# Time for optimism in amyotrophic lateral sclerosis

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## Abstract

**Background and purpose:** Amyotrophic lateral sclerosis (ALS) is among the most common motor neuron diseases in adults. Nevertheless, ALS remains fatal, despite decades of research and clinical trials, which has led to negative conclusions until recently in regard to four specific treatments. It is well known that we can learn from failures, and we consider that the time has come to present positive insight on this disease.

**Methods:** We did a literature search using PubMed and Scopus for articles published in English from 1 January 2016, to 30 June 2022 dealing with "amyotrophic lateral sclerosis", diagnosis, treatment, and biomarkers.

**Results:** A comprehensive review of the literature on diagnosis, monitoring, and treatment of this condition showed convincing evidence that we are now able to diagnose earlier as well as to better monitor and treat ALS.

**Conclusions:** Although ALS is often difficult to diagnose and remains incurable, there are many indications that an optimistic view of ALS management in the coming years is now realistic.

**KEYWORDS**
amyotrophic lateral sclerosis, genetics, neurofilaments, *SOD1-C9orf72*

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by the degeneration of both upper motor neurons (UMNs) and lower motor neurons (LMNs) in the cortex, bulbar, and spinal regions, leading to death after 36 months on average by respiratory failure [1]. Although the original description was made by Jean Martin Charcot >150 years ago, numerous questions remain unresolved, emphasizing the high level of complexity of this disease.

The determining advance in our understanding of ALS is the worldwide knowledge that the disease is extremely heterogenous regarding the phenotype, particularly the age and type of onset and rate of progression, the pathogenic pathways, and the genotype [2–6]. Clinically, heterogeneity depends on the balance between UMN and LMN signs, which deeply varies from one patient to another.

Moreover, between 50% and 60% of patients will have frontotemporal impairment [7]. Among these, approximately 15% will either present with or develop during the course a frontotemporal lobar dementia (FTLD). The profile of progression is heterogenous, from a slow to a fast progression [8]. This clinical heterogeneity combined with the lack of reliable diagnostic biomarkers mainly explains the delay of diagnosis of approximately 9–12 months, which represents approximately one third of the total duration of the disease from the onset of the first symptoms [9].

In approximately 10% of cases, the disease is familial, with in a majority of cases a dominant inheritance of the pathogenic trait; the remaining cases are sporadic [1]. Since 1993, which dated the identification of the first causative gene, the superoxide dismutase 1 (*SOD1*) gene, heterogeneity is also genetic, with >30 genes that have been linked to the disease [10].

Despite a large body of literature, there is no cue to reliably distinguish familial from sporadic cases of ALS. However, the onset is often earlier, more frequently at lower limbs in familial ALS patients. The duration of the disease also draws a bimodal distribution, with a small group with a duration < 2 years, whereas the main cohort lives > 5 years in familial ALS cases compared to sporadic ALS classically [11]. Moreover, mutations in these causative genes are found in almost 10% of sporadic cases [11, 12]. Genetics of ALS is also extremely heterogenous and complex due to allelic heterogeneity and pleiotropism, and this complexifies the understanding of a unifying pathophysiology of ALS [3].

Currently, there is an urgent need to find a curative treatment for this complex and heterogenous disease, and after > 30 years of clinical trials, only two drugs, riluzole and edaravone, are approved—worldwide for riluzole and only in some countries for intravenous edaravone (Radicava)—for treating ALS, with only a modest effect on survival or functional status, respectively [13]. Recently, a third treatment, a coformulation of sodium phenyl butyrate and ursodoxicoltaurine (Albrioza, Relyvrio), received conditional approval in Canada and the United States pending the results of an ongoing phase 3 trial (NCT04577404) [14]. Since a few months previously, patients with an *SOD1* mutation have had access to a targeted gene therapy, tofersen, an antisense oligonucleotide (ASO) [15].

Without trying to minimize that ALS remains today a complex and dreadful disease whose diagnosis and care remain challenging, it is worth noting that during the past decade, we have experienced numerous advances in the diagnosis, the treatment, the prediction, and the monitoring of ALS, owing to identification of biomarkers and machine learning, which have changed both our clinical and our experimental approach to the disease. Henceforth, we are entering into a promising time for ALS care and research.

