Amyotrophic Lateral Sclerosis, a rare neurodegenerative disease: European landscape assessment and policy recommendations for improved diagnosis, care, and treatment.

Let's act together now. Time is precious and running out fast for people living with ALS.

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Why ALS?

ALS is a **unique example of a life-threatening, neurodegenerative disease** that is **highly complex** to manage due to its extremely rapid progression and diverse range of symptoms. PLWALS experience a relentless and irreversible loss of muscle function, and most **succumb** to the disease in just **2 – 5 years**. ALS affects **~32,000 people** in Europe, yet these PLWALS continue to face **significant challenges** due to low levels of disease understanding, delays in diagnosis, suboptimal treatment pathways and a scarcity of treatments. **Much can be done to solve the challenges in ALS, and with that, those of other severe and complex neurological disorders!**

Policy recommendations

Ten policy recommendations to improve the lives of PLWALS are proposed below. Policy actions and best practice examples are provided for each policy recommendation throughout the paper

Optimised diagnosis

In diagnosing ALS, **time is of the essence.** Time from initial symptom onset to confirmation of diagnosis must be **shortened**, and **misdiagnoses reduced** across Europe. Diagnosis must be **expert led** from point at which ALS is suspected. Diagnosis should be a **continual process** to advance disease understanding by characterising subtype and individual progression, and **robust supports** must be provided to PLWALS and their families, coming to terms with an ALS diagnosis.

1. Enhance capabilities of primary care physicians and other first line health providers to conduct timely referrals to NMD/ALS specialists, and ensure expert-led diagnostic assessment, subtype characterisation, and continued evaluation is conducted from point at which ALS is suspected
2. Provide counselling and support to PLWALS and their families on ALS, receiving an ALS diagnosis and on disease management options

Matched care

Living with ALS is a **constantly shifting reality** with health and social care systems **ill-equipped** to manage such a complex and rapidly progressing condition. **Urgent solutions** and **changes in the model** of care are needed. The ability to **match the needs of PLWALS** must be improved and for that care must be **proactive,** multidisciplinary care **gaps must be plugged** and **social care** services **strengthened.** Improvements to care must **maximise QoL** and **independence** of PLWALS and will undoubtedly have a wider impact by **alleviating burden** on healthcare systems and society in the future.

3. Increase co-ordination between ALS and non-ALS specialists, and involvement of essential multidisciplinary professionals, leveraging alternative approaches to care, collaboration and communication
4. Speed up access to fully reimbursed assistive technological devices for PLWALS
5. Improve availability of non-hospital-based care for PLWALS unable to remain in their home as their disease progresses
6. Recognise the essential role of family and caregivers in the care of PLWALS and provide appropriate social, psychological, and financial supports

Work towards a better prognosis

Just one treatment for ALS has been approved in Europe **in over 25 years, as R&D in ALS comes with unique challenges.** But disease knowledge is advancing and the number of ALS clinical trials is steadily increasing. Once new promising medicines arise, **approval and access must be prioritised and barriers minimised as** PLWALS have **no time to wait**. Access to the new wave of medicines will **ignite further innovation** and pave the way towards a **future** where **several effective treatment options** are widely available and address the huge unmet needs of PLWALS.

7. Augment research to further disease understanding and treatments for ALS and increase awareness of and accessibility to ALS clinical trials
8. Improve alignment between researchers, clinical experts, medicine developers, regulatory and payers on trial design (incl. acceptable clinical trial endpoints) accounting for patient evidence and opinions
9. Expedite and support the approvals of new treatments for PLWALS considering the urgency and breadth of their unmet needs, ensuring ALS expertise is accounted for in drug evaluations
10. Provide timely access to new treatments targeting life-threatening diseases with extremely high unmet need via fast-track and conditional reimbursement processes, that consider the holistic value of medicines

Glossary of Abbreviations

AAP	Autorisation d'accés précoce (Early Access Authorisation)
AIFA	Italian Medicines Agency
ALS	Amyotrophic Lateral Sclerosis, also known as Motor Neuron Disease, Charcot Disease or Lou Gehrig Disease
ALSFRS-R	ALS Functional Rating Scale Revised
ARC	ALS Research Collaborative
ARSLA	Association pour la Recherche sur la Sclérose Latérale Amyotrophique (Association for the Research of ALS)
ASMR	Amélioration du Service Médical Rendu (Improvement in medical benefit)
ATDs	Assistive Technology Devices
CMI	Carte Mobilité Inclusion (mobility card)
EAN	European Academy of Neurology
ENCALS	European Network for the Cure of ALS
ENT	Ear, Nose and Throat
ERN-EURO NMD	European Reference Network on Neuromuscular Diseases
EU	European Union
FDA	Food and Drug Administration
FILSLAN	French Rare Diseases Healthcare Network
HAS	Haute Autorité de Santé (French National Authority of Health)
HCPs	Healthcare Professionals
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IMNDA	Irish Motor Neurone Disease Association
MALS	Management of Amyotrophic Lateral Sclerosis
MDT	Multidisciplinary team
MiToS	Milano-Torino staging
MND	Motor Neurone Disease
MS	Multiple Sclerosis
NICE	National Institute of Health and Care Excellence
NMD	Neuromuscular Disorder
OMP	Orphan medicinal products
PACE	Patient and Clinical Engagement
PLWALS	Person/People living with ALS
PRIME	European Medicines Agency Accelerated Approval for Priority Medicines
P&R	Pricing and reimbursement
QoL	Quality of Life
RCTs	Randomised Control Trials
R&D	Research and Development
RRMS	Relapsing-remitting Multiple Sclerosis
SPIKES	Setting, Perception, Information, Knowledge, Empathy, Strategize
TiM	Telehealth in Motor Neurone Disease
TRICALS	Treatment Research Initiative to Cure ALS
UMCU	University Medical Centre Utrecht

Introduction to the European ALS Coalition

The European ALS Coalition was formed at the beginning of 2023 with the overarching aim of fostering a positive policy environment that will improve the lives of people living with ALS (PLWALS) and their carers in Europe. The coalition brings together a diverse range of experts with a variety of experiences and perspectives on ALS in Europe. Members of the coalition comprise expert neurologists and nurses in ALS, patient representatives, an ethicist, payers and HTA experts, policy makers and industry representatives from various members of the European Union, and the United Kingdom. At date of publication, six members of the European Parliament are supporting the coalition as ambassadors of the initiative.

With this policy paper, the Coalition aims to shed light on what it means to receive a diagnosis and live with ALS in Europe today. It also highlights the gaps and unmet needs around the diagnosis, care and prognosis of PLWALS that require urgent attention and provides implementable policy recommendations on changes that can contribute to addressing these. The Coalition is committed to continue to work together with relevant European stakeholders and policy makers, aiming for ALS to become a political priority and laying the foundations for ALS to be considered in future national and European policies and plans, ultimately to make a tangible difference to the lives of PLWALS, their families/caregivers and the medical community responsible for their care.

The current members of the European ALS Coalition are listed below:

European ALS Coalition members

Prof. Dr. med. Julian Grosskreutz - Coalition Chair

Prof. Dr. med. Julian Grosskreutz is a clinician scientist and independent researcher with a strong interest in translational neuroscience to develop new therapies in neurodegenerative diseases. He has run a large translational clinic for patients with neuromuscular and MND in Thuringia and is currently Chair of Precision Neurology at the University of Lübeck. He cooperates on a national, European**,** and global level with MND researchers and clinicians to model disease progression and biomarker/neuroimaging driven stratification to facilitate clinical trial development.

Olivier Goy - Coalition Vice-Chair

Olivier Goy is an entrepreneur and an ALS sufferer. He is highly engaged in fighting ALS as board member of the French association ARSLA, ambassador of the Paris Brain Institute, and co-producer & actor of the movie INVINCIBLE ÉTÉ (**https://www.invincible-ete.com/**).

Sheela Upadhyaya - Coalition Moderator

Sheela Upadhyaya is an independent consultant to the life sciences industry working in the rare disease space for over 15 years with extensive experience in understanding the issues facing rare diseases, diagnosis, service provision and access to therapeutics.

Andrea Gasper

Andrea Gasper is a nurse trainer for palliative care, certified case and care manager and is active in this function in the ALS special outpatient clinic of the University Hospital Bonn.

Antoni Montserrat Moliner

Antoni Montserrat Moliner has been the Senior Policy Officer for Rare Diseases and Cancer in the Directorate of Public Health of the European Commission. He's always Active Senior for the European Commission, Vice-president of the Luxembourg Rare Diseases National Committee, Vice-President of ALAN Maladies Rares in Luxembourg, member of the EURORDIS Working Group on Newborn Screening and works with international patient advocacy groups and with other public and private policy makers.

Dirk De Valck

Dirk De Valck is PhD in Molecular Biology working as staff at EUpALS, the European Organisation for Professionals and Patients with ALS (www.ALS.eu). EUpALS unites 28 national ALS/MND Associations from 22 European countries. Together, we create equal rights for all European people living with ALS, providing them better access to ALS clinical trials and information about it.

