honoraria from Biogen and Amylyx, and participation on a Data Safety Monitoring Board for Ely Lilly and ABScience and advisory board for Mitsubishi Tanabe, Roche, Denali Pharma, Cytokinetics, Biogen, and Amylyx. MCK has an honorary role as President of the Brain Foundation and as Editor-in-Chief of the Journal of Neurology, Neurosurgery and Psychiatry. ELF declares a patent "Methods for treating amyotrophic lateral sclerosis". MGS declares no competing interests.

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