In light of recent literature on ALS and of learning from past research, we are convinced that the time is coming for clinicians to be confident in the future of ALS for the diagnosis, the prediction, and the management of the disease. We propose in this review to point out major evidence supporting that optimism is justified in ALS.

## Search strategy and selection criteria

We did a literature search using PubMed and Scopus for articles published in English from 1 January 2016 to 30 June 2022. We used the search terms: "amyotrophic lateral sclerosis", "motor neuron disease", "diagnostic criteria", "antisense oligonucleotide", "RNA interference", "*SOD1*", "*C9orf72*", "TDP-43", "biomarker", "edaravone", "riluzole", "MRI", "neuroimaging", "prediction model", and "treatment". Additional articles were identified by reviewing the reference lists from relevant articles. We also included references from publicly available websites and ClinicalTrials.gov. We prioritized material published between 2016 and 2022. We included references published before 2016 only if they were essential to the field. The final references were chosen on the basis of their relevance to the topics covered in this personal view.

## Optimism for the diagnosis of ALS

Until now, there has been no specific diagnostic test in ALS. This compels the clinician to rely in his diagnosis on the results of the clinical examination and the profile of progression to diagnose ALS, together with electrophysiologic tests, other paraclinical investigations being only performed for excluding ALS-mimicking syndromes [1–4].

The diagnosis of ALS mainly relies on clinical criteria. Until 2020, the gold standard criteria were the El Escorial revised criteria, then the Awaji criteria, which require the presence of UMN and LMN signs in at least two body regions [16, 17]. The new criteria, the Gold Coast criteria, tend to make the diagnosis easier and earlier, with the ascertainment of ALS in the presence of UMN and LMN involvement in at least one area or LMN involvement in two body regions [18]. These criteria facilitate the diagnosis of atypical forms of the disease and enable earlier diagnosis of ALS, allowing protection of a larger pool of motoneurons.

Identifying biomarkers, to reduce the diagnostic delay, is one of the most encouraging paths of research in ALS. Many metabolomics and proteomics analysis have been performed from different types of biofluids to search for diagnosis but also prognosis biomarkers. Even if none of this omics strategy supports a specific metabolic profile useful in routine for diagnosis, our enthusiasm for these powerful strategies is founded on the wonderful progress in analytical techniques, especially in their sensitivity, and on our ability to manage different types of data, from different sources, considered as big data, in the same statistical analysis. One of the most studied and more promising biomarkers seems to be blood and cerebrospinal fluid (CSF) light neurofilament chain (NfL) [19]. Neurofilaments are expressed in blood and CSF, and their level bespeak the severity of neuronal death. Recently, it has been shown that NfL displayed the best diagnostic performance in discriminating ALS from healthy controls (area under the curve [AUC] = 0.990), other neurodegenerative disorders (AUC = 0.946), and ALS mimic disorders (AUC = 0.850), the meaningful difference being mainly explained by the rapid loss of motoneurons in ALS conversely to what is observed in other situations [20]. To date, the analysis of the blood concentration of NfL seems easily measurable, sensitive, suitable, and reproducible, because this is correlated with that observed in the CSF. These promising results might tempt to make this assay more widely and easily available in clinical practice, as high blood level of NfL might be a biological biomarker of ALS in individuals with motor weakness.

Neuroimaging in ALS has gained unprecedented momentum in recent years and has now emerged as a sensitive clinical tool with true biomarker potential [20, 21]. Another important development is the characterization of presymptomatic changes in cohorts carrying pathological mutations, paving the way for predicting the onset of symptoms and determining the optimal therapeutic window for preventive treatments [22–24].

## Optimism for the treatment of ALS

Hope also involves the therapeutic aspects of the disease. After 3 decades of relentless failures in clinical trials, four drugs have been or are about to be approved in ALS over the past 5 years [25].

Gene therapy, pioneered with tofersen in ALS for patients with *SOD1* mutation, might be considered one of the major conceptual therapeutic advances in ALS [15]. Although the clinical efficacy was not as high as expected, due mainly to high heterogeneity in patients enrolled in the study, with some patients considered fast progressors from the classical phenotype linked to these mutations or from the slope of progression of the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) score ($n = 60$) and others termed slow progressors ($n = 48$), a lowering of the SOD1 protein level for patients treated with 100 mg of tofersen and also of NfL blood concentration has been observed for patients treated with tofersen, representing an encouraging message for the future of the therapy for ALS [26].