Prof. Fabrizio Gianfrate

Prof. Fabrizio Gianfrate is a full professor of Health Economics and Outcome Research, ex AIFA, ex Regions, former Director of Ministry of Health.

Karolina Koucká

Karolina Koucká is chief coordinator of social and health services, representative of ALSA, an ALS patient organisation in Czech Republic.

Lugdivine Le Dez

Lugdivine Le Dez has worked with International, European, and national patient advocacy groups, NGOs, and policy makers on behalf of pharmaceutical organizations for close to 20 years. Lugdivine is currently Head of Patient Advocacy and Government Affairs EMEA at Amylyx Pharmaceuticals EMEA B.V.

María José Arregui

María José Arregui is Executive President of Luzón Foundation, and widow of its founder, Francisco Luzón, who died from ALS. She studied Law, Board School, Direction of Foundations, Social Leadership, and Fundraising. This, together with her passion and studies of Portuguese led her to start her path as an entrepreneur becoming the CEO of her Portuguese academy Agoralingua, a Spanish referent.

Dr. Mark Sheehan

Dr. Mark Sheehan is Associate Professor and Oxford Biomedical Research Centre (BRC) Ethics Fellow at the Ethox Centre at the University of Oxford. He has 20 years' experience

working in research ethics and policy with a special concentration on research, development, and access in the context of rare diseases.

Melqui Calzado

Melqui Calzado has spent the last 20 years in the biomedical sector fostering new treatments for different conditions. Melqui is currently Corporate Public Affairs & Patient Advocacy Manager at Ferrer where he is really passionate of involving patients in all Ferrer activities.

Prof. Nicola Ticozzi

Prof. Nicola Ticozzi directs a large tertiary ALS Center in Italy. He is a clinical neurologist involved in the care of PLWALS for 20 years and an internationally recognized researcher in ALS genetics.

Prof. Orla Hardiman

Prof. Orla Hardiman is a Clinician Scientist, and Professor of Neurology at Trinity College Dublin, Ireland. Her research group comprises over 50 individuals working in Neurodegeneration, with particular focus on Amyotrophic Lateral Sclerosis (ALS) and frontotemporal dementia.

Prof. Pier Luigi Canonico

Prof. Pier Luigi Canonico, MS, is a Professor of Pharmacology at the Università del Piemonte Orientale, Novara, Italy. He is a former President of the Italian Society of Pharmacology, actual Vice-President of the Italian Society of neuropsychopharmacology, and President of ISPOR Italy Rome Chapter. He has been part of the Committee for Drug Approval and Reimbursement at National level.

Stéphanie Hoffmann-Gendebien

Stéphanie Hoffmann-Gendebien has spent more than 20 years in the orphan drug field in Europe and worldwide, including leadership roles with various pharmaceutical organizations and consulting services around rare diseases and orphan drug development. Stephanie is currently Head and General Manager for EMEA at Amylyx Pharmaceuticals EMEA B.V.

Tatiana Foltánová

Tatiana Foltánová is a pharmacologist, working at the Faculty of Pharmacy of Comenius University in Bratislava. Her main area of interest are rare diseases. She works as an expert for the Slovak Alliance of Rare Diseases - a patient umbrella organization for rare diseases in Slovakia.

For any questions regarding the European ALS Coalition or this paper, please make contact via the following email address: contact@ALScoalition.eu

Introduction – Why Amyotrophic Lateral Sclerosis?

Amyotrophic Lateral Sclerosis (ALS) is a universally fatal disorder that affects motor neurons in the brain and spinal cord, reducing muscle function and the ability to perform activities such as speaking, swallowing, walking, and breathing. Depending on which body parts are first affected, it can be classified as spinal or limb onset with symptoms beginning in the limbs[1-3] (70%–80% of cases), bulbar onset which result in slurred speech and difficulty chewing or swallowing[2-4] (25% of cases), and respiratory onset with shortness of breath as the earliest symptom[2] (3% of cases). Up to 50% of people living with ALS (PLWALS) will also develop a cognitive impairment, which may be associated with frontotemporal dementia[5], and experience behavioural and personality changes such as emotional lability, impulsivity, and loss of interest and motivation[6, 7] (Figure 1). The extremely rapid progressive and multifaceted presentation of symptoms makes ALS a unique and highly complex disease to manage, including for those diagnosed, their families and caregivers.

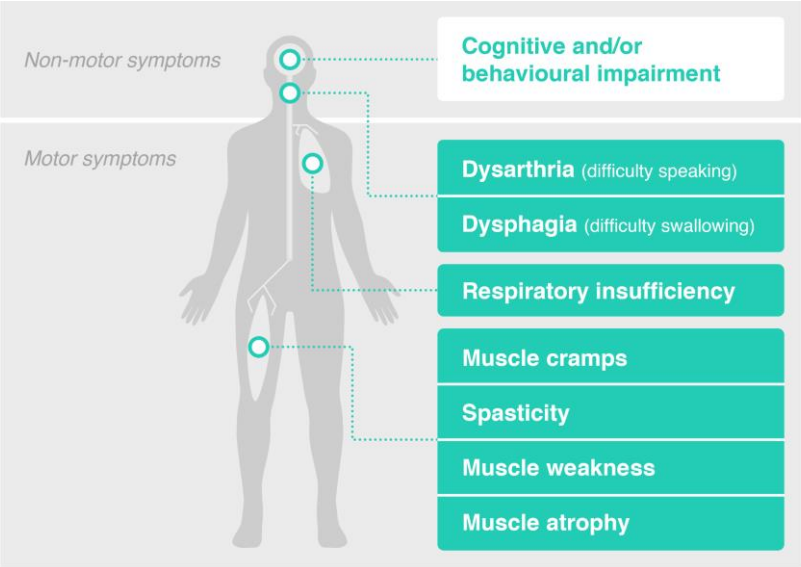


Figure 1. Clinical manifestations of ALS[1-3]

ALS is indiscriminate and can potentially affect people at any age. Recent studies have shown that the mean or median age of ALS onset is between 51 and 66 years[8]. Within about 18 months of symptom onset, PLWALS rapidly lose their independence, relentlessly and irreversibly, until they reach states of complete paralysis[9-13]. The disease is universally fatal, with a life expectancy in the majority of people of 2–5 years after symptom onset,[10] only approximately 10% of people survive 10 years or more[3, 14]. It is estimated that half of PLWALS die from respiratory failure within 3 years of symptom onset[15].

ALS is considered a rare disease in Europe[*16], where approximately 32,000 people are living with the disease (figure 1)[17]. It is estimated that every 45 minutes someone with ALS dies[†] causing around 10,000 deaths each year[18]. The stark reality is that the prevalence remains low due to the high mortality rate, but ALS is not that infrequent, its lifetime risk is about 1 in 300[19].

Figure 2. ALS prevalence and mortality rates in Europe
Note: A prevalence of 32,000 in Europe (EU+UK) is estimated based on a pooled prevalence rate of 6.22 per 100,000 persons as reported in Brown et al[17], and on a population size of 515 million as estimated by the United Nations Population Division[20].

While ALS is a rare and neurodegenerative disease, it is unique in that it encompasses all aspects of a rare disease, making it difficult to diagnose on time and to manage. Despite the increasing awareness and efforts focusing on rare diseases, people living with ALS and other rare diseases in Europe continue to face significant challenges related to low levels of disease awareness, delays in receiving an accurate diagnosis, suboptimal treatment pathways and a lack of approved treatments[21]. The following three main challenges exist in ALS and will be the focus of this paper:

1) **Diagnosis:** ALS is often misdiagnosed at first and the time between onset of first symptoms and diagnosis typically takes more than one year. The lack of knowledge about ALS and the fear of giving an ALS diagnosis are two of the main causes for this delay. Late diagnosis means the initiation of appropriate care and support are delayed and can be detrimental for PLWALS and their families.