Owing to these encouraging results, the ATLAS clinical trial is currently running (NCT04856982), with the aim of evaluating the efficacy of tofersen when it is initiated before the clinical onset of the disease in presymptomatic adult carriers of an *SOD1* mutation [27]. Gene therapy also bespeaks new hope in ALS, with the possibility of treating some patients with ALS earlier tomorrow than what is practiced today. It becomes realistic to initiate a treatment, in some situations for now, before the clinical onset of the disease. This relies on the dosage of NfL in blood, the concentration of which increases months before the occurrence of LMN and UMN signs; this biological modification precedes by from 12 to 42 months the obvious clinical onset of the disease in *SOD1* and *C9orf72* carriers, respectively [28].

A regular monitoring of NfL level in blood in presymptomatic carriers would allow starting treatment at the beginning of the neurodegeneration process; this would probably increase the effect of treatment in this population, because the earlier the treatment is initiated, the more the important pool of motoneurons will be protected.

Genetic therapy strategies are currently also being developed for other pathogenic genes in ALS. Unfortunately, recently Biogen announced the topline results of the clinical trial for patients with ALS linked to *C9orf72* treated with BIIB078 (NCT04288856), a selective ASO directed against G4C2 expansion, which did not meet any primary or secondary efficacy endpoints and did not demonstrate clinical benefit (https://www.biospace.com/article/releases/biogen-and-ionis-announce-topline-phase-1-study-results-of-investigational-drug-in-c9orf72-amyotrophic-lateral-sclerosis/).

Interestingly, in this trial the level of NfL increased in the subjects treated with ASO compared to those treated with the placebo. However, ASOs are currently in progress and being tested against *FUS* and *Ataxin2* (*ATXN2*; NCT04768972, NCT04768972, respectively) and remain a promising and hopeful avenue of research for the cure of ALS [29].

The influence of genetics in approach to treatment has been perfectly demonstrated in cancer [30]. In ALS, several post hoc analysis stressed that the efficacy of lithium in ALS was dependent on the genotype of the *UNC13A* gene; patients who carried the C/C genotype showed a better evolution of their disease compared to A/A and A/C genotyped patients. It has been shown that the effect of lithium in ALS depends on the C/C genotype, as the number of deaths has been reduced by 70% under lithium in this subgroup, whereas no effect has been observed when comparing people with ALS without the C allele [31]. Owing to these promising results, a specific randomized double-blind placebo-controlled clinical trial on the effect of lithium in patients with ALS homozygous for the C allele will be conducted soon [32].

Owing to these recent events linked to gene therapy, a systematic genetic screening of the main pathogenic genes linked to ALS is currently offered to the majority of patients regardless of whether there is a familial history.

## Optimism for the prediction of ALS

Heterogeneity of ALS involves also the profile of progression of the disease and the occurrence mainly of malnutrition and respiratory insufficiency requiring assistance, which both have a negative and independent prognostic effect on the disease [33]. Becoming able to predict the necessity of nutritional and respiratory support would improve the impact of these.

Over the past years, numerous groups purposed to set up predictive models. Today, it is becoming possible to anticipate disease evolution using predictive models and machine learning [34–36]. These models rely on clinical and paraclinical data, which are for the majority available from the diagnostic phase. A recent model integrated into this strategy the level of NfL in blood to help clinicians to predict the profile of evolution of the disease [37]. Being able to predict this allows anticipation of the occurrence of complications and setting up appropriate care earlier.

Another example of a tool to predict the prognosis (but also diagnosis) of ALS is artificial intelligence from routine clinical, paraclinical, and biological data. Machine learning approaches have been shown to be accurate methods applied to diagnostic classification of ALS patients based on cerebral or spinal cord multimodal magnetic resonance imaging [38, 39]. Because progress has been made in storing and protecting health data with appropriate ethical considerations, these data can now be analyzed by researchers independent from the heath field and specialists in deep learning and machine learning. This process supports the promise of a better exploitation of easily available data.