2) **Care:** PLWALS require intensive medical and multidisciplinary care along with significant caregiver support. This places a considerable clinical, humanistic, and economic burden on health and social care systems as well as on individual

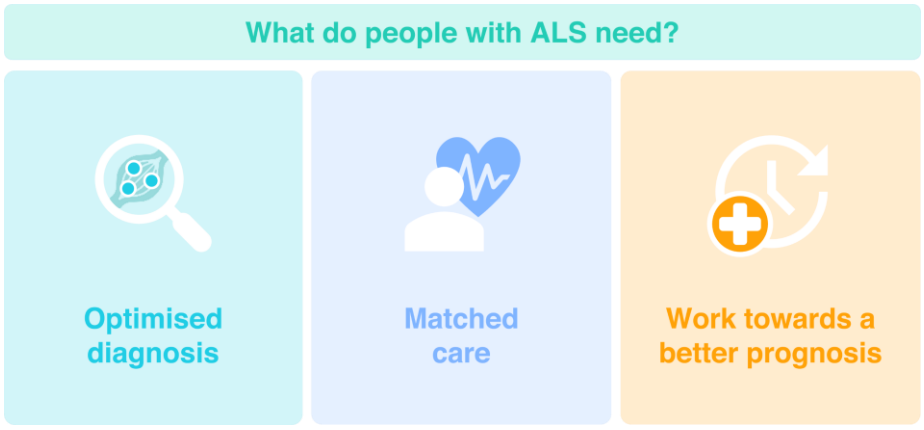
[*] Europe: defined as the 27 Member States of the European Union and the United Kingdom
[†] Estimated based on a total population in Europe (EU + UK) of approx. 515 million and based on an incidence of 2.31/100.000 as reported in Brown et al., this is equivalent to ~12.000 newly diagnosed patients per year in Europe. As prevalence is generally stable, incidence and mortality rates are approximately the same and therefore it is assumed that 12.000 patients die annually due to ALS in Europe (EU+UK).

families. The lived experience of PLWALS is highly dependent on the ability of the health and social care system to respond, in a timely manner, to the individual needs of each PLWALS. The highly aggressive and rapidly progressive nature of the disease may lead to even greater complications if not appropriately managed.

3) **Prognosis:** There have not been any newly approved treatments in the EU for over 25 years, leaving PLWALS and families with no choice but to hope for the availability of and access to new effective treatments. Moreover, R&D in ALS face numerous challenges, and access to ALS clinical trials and to approved rare disease medicines in Europe is not always timely and equitable.

Although the term 'ALS' is widely recognised, little is truly understood about what it means to live with this disease. The delayed diagnosis, the complexity and urgency of care and the work needed towards a better prognosis means that PLWALS and their families face a constant and increasing number of challenges in a short and intensive period, all while losing their voice and ability to advocate or tell their story. Furthermore, the rapid rate at which people succumb to the disease means the lived experience of some PLWALS and their legacies could become lost.

This paper aims to shed more light on what it means to receive a diagnosis and live with ALS. It describes the challenges that PLWALS and their families face and provides policy recommendations on the changes that can contribute to improving, respectively, the diagnosis, care, and prognosis of PLWALS. This includes accelerating access to innovative treatments and care modalities, in light of the very rapid progression of the disease.



The vision and actionable policy recommendations outlined in this paper have the potential to make a real and immediate difference not only to the everyday lives of PLWALS, but also to a great number of people living with similarly rare and complex diseases in Europe. If we solve the challenges in ALS, we can tackle other severe and complex neurological disorders!

1. What do people living with ALS need? – Optimised diagnosis

Time is of the essence…

The median time from symptom onset to diagnosis is approximately 12 months[2, 9, 13, 22, 23]. Significant variation in time to diagnosis is observed both within and across European countries[2, 9, 13, 22, 23].

The presentation of symptoms in ALS varies from person to person. This heterogeneity of symptoms and their presentation, coupled with limited disease understanding and a lack of known biomarkers often causes a delay in ALS diagnosis. Initial symptoms, often characterised by subtle weakness and slight changes in functioning, can develop slowly and may be underestimated or dismissed, resulting in delays in visiting a healthcare professional[22]. Studies have found that PLWALS tend to wait three to six months after symptom onset before seeing a physician[23].

But the first visit to a physician does not guarantee a diagnosis. Approximately 40% of people are misdiagnosed, initially being told they have another disease such as cervical myelopathy, neuropathy, and myasthenia gravis and even in some cases stroke[23-25].

Moreover, frequent referrals to specialists can cause further delays in the diagnosis[23]. It is estimated that PLWALS see an average of three different physicians before the diagnosis of ALS is confirmed[22]. Most patients are first evaluated by non-neurologists, usually general practitioners and orthopedics, otolaryngologists (ENT) and neurosurgeons[26, 27]. After the initial visit, about 60% of patients are then referred to neurologists while the remaining 40% are referred to non-neurologists[20].

> **“At first the doctors did not know what was causing my wife's complaints, and no one dared to speak of ALS. It took 4 years and 4 neurologists before a referral to an ALS reference centre was made. After that, diagnosis was confirmed in 1-day. If more was known about ALS and the symptoms, my wife could have been referred to a specialist centre much earlier.**
>
> — Kees Dejil, caregiver of *person living with ALS*

The time taken to receive a diagnosis is further exacerbated by a general lack of knowledge of the disease, by the physician’s fear in giving such a devastating diagnosis unless certain, but also a perception that nothing can be done so there is no rush (e.g. therapeutic nihilism)[23, 28]. General practitioners will see only one or two ALS cases during their careers[23] and two-thirds of primary care physicians self-report their degree of ALS-related training as low, with many expressing an overall lack of knowledge of ALS clinical signs and symptoms[29, 30]. Although the likelihood of seeing a patient with ALS is higher among neurologists, most general neurologists will only evaluate a few

cases of ALS per year and their knowledge of classic ALS presentations may be insufficient to make the appropriate diagnosis[23]. While better education of physicians on ALS may be a solution, it may not necessarily have a significant effect in improving their ability to optimally diagnose the few cases of ALS they may encounter in their careers.[31] However, it may trigger more timely referrals to ALS and neuromuscular specialists in order to confirm diagnosis and commence appropriate disease management[23].

Incorrect and delayed diagnosis often results in PLWALS undergoing unnecessary and potentially painful tests, further delaying the time to an accurate diagnosis[23]. Such delays to receiving an ALS diagnosis today are associated with increased costs for the healthcare system and prevents timely initiation of treatments, multidisciplinary care and entry into clinical trials and research studies[32]. It also delays provision of financial and other social support and may result in emotional distress[22] and cause a detrimental impact on the outcomes of PLWALS and their families[22, 33, 34].

Once a diagnosis is confirmed, this can be devastating for the person affected, their family and surroundings. PLWALS are immediately faced with the realities of their condition, including an inevitable change in work status, likely loss of income, and a momentous shift in future hopes and plans. The psychological impact of processing an ALS diagnosis and the weight of sharing the news with loved ones cannot be underestimated. In some cases, accepting outside help is difficult for both the PLWALS and caregivers[35]. As the gravity of an ALS diagnosis becomes apparent, PLWALS learn of the severely limited treatment options and the expectation for a positive prognosis disappears.

> **“It’s a shock and from this shock nothing will be better, in fact I have to learn to live a life in which death reigns.**
> — Olivier Goy, *person living with ALS*

In many cases, after a diagnosis of ALS is given, the diagnostic period comes to an end, leaving PLWALS and their families fearful and uncertain of what is yet to come. Little is known at point of diagnosis about the type of ALS nor the nature of an individual’s progression. A frequent lack of continued observation beyond the diagnostic period not only results in significant apprehension for PLWALS and their families but may also hamper the ability of the medical team to provide timely and appropriate interventions based on an individual’s unique ALS presentation and progression.

Diagnosis should not be seen as a one-time event and rather a continued process. Constant monitoring would help to further characterise the subtype of ALS and the rate of progression and could be done by monitoring disease staging through the King's staging system[36] or by using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)[37] based on the MiToS staging system[38]. The latter is the most

widely used and validated ALS rating scale in clinical practice and in ALS clinical trials with changes in scores found to predict survival and correlate with quality of life measures[37, 39-41].

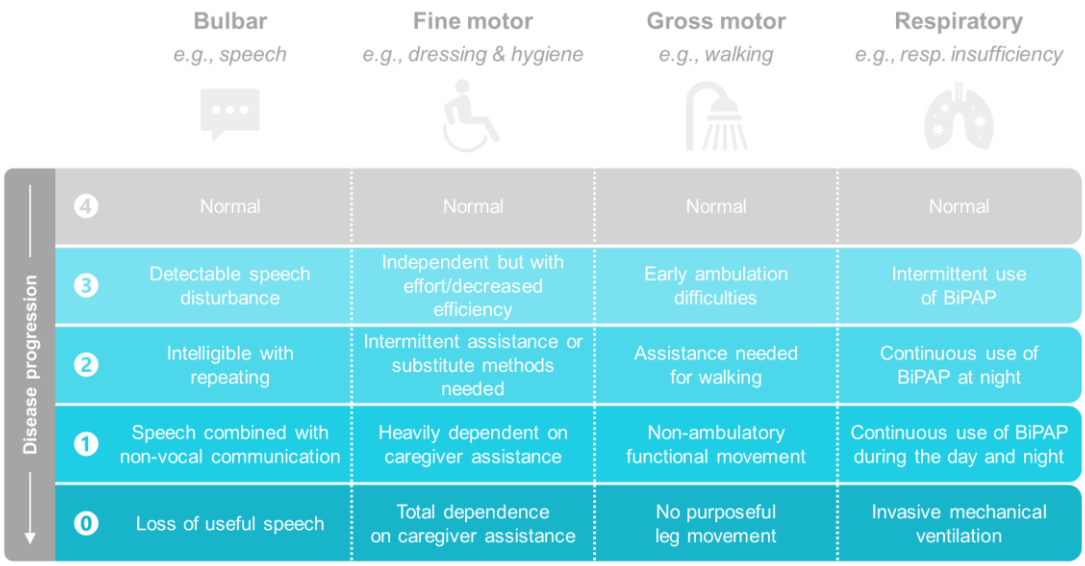


Figure 3. ALSFRS-R domains and example physical function scales[39]
Note: non-exhaustive list of items within the domains

In diagnosing ALS, time is of the essence. Time from initial symptom onset to confirmation of diagnosis must be shortened, and misdiagnoses reduced across all EU countries. Research efforts into the presentation and progression of ALS must be enhanced and a greater number of biomarkers identified. Advances in disease understanding must be rapidly translated into clinical practice. Diagnostic practices must be harmonized across all EU member states and driven by clinical experts, with EAN guidelines* swiftly implemented. As a first step, better capabilities and more support are urgently needed for an earlier and more precise diagnosis and a number of immediate policy actions can be taken.

* EAN guidelines: Guidelines on ALS from the European Academy of Neurology. This comprises two publications: EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. First published in November 2005[1]; and EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. First published in September 2011[2]. At date of publication, current guidelines are under review and updated guidelines are expected to be published in 2023.

Policy recommendation 1

Enhance capabilities of primary care physicians and other first line health providers to conduct timely referrals to NMD/ALS specialists, and ensure expert-led diagnostic assessment, subtype characterisation, and continued evaluation is conducted from point at which ALS is suspected

	Policy actions	Best practice examples
i	Develop an EU-wide ALS Early Detection campaign and roll-out practice-based workshops for first line healthcare providers (e.g., primary care physicians, community nurses, etc.) to raise awareness on first signs and symptoms of ALS, dispelling common ALS misconceptions	**UK:** Red Flag Tool for MND developed by MND association provided to General Practitioners[42] **UK:** Medics for Rare Diseases training to HCPs on detecting rare diseases[43]
ii	Implement most up-to-date European Academy of Neurology guidelines[44] in clinical practice to ensure expert-informed diagnosis and management decisions	
iii	Embed expert developed decision aids including diagnostic guidelines, algorithms and decision support software into medical record software used routinely by primary care physicians	
iv	Offer genetic profiling and counselling routinely in ALS diagnosis to enhance likelihood of identifying ALS biomarker (and contribute to advancing disease knowledge)	
v	Provide continuous monitoring in order to characterise the subtype of ALS and rate of progression after diagnosis	
vi	Provide psychological support to healthcare professionals involved in the diagnostic process, and training on how to give a diagnosis of ALS	SPIKES (a six-step protocol for delivering bad news)[45]

Policy recommendation 2

Provide counselling and support to PLWALS and their families on ALS, receiving an ALS diagnosis, and on disease management options

	Policy actions	Best practice examples
i	Develop and roll-out education and counselling programmes (support package) to be provided to all PLWALS as soon as 'a probable ALS' diagnosis is confirmed	**NL:** ALS roadmap provided for each stage of disease[148]

2. What do people living with ALS need? – Matched care

Living with ALS is a constantly shifting reality…

The relentless and irreversible decline in gross and fine motor skills and vital functions is universal in ALS, even if the disease course varies from one person to another. As ALS progresses to impact more regions of the body, a rapid loss of independence ensues. It becomes increasingly difficult for PLWALS to participate fully in day-to-day life including time spent with friends and family, and health-related quality of life rapidly declines [39, 46-48].

> **One of the worse things for me is that I can´t hug my two kids anymore, I can only wait until anyone touches me.**
> — *Person living with ALS (ALSA, Czech Republic)*

The speed of progression means PLWALS must constantly and urgently adapt their physical environment. But heterogeneity in presentation makes it extremely difficult to predict adaptation requirements before they arise. Over time, need for, and reliance on, supportive aids increase with many PLWALS requiring communication devices to maintain the ability to communicate and interact with their environment, electronic wheelchairs to travel outside of home and major interventions to eating including feeding tubes for essential nutrition[49, 50]. The pace and number of risks arising due to the rapid progression of ALS is unparalleled. Without timely and appropriate interventions or adaptions, PLWALS are at high risk of being malnourished and dehydrated, aspirating food or saliva and developing pneumonia, to name but a few[51].

> **ALS deprives you of everything, from simple movements to the possibility of deciding what to do with the time you have left to live; it doesn't give you a date…everything hangs by a thread.**
> — Nicoletta De Rossi, *caregiver of person living with ALS (Associazione conSLAncio Onlus)*

Alongside PLWALS are families and caregivers for whom little attention is given to their unique experiences and support needs from the point of ALS diagnosis to bereavement and beyond[52, 53]. The emotional and physical toll on family and caregivers is immense, with 52% of caregivers found to experience a high burden[54]. Caregiving often becomes a full-time job for family members, but little respite is available, and many caregivers experience psychological distress and a deterioration in quality of life[54, 55]. The burden associated with providing and coordinating multidisciplinary care for PLWALS is immense and exacerbated further by the number of decisions required in a short period of time, prompting what feels like a race against the clock.

Furthermore, the financial impact of an ALS diagnosis for families and caregivers is significant due to a loss of household income and the substantial increased costs of care and supports required (figure 4). Although the majority of PLWALS may tragically pass away soon after a diagnosis, the psychological and financial hardship for families continues long after PLWALS succumb to the disease, with many families struggling to cope years after the death of their loved one[56].

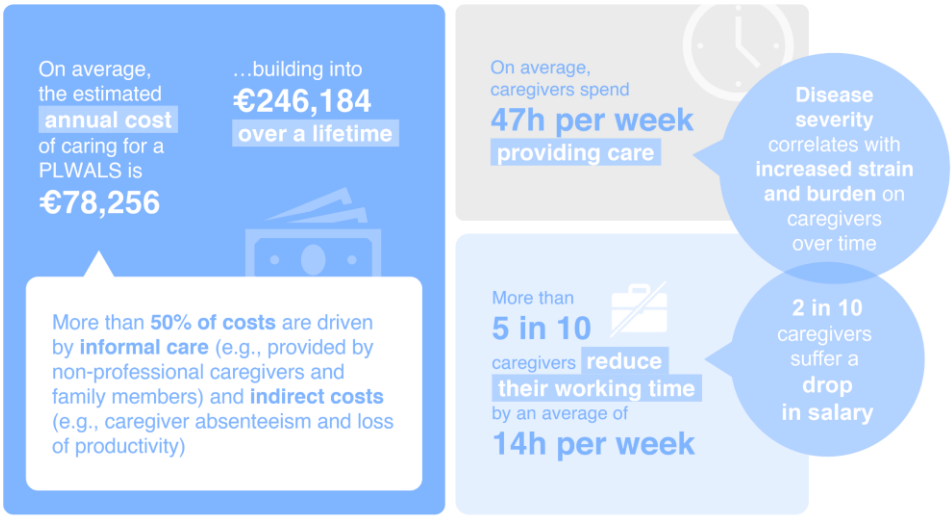


Figure 4. Economic burden of ALS for families and caregivers[55, 57]
Note: Based on studies conducted in Germany between 2018 and 2020

> **Palliative care should also go beyond when the family loses their loved one. After the PLWALS dies they are left alone with their grief, nobody takes care of the family after.**
> — Prof. Nicola Ticozzi, *Director of the Neurology Unit, Istituto Auxologico Italiano, Università degli Studi di Milano*

To alleviate the burden associated with the realities of ALS, our ability to match the needs of PLWALS must be improved…

The management of ALS is significantly more costly than many other neuromuscular disorders both for the PLWALS and families affected and for healthcare systems[57]. But, with improved care, there is an important opportunity to decrease the economic burden associated with ALS. However, improving ALS care depends on the health and social care system's ability to provide for each person's needs – or in other words matching the needs of PLWALS. Not only must the health system be able to match the needs of PLWALS, but it must do so at the right time, making it essential to anticipate and proactively address the needs of PLWALS before they arise. Improvements in medical and multidisciplinary care for PLWALS must be underpinned by the fundamental

objectives of maximising quality of life, maintaining independence and avoiding hospitalisations for as long and as much as possible.

> **It is often the case that primary care physicians who take care of PLWALS don't have enough information about the disease. Our registered clients have to ask them for aids or special examinations based on information they get from our organisation.**
>
> — Karolina Koucká, *Chief coordinator of social and health services, representative of ALSA, patient organisation in Czech Republic*

To match the needs of PLWALS, medical care must be proactive, not reactive…

The medical care provided to PLWALS varies within and across countries in the EU today, making it difficult to effectively match the needs of all PLWALS. For example, most of the established European Network to Cure ALS (ENCALS) centres, are located in Western Europe, with very few centres based in Eastern Europe[58]. Some EU member states do not have any specialist ALS centres available for their citizens living with ALS[58]. Moreover, centres that are specialised in ALS are typically located in big cities, leaving PLWALS residing in more remote areas with long and logistically difficult journeys and significant challenges in accessing timely and effective medical care[59].