Many countries have increased financial support of research on numerics and artificial intelligence, and this represents a perfect opportunity to benefit from these grants and make progress in the workflow of big data optimization in ALS. Similarly, the ENCALS predictive model estimates survival from eight values

available at the first consultation: the age at onset, the delay to diagnosis, the slope of progression on the ALSFRS-R scale, whether disease onset is bulbar, the revised Airlie House diagnostic criteria, the forced vital capacity, whether there is FTLD, and lastly the *C9orf72* status; these values enable prediction of the survival outcome without tracheostomy and ventilation for >23 h/day. It then becomes possible to split the ALS population into five groups with different profiles of evolution: very short, short, intermediate, long, very long (median predicted time, 17.7, 25.3, 32.2, 43.7, 91.0 months, respectively) (http://www.encalssurvivalmodel.org) [40]. This model has demonstrated a 95% probability of generating a good performance. The use of this model may certainly be helpful in clinical trials to better focus on a homogenous group of patients but, as usual in ALS, raises issues in daily practice especially concerning ethical aspects when the result bespeaks a poor prognosis.

This improvement in the prediction of the evolution of ALS would also benefit to trials in the demise of new designs more representative of our daily practice. Currently, inclusion criteria lead to the exclusion of numerous patients because progression is too fast or too slow (ALSFRS-R slope of progression of ≤0.3 or ≥1.0, respectively); if it can be considered fair to exclude a patient 1 year under the age limit with a vital capacity just under the upper limit, it is unreasonable to exclude a patient 1 year older with a perfect vital capacity [8].

We have to enroll patients with a multimodal approach, rather than by a grid of inclusion criteria, enabling recruitment of a more homogenous ALS population or better stratification in the clinical trial arms of more homogenous patients. This becomes possible thanks to the predictive models.

## Optimism for the monitoring of ALS

International recommendations have stressed the importance of a quarterly multidisciplinary approach [41]. However, this becomes difficult to apply when the disease leads to a severe disability for patients living far from an ALS center or who have difficulties traveling due to the burden of the disease. The COVID-19 period forced clinicians to conceive alternatives for managing patients remotely for carrying out the continuity of care. Teleconsultations and devices that collect and send to the ALS center relevant clinical values gained advantage during the pandemic. We are now able to monitor patients living far from any ALS centers. Moreover, technological progress enables compensation for disturbances in communication due to phonatory disturbances and loss of motricity that makes it impossible for the patient to correspond in writing; eye-tracking and assistant virtual speakers offer hope by giving the opportunity to maintain social relationships despite the loss of communication abilities [42]. Communication abilities may be maintained beyond the patient's natural abilities. This can dramatically change the quality of life of the patients, who remain integrated within their family and social community longer.

## We must remain aware that ALS is still not cured

Although we have dramatically improved our scientific knowledge and medical management, challenges remain significant regarding numerous aspects of the disease.

The development of participatory research creates the opportunity to increase the quality of patients' monitoring by the free sharing of information and the optimization of communication tools between the medical and scientific community and general population. This is crucial to achieve to cure ALS.

Easy access to progress in other heath fields may encourage researchers to change their politic and strategic considerations in ALS research. Some projects focusing on environment and microbiota are examples of thematic transfer from ancillary discoveries. Collaborations between startups and academic groups have been encouraged by the relative improvement of administrative process; this kind of collaborative project is particularly innovative and provides hope of real medical impact.

The management of ALS, which is currently undergoing encouraging progress, cannot be satisfactory in the absence of reliable (biological, imaging, or histological) diagnostic biomarkers. These caveats lead to reconsideration of our management of the disease and highlight the necessity to set up reliable diagnostic biomarkers for earlier diagnosis, and to promote personalized management.

We have to remain realistic and aware that currently there is no cure for ALS. Nevertheless, we can conclude that a new era is coming that should offer hope for patients with ALS. This hope will rely on a more incisive management stressing earlier initiation of care and a personalized treatment as developed with tofersen. The road is still full of hurdles and pitfalls in ALS. The central issue for the next decade will be to diagnose ALS at the very early onset of the disease for sporadic patients for whom genetics is not as helpful as it is for presymptomatic relatives and for whom we currently do not have any means to diagnose ALS before the occurrence of clinical signs.

### CONFLICT OF INTEREST STATEMENT
All authors have nothing to disclose.

### DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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