> **The number of ALS specialists is declining… it is estimated that in the next 10 years or so, the number of practicing specialists will be halved while the number of people living with ALS worldwide will increase.**
>
> — Prof. Dr. med. Julian Grosskreutz, *Chair of Precision Neurology, University of Lubeck*

Not only are specialist centres few and far between but there is also an urgent shortage of neurologists in Europe. According to the European Academy of Neurology, only ~43,000 neurologists are available to provide care for around 500 million citizens across Europe[60]. This lack of ALS specialist centres and neurologists will only be exacerbated in the coming years, as the population ages and the number of PLWALS and other neurodegenerative disorders continue to grow[61]. In fact, it is estimated that the number of PLWALS in the EU will increase by 20% between 2015 and 2040[62].

> **The system is designed for common diseases, but not for fast progressing diseases, they do not fit in the current model.**
>
> — Olivier Goy, *person living with ALS*

Despite the scarcity of ALS specialists, it is often the case that most management decisions lie with the neurologist, including those that other specialists in the multidisciplinary team (MDT) are more than qualified to make. For example, in

Germany, it is a requirement that a physician signs off on the need for a wheelchair for PLWALS, creating unnecessary workload for already overprescribed specialists. In working within such capacity-constrained systems, overburdened physicians can typically only react to the ever-changing needs of PLWALS, rather than provide pre-emptive and proactive care. This leads to a mismatch between the type and timing of care provided and the needs of PLWALS, with a potentially detrimental impact on the outcomes of PLWALS.

> **The mismatches between patient needs and the care they receive may result in unnecessary complications and further reduces the little time they have with their families.**
> — Prof. Dr. med. Julian Grosskreutz, *Chair of Precision Neurology, University of Lubeck*

To truly match the needs of PLWALS, gaps in multidisciplinary care must be plugged…

European guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) and NICE guidelines on the assessment and management of MND[63] endorse a multidisciplinary care approach with a variety of specialists recommended as part of the MDT, including dieticians, occupational, physical, respiratory and, speech therapists, social counsellors, and psychologists, among many others (figure 5)[44]. Several European studies have shown the benefits of multidisciplinary care including advantages in survival[64-70] and an improvement in quality of life (QoL)[149].

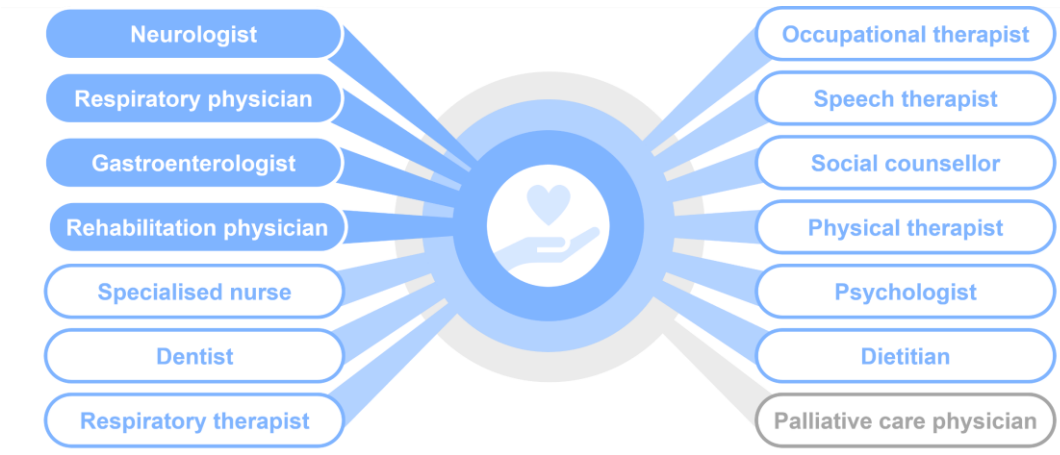


Figure 5. Multidisciplinary specialists involved in ALS management[44]

However, disparities in the availability and access to multidisciplinary care for ALS is seen both across Europe and within individual countries. A recent comparative analysis of care for PLWALS reported that Belgium, France and the Netherlands devote more resources to coordinating health and social services and to managing ALS than Spain, Portugal, and Italy which are characterised by scarce resources, limited involvement of

MDTs and unequal access to supportive devices[59]. Essential professionals often have limited involvement from the point of ALS diagnosis. For example, in the comparative analysis of care for PLWALS in Europe [59], out of six countries, only two (France and the Netherlands) reported having established psychological support programs for PLWALS.

> **There is huge variety in the services and care provided to PLWALS… in the worst cases people are told there is nothing to be done, go home and put your affairs in order.**
> — Prof. Dr. med. Julian Grosskreutz, *Chair of Precision Neurology, University of Lubeck*

The rapid and relentless progression of ALS makes coordination of the multitude of services required particularly challenging and care decisions especially complicated. PLWALS are faced with a severely limited amount of time to seek input from an extensive number of healthcare professionals and are often required to make multiple care-related decisions at one time[71]. However, where gaps in multidisciplinary care exist, PLWALS and their caregivers are left to plug the gaps despite having a lack of support and information on how to navigate the system. National voluntary organisations also play an important role in supplementing multidisciplinary care needs in many European countries. These multidisciplinary care gaps delay the initiation of appropriate interventions and render PLWALS and caregivers unprepared for serious care-related decisions, including those related to the introduction of mobility equipment, or the appropriate and timely initiation of assisted ventilation or gastrostomy insertion. In addition, the burden of coordinating and leading care decisions for PLWALS takes a significant toll on caregivers but limited respite or mental health support services are available.

> **When PLWALS and families get the diagnosis, they are overwhelmed or confused about what they need to do and what to do first. A lot of time is spent coordinating care and adapted to the course of the disease. They need advice and control in the care process.**
> — Andrea Gasper, *Coordinator and palliative care nurse, Bonn, Germany*

Nonetheless, examples of improvements in the availability and coordination of multidisciplinary care exist. For example, in Belgium and France, the state provides an annual budget to Reference Centres to organise patient care in an outpatient setting. While in the Netherlands, the ALS Care Network offers home care teams that coordinate with the multidisciplinary treatment team and the primary care physician [59]. In Ireland, multidisciplinary care is coordinated by a fully funded centralised service that also provides home visits. Patients are reviewed at 6-week intervals and case managers (specialist nurses) integrate all care with community-based services to provide seamless care from diagnosis to end of life.

…and social care services strengthened.

In addition to variability and gaps in multidisciplinary care services, the social care system typically does not have capacity to provide for the needs of PLWALS and their caregivers as fast as required and places unnecessary administrative hurdles in way of accessing assistive technology devices (ATDs) or financial supports. These barriers have been reported in numerous healthcare systems in Europe[50, 72-75]. One common example is the significant variability in time taken to receive electronic wheelchairs and other necessary aids across EU member states, in some cases taking more than a year from request to access[59]. When ATDs are not supplied in a timely manner or are insufficient for PLWALS, families and caregivers will often pay out-of-pocket to ensure the needs of their loved ones are met[76].

> **In Czech Republic, the approval of aids by insurance companies takes a few months; it is not exceptional that it could take up to 6-months, especially for wheelchairs. It often happens that once the aid is approved, the patient needs a completely different one.**
> — Karolina Koucká, *Chief coordinator of social and health services, representative of ALSA, patient organisation in Czech Republic*

Delays in receiving disability status or a disability card poses yet another barrier to accessing ATDs and financial supports for PLWALS. For example, in France in 2018, the average time for granting the disability and priority “carte mobilité inclusion” (CMI) ranged from 3.4 months to 4.4 months[77]. Some countries have sought to improve the time taken to recognise the disability of PLWALS. For example, in Ireland the interval between application and granting of a disability card is now less than 10 days*. In Spain, a bill was presented in March 2022 aiming to speed up the bureaucratic processes to granting aid and benefits for PLWALS, reducing the time from request to resolution[78]. Among other implications, with this initiative PLWALS would be recognized with a 33% disability from the point of diagnosis, regardless of the disease presentation or progression[78]. However, after more than a year since the approval of this initiative, the bill is pending approval into law and the deadline for amendments has been extended more than 40 times.

> **Why wait 9 months for a disability card when you have an orphan and deadly disease?**
> — Olivier Goy, *person living with ALS*

Often, PLWALS will reach a point where they can no longer be cared for in their own home. However, few alternative options are available. Home assistance is often limited, as is the case in Spain and Portugal, where in Spain general home assistance granted

* Based on expert input

to people with severe dependency amounts to only two and a half hours from Monday to Friday; and in Portugal home assistance for daily care is scarce and insufficient[59]. Alternatives such as nursing homes may be considered, but in most countries these are only available for people over a certain age, and even where possible, are not necessarily the most appropriate setting for PLWALS. The paucity of social care services available to allow PLWALS to be cared for appropriately at home, often prompts unnecessary and expensive inpatient admissions and long-term hospital stays.

Nevertheless, new initiatives are emerging, such as in Madrid, where the first public residential centre in the world dedicated exclusively to PLWALS over the age of 18 years and in any phase of illness will be established. The centre is expected to provide comprehensive care for full-time and temporary residents as well as outpatient services[79]. This is a first step to improving the social care services for PLWALS in Madrid and may provide a best practice example for other regions and countries to follow.

Current pathways of medical and multidisciplinary care are unsustainable for such complex and rapidly progressing conditions. Urgent solutions and changes in the model of care are needed. A model that supports proactive ALS disease management could reduce avoidable inpatient and intensive care unit (ICU) admissions and ensure optimal timing of costly interventions such as invasive ventilation, with associated cost savings. Better coordination among health, social care and patient organisations would enhance access to multidisciplinary care and lead to improved survival and quality of life for PLWALS and their caregivers. In the long-term, full integration of multidisciplinary care into ALS disease management would guarantee its access for all PLWALS.

Improving the management of ALS now will undoubtedly help to mitigate the burden on healthcare systems and society in the future. As a first step, several policy recommendations can help move towards a more proactive, expert led, and integrated model of care for ALS:

Policy recommendation 3

Increase co-ordination between ALS and non-ALS specialists, and involvement of essential multidisciplinary professionals, leveraging alternative approaches to care, collaboration, and communication

	Policy actions	Best practice examples
i	Establish national networks of ALS specialists and/or centres of excellence to be accessed by non-ALS specialists who have a PLWALS on their caseload, to streamline communication and liaison	**FR:** FILSLAN network of Centers of Excellence with government funding[80] **IRL**: National ALS/MND service* **NL:** UMCU[81]
ii	Leverage telemedicine a) to enhance supports and guidance provided for non-ALS experts by ALS Centres of Excellence and b) for regular monitoring of PLWALS symptoms, allowing for updates on disease status and progression to be shared with the MDT in real time, and appropriate and timely care implemented	**IRL and UK:** Telehealth in Motor Neurone Disease (TiM); PLWALS and carers enter information about their condition on a weekly basis, with answers shared to the MND care team to inform care decisions[82] **IT:** Nutritional support through Chatbot app[83], telemedicine with MDT through online platform Ticuro Reply[84] and assessments through phone calls
iii	Establish mobile health units for provision of ALS expert-led medical care for PLWALS at home/in local area, supporting physicians responsible for day-to-day care	**SL:** ALS-dedicated mobile health units established* **IRL:** MDT covers hospital and community-based care*
iv	Appoint specific healthcare worker responsible for PLWALS and their family to act as liaison and coordinator of all multidisciplinary care required	Nurse as a coordinator in Parkinson's Disease in different countries[85] **IRL:** Specialist nurses have been case workers since 1996*
v	Develop and fund national certified training courses for healthcare professionals to specialize in ALS or NMD management	

* Based on expert input

Policy recommendation 4

Speed up access to fully reimbursed assistive technological devices for PLWALS

Policy actions	Best practice examples
i Recognise ALS associated disability status immediately upon diagnosis confirmation with associated rights to and reimbursement for ATDs	**FR:** Carte mobilité inclusion (CMI) **FR:** Full reimbursement of wheelchairs[86] **IRL:** Medical cards provided within 10 days of application* **SP:** New bill (awaiting law approval)[78] **US:** ALS Disability Insurance Access Act eliminates the required five-month waiting period[87]
ii Mandate maximum time frame in which a request for an ATD must be fulfilled	**SE (region specific):** MDT professional input guaranteed within 2-weeks of diagnosis in the home of PLWALS[88] **BE:** MDT part of a Neuro Muscular Reference Centre Network with responsibility for ALS* **IRL:** Waiting list of less than 4 weeks for ALS clinic* **IRL:** Specialised equipment banks, curated by IMNDA and supported by government funding* **UK:** Scrap 6-months programme, eliminating wait for benefits for people with terminal illness[89] **BE (Flanders):** Government recognises ALS as rapidly progressive disorder, fast-tracking application for mobility aids and financial assistance*
iii Provide EU or government funding to ALS associations if they are responsible for sourcing and providing ATDs for PLWALS	**NL:** Government funding provided to paying members of patient associations* **IRL:** Equipment banks curated by IMNDA supported by government funds[90] **UK-ENG:** Grants given to PLWALS via MND association*

* Based on expert input

Policy recommendation 5

Improve availability of non-hospital-based care for PLWALS unable to remain in their home as their disease progresses

	Policy actions	Best practice examples
i	Establish long- and short-term residential facilities where all PLWALS can receive optimal and multidisciplinary care in a humanised environment	**SP:** Establishment of residential facility in Madrid[79] **BE (Flanders):** Reimbursement for stay at specialised residential care centres associated with expert clinics[91] **IRL:** Dying at home prioritised, services in place*

Policy recommendation 6

Recognise the essential role of family and caregivers in the care of PLWALS and provide appropriate social, psychological, and financial supports

	Policy actions	Best practice examples
i	Develop and implement caregiver training for all family/caregivers to be provided immediately upon diagnosis of ALS	**IT:** Free caregiver training course available 24/7 (by ALS association)[92, 93] and free training for families and caregivers (ProFAD) with 300h of theory and practice[94] **PT:** ALS association every year has a formation plan with theorical and practical sessions, training, and specific courses (e.g., basic life support, nutrition management) addressed for informal caregivers*
ii	Guarantee mental health support for family/caregivers as part of multidisciplinary care provided to PLWALS	**NL:** Patient advisory council: App-based forum for caregivers of PLWALS to share experiences (established by ALS association)* **IRL:** Caregiver support provided by MDT* (combined programme between psychology & medial social work)
iii	Provide government funding for respite care either via ALS associations or directly via social care systems	
iv	Ensure full and immediate implementation of measures included in the European Care Strategy by EU member states (i.e., supporting families in their fundamental role as caregivers)	

* Based on expert input

3. What do people living with ALS need? – Work towards a better prognosis

People living with ALS should not be left behind…

The unmet needs in ALS are tremendous. Most PLWALS will succumb to the disease within 2 – 5 years from the onset of their symptoms and, in the short period of time they live with this severely disabling disease, their health-related quality of life is significantly impacted. The fact is that the harsh realities of this disease prevail over time, with the only treatment for ALS approved in Europe more than 25 years ago. This leaves people and families who receive a diagnosis of ALS with no choice but to hope for the availability of and access to new effective treatments.

But for this, changes are needed. PLWALS should be able to participate in clinicals trials for which they are suitable, as is the case for many other life-threatening diseases. Achieving this will require a strong commitment and a disproportional up-front investment. Research and development (R&D) in ALS must continue to be encouraged, streamlined, and funded. Where new ALS treatments are available, timely access and reimbursement across Europe must be ensured. PLWALS do not have much time, so there is an urgent need to act and no time to waste.

A new wave of innovation has begun…

The number of clinical trials in ALS has steadily increased over the past decade, many driven by international initiatives. One example has been the creation of the Treatment Research Initiative to Cure ALS (TRICALS), the first international research initiative uniting patients, leading researchers and ALS foundations from 15 European countries with an overarching goal of finding an effective treatment for ALS[95].

New treatments do not usually materialise overnight, but initiatives such as TRICALS help advance this long and complex road towards achieving innovation with novel medicines in disease areas with unmet need. Further enhancing R&D in ALS requires an understanding of how developing new medicines in areas of unmet need happens, and where a disease with such high unmet need and low disease knowledge sits within that journey. Progress towards the availability of new treatments happens incrementally through three phases: 1) pre-innovation, 2) innovation and 3) stabilisation, as outlined in figure 6.

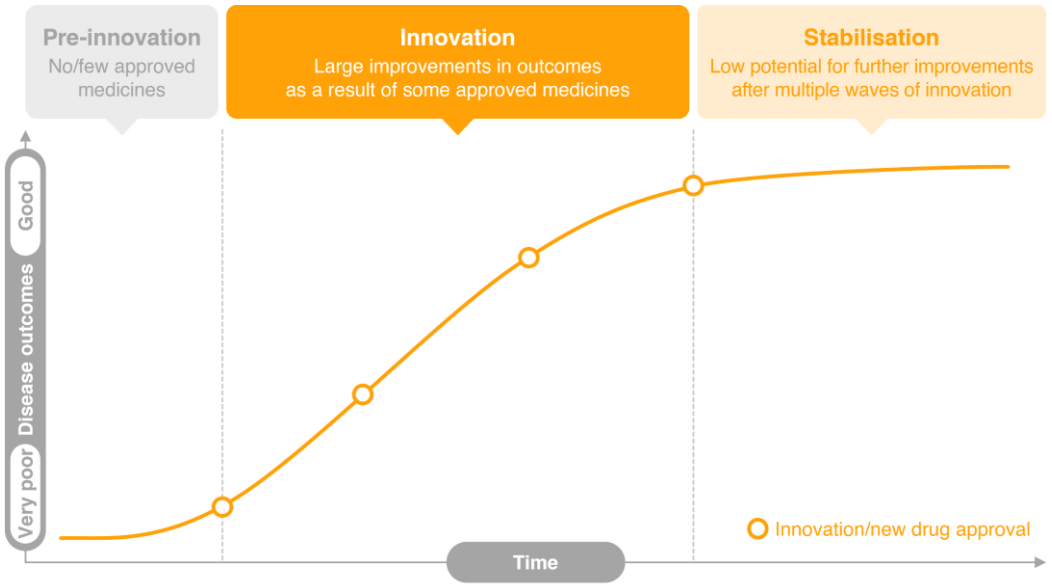


Figure 6. Three phases of pharmaceutical innovation in diseases with high unmet need
Note: illustrative

1) The ***'pre-innovation phase'*** is characterised by low numbers of new medicine approvals and very high unmet need and reflects the current situation for ALS. Disease outcomes are poor, and as new innovations are yet to arise, care is often symptomatic or palliative. Healthcare system spending on medicines is typically low in this phase of innovation, as is the case for ALS today. However, the disease outcome trajectory is dependent on the success of early innovations and extent of further investment in future new medicines.

2) During the ***'innovation phase',*** treatments become clinically and economically viable due to a combination of advances in disease understanding and changing priorities of policymakers. Disease outcomes improve incrementally with every new drug approval and healthcare system spend on medicines rapidly increases. This is the immediate next step for ALS, with each new medicine offering a stepwise improvement in prognosis.

3) As a disease enters the ***'stabilisation phase'***, unmet need has been much reduced through multiple waves of new drug approvals, and the potential for further health improvements falls. Healthcare system spend on medicines becomes constant and the frequency of new medicines in that area declines. This would be the future aim for ALS, where PLWALS have a variety of treatments to choose according to their disease type and needs.

Across all phases of innovation, there have been and will continue to be many failures. But these are necessary and are paving the way towards new treatments by

continually contributing to a better understanding of the disease and how to treat it. This journey to bring new medicines in ALS initially requires disproportional funding and investments to move from the 'pre-innovation' to 'innovation' phase. In the long-term, this will lead us to the 'stabilisation' phase where the prognosis for PLWALS would be significantly improved.

…but research and development in ALS is not without challenges.

It is important, however, to recognise the challenging conditions in which R&D for rare and complex diseases, such as ALS, takes place. Disease complexity and limited understanding, small, widely dispersed, and heterogeneous populations, and sub-optimal use of data collection registries, all contribute to difficulties for R&D for rare diseases[96, 97]. Furthermore, there is frequently a disconnect between basic research in the laboratory and clinical practice, meaning that basic science discoveries are not always translated into results that directly benefit human health.

In particular, significant heterogeneity of the ALS population renders R&D challenging[98]. Often, the more inclusive a clinical trial is of a heterogenous group of patients, the more difficult it is to prove benefit of a new medicine across the whole population. A difficult trade-off is required between patient inclusivity and homogeneity of the population enrolled in a clinical trial. The more precise the inclusion criteria are, the more exclusive a trial becomes, prompting the need for a greater number of clinical trials to find effective new medicines for all PLWALS[99-102].

Little is still yet known and understood about the ALS disease mechanism making it inherently difficult for researchers to identify and select appropriate endpoints in clinical trials. It is therefore important for severe and complex conditions with limited treatment options, that trial sponsors seek and receive early scientific advice for a drug in development with regulatory and payer authorities on the trial design and endpoints to ensure evidence packages meet regulatory and national reimbursement requirements. Routine inclusion of patient and clinical expertise in these early dialogue opportunities should be maximised to help ensure inclusion of patient-relevant endpoints.

> **"We must bridge the gap between the lab and our patients. Sometimes we study a mechanism for the sake of knowing what happens in the cells, without keeping PLWALS in mind. Moreover, research and clinics are often seen as two worlds apart by the administrations at hospitals and universities.**
>
> — Prof. Nicola Ticozzi, *Director of the Neurology Unit, Istituto Auxologico Italiano, Università degli Studi di Milano*

Several unique and clinical factors of ALS further complicate R&D in this disease area, as described in figure 7. Medicines targeting the underlying mechanism of neurodegenerative diseases must reach the brain and therefore need to cross the blood

brain barrier. This restricts R&D to compounds that can act on the brain and as little is known about the functioning of the blood brain barrier, it is difficult to prove that medicines are in fact passing through it. New research also suggests that neurodegenerative diseases alter the blood brain barrier, further exacerbating the challenges[103-105]. In addition, given that degeneration of neurons affects the whole body, complications are difficult to predict and often complex, increasing the risks and costs associated with R&D in ALS[106]. Finally, long diagnosis timelines and speed of disease progression means PLWALS enrolled in clinical trials have already experienced irreversible degradation, potentially limiting the efficacy of a medicine once treatment begins[22, 107].

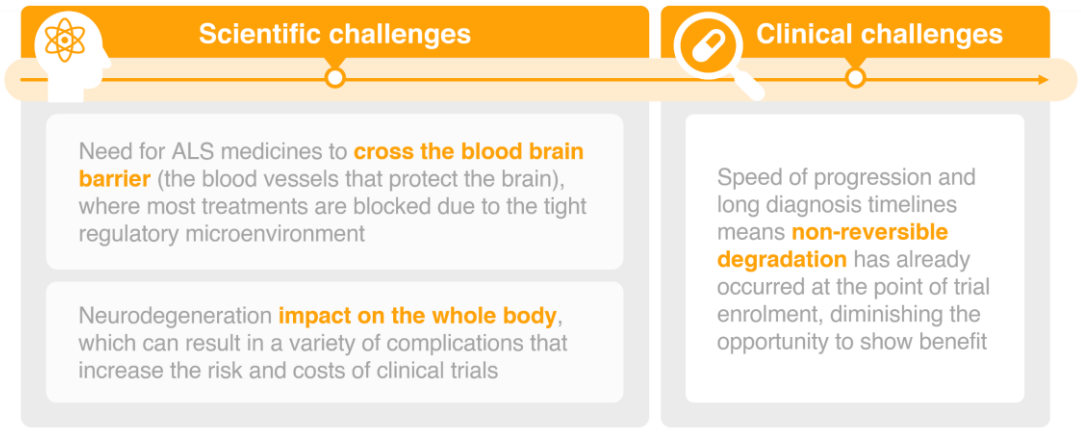


Figure 7. Scientific and clinical challenges unique to developing medicines for ALS and other rare neurodegenerative diseases[22, 103-107]

The high rate of clinical trial failures and unique challenges of R&D in ALS underscore the heightened risks associated with investment in ALS. More than 80 failed randomised clinical trials (RCTs) have been conducted investigating medicines for ALS, but riluzole, approved in 1996, remains the only approved therapy in the EU today[108, 109]. However, it is important to recognise that all these efforts have contributed to advancing disease knowledge and paved the way for existing and future treatments being developed and recent initiatives, such as PRECISION ALS[110], provide improved platforms for advancing and sharing of disease knowledge, addressing historical challenges encountered at European level. We must continue to support such efforts and initiatives by bolstering research infrastructures to speed up initiation and increase the number of research studies and clinical trials conducted. In addition, we must continue to streamline processes for the prompt sharing of advances in disease understanding and communication between researchers and clinical experts. Lastly, improvement is needed in the alignment between researchers, clinical experts, medicine developers, regulatory and payers on trial design and endpoint acceptability. In all of these processes PLWALS and their carers need to be involved as partners[111].

To achieve these goals, several policy actions can be taken:

Policy recommendation 7

Augment research to further disease understanding and treatments for ALS and increase awareness of and accessibility to ALS clinical trials

Policy actions		Best practice examples
i	Continue to provide funding for/to: a) research on disease mechanism, biomarkers and subtypes; b) long-term research; c) bolster infrastructures for knowledge sharing and research collaborations; d) increase number of clinical trial sites; and e) increase training for conducting clinical trials	**USA:** Accelerating Access to Critical Therapies for ALS Act (Act for ALS) is a law that implements a Public-Private Partnership for Rare Neurodegenerative Diseases such as ALS and establishes grant programs to cover costs of research[112] **Australia:** NSW government announced $2m to support research on regional MND hotspot[113] **EU:** EU Joint Programme – Neurodegenerative Disease Research[114] **FR:** BaMaRa National database of all rare diseases[115] **TRICALS:** PRECISION ALS[110] **UK:** £50M government funding provided for translational research incl. establishing virtual MND institutes for enhanced collaboration and increased number of ongoing clinical trials and patient access[116] **BE (Flanders):** FWO-Flanders funding programme for academic investigator-initiated ALS trials w/out industry interest[117]
ii	Support the availability and long-term sustainability of a European-wide registry for ALS (e.g., PRECISION ALS)	**TRICALS:** PRECISION ALS[110] **USA/Global:** ALS Research Collaborative (ARC) is a global initiative that aims to collect natural history data from PLWALS through the ARC Data Commons, an innovative data-sharing platform powered by Google Cloud and Google's Looker application[118]
iii	Establish an online European platform for the sharing of information about ongoing clinical trials in a patient-friendly manner	**IT:** First live international ALS clinical trial database launched in 2019[119, 120]
iv	Leverage telemedicine and/or decentralised clinical trials to facilitate wider participation in and access to clinical trials, irrespective of geographic location	**FR:** Use of web-based monitoring for lung cancer patients in a multicenter phase III trial[121]

Policy recommendation 8

Improve alignment between researchers, clinical experts, medicine developers, regulatory and payers on trial design (incl. acceptable clinical trial endpoints) accounting for patient evidence and opinions

Policy actions		Best practice examples
i	Standardise inclusion of PLWALS and family/caregiver opinion in systematic manner into clinical trial design decisions and endpoint development and selection	**USA:** ALS Clinical Research Learning Institute is a two-day programme that empowers attendees to be strong advocates in the field of ALS by educating them on clinical research and the therapy development process. Certification as an ambassador provides opportunities to influence and improve the ALS research process[122]
ii	Improve communication channels between research and clinical communities for translational research to ensure clinical relevance of endpoints	**UK:** Virtual MND institutes for translational research[123]
iii	Ensure communication via early dialogues between the clinical community, patients, medicine developers, regulatory, and payer authorities to ensure alignment on trial design, selection and acceptability of endpoints that matter most to patients	**EU:** Parallel EMA/EUnetHTA 21 Joint Scientific Consultations[124] **EU:** Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA)[125]

PLWALS have no time to wait to access new ALS medicines…

Besides riluzole, ALS has seen no newly approved medicines in Europe for over 25 years. But ongoing R&D has significantly advanced the field of ALS over the last decade and the identification of several biological pathways has led to a promising pipeline of preclinical approaches and clinical trials[126]. As the ALS community anticipates to benefit from these advances, it is imperative that European healthcare systems are prepared to provide access to new innovations to PLWALS as soon as they become available either via clinical development programmes or following clinical trial completion.

…but clinical trials are not easily accessible…

Clinical trials offer hope to PLWALS with an opportunity to access new medicines under development, especially when faced with the realities of their prognosis. However, even if eligible for a clinical trial, several logistical access barriers exist (figure 8).

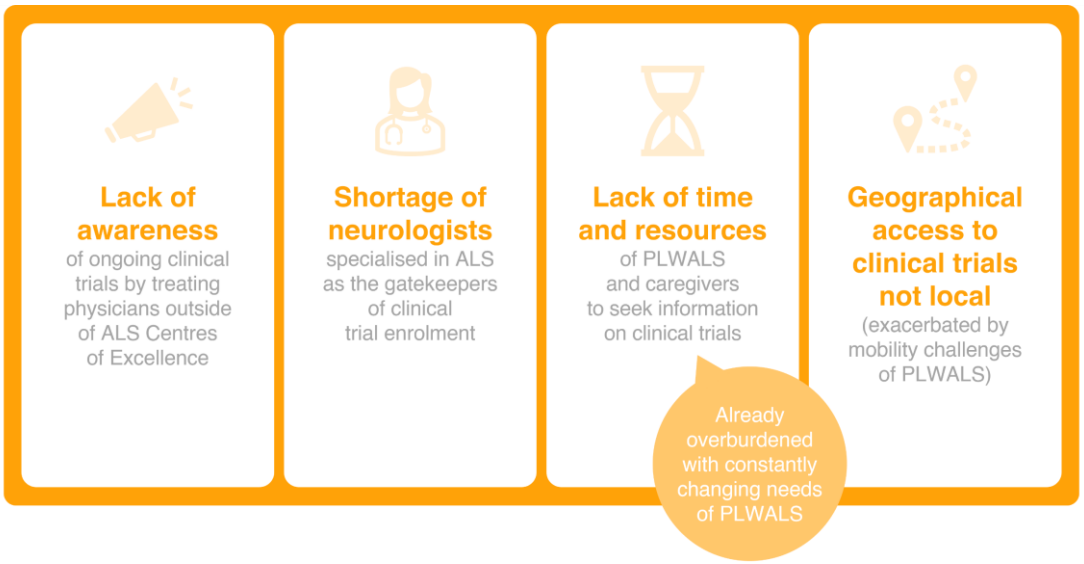


Figure 8. Logistical barriers to accessing clinical trials for PLWALS

> **All patients from geographically dispersed areas should be able to access clinical trials at main hospitals. To this end, financial resources are needed to facilitate transportation and accommodation.**
>
> — Maria Jose Arregui, *Executive President, Fundación Luzón*

The rapid and unrelenting pace of disease progression means PLWALS may only have one chance to enrol in a clinical trial and simply do not have time to wait for the next one. Logistical challenges to accessing ongoing clinical trials severely limits the potential one and only opportunity for PLWALS to benefit from promising medicines.

…and reimbursement of newly approved medicines is not always timely.

Barriers to achieving timely and equitable access to rare disease medicines in Europe are widely reported and well understood[127, 128]. While ALS is unlikely to be an exception, these access barriers must be minimised for PLWALS for two crucial and unique reasons:

1. ***Unmet need:*** Treatment options for PLWALS are severely limited, the unmet need for new and effective medicines is tremendous.
2. ***Time:*** The sheer pace of ALS progression means most PLWALS today will not live to receive or benefit from newly approved treatments in the future. PLWALS have no time to wait.

> **The latest innovative treatments bring hope of invaluable months of extra life… except their authorization is slow in Europe, to the great displeasure of the patients who often don't have time to wait.**
>
> — Olivier Goy, *person living with ALS*

To reflect the urgency and extent of unmet needs in conditions such as ALS, speed in regulatory and national reimbursement decisions is crucial. Existing processes at regulatory level that support in expediting decisions, including PRIME designation and accelerated assessment, should be maximally leveraged. At national level, time to access should be minimised, for example, via national early access programmes pre- and/or post-regulatory approval. Once marketing authorisation is achieved, access to fast-track reimbursement pathways should be offered. As clinical and real-world evidence for new medicines evolves, flexibility in existing processes, such as conditional marketing authorisation and national managed access programmes, can be used to support faster access while accounting for new evidence over time.

Considering the complexity of rapidly progressive neurological conditions like ALS and given that lack of new treatments that have been evaluated at regulatory or national level in over 25 years, it is likely that questions and uncertainties will arise in relation to clinical trial design, acceptability of endpoints and the patient relevance of clinical data. Delays in access can arise where uncertainties perpetuate or misalignments between regulatory and payer bodies occur. To minimise potential delays, opportunities for the involvement of specialist clinical expertise and patient opinion in regulatory and national evaluations should be maximised. The routine involvement of these clinical and patient insights in a standardised manner is critical for the translation of clinical evidence in what it means in the real world for patients. To reflect the wider impacts of ALS on PLWALS and their caregivers, it will be important that these be considered more holistically in value assessments to ensure disease and treatment impacts are appropriately captured.

Today marks a turning point for ALS in Europe. Finally, the ALS community has hope for accessing new and effective medicines. It is critical that we keep this momentum going by supporting new innovations while attracting more investment in R&D. It is important to recognise that 25 years of research failures cannot be discounted, but considered an investment that has contributed to advancing our understanding of ALS and how best to treat it. If access to the new wave of medicines for ALS is achieved, it will undoubtedly ignite innovation in this disease area, paving the way towards a future where several effective treatment options are widely available for PLWALS in Europe. Such a path of innovation has been seen for other neurodegenerative diseases like multiple sclerosis (MS), where in 1993 the first therapy proven to be effective in altering the natural history of relapsing-remitting MS (RRMS) was approved[129]. Since then, several MS medicines have been developed, approved, and reimbursed, furthering our understanding of the disease, and providing people living with MS the opportunity to live fuller lives[129, 130]. We can reach this point in the future for ALS, and several policy actions can support in getting there:

Policy recommendation 9

Expedite and support the approvals of new treatments for PLWALS considering the urgency and breadth of their unmet needs, ensuring ALS expertise is accounted for in drug evaluations

Policy actions		Best practice examples
i	Routinely seek and account for specialist clinical expertise and the patient voice in the regulatory evaluations of complex and severe conditions such as ALS to support translation of the clinical evidence (e.g., what the evidence means in clinical practice / in real life for PLWALS)	
ii	Ensure that the urgency, extent of unmet need, rapidly progressive and life-threatening nature of ALS is recognised and warrants access to early dialogues/scientific advice and existing expedited pathways (e.g., conditional marketing authorisations), ultimately ensuring alignment on evidence packages required and providing greater opportunity to receive prompt marketing authorisation	**EU:** PRIME[131], accelerated assessment[132] and conditional/exceptional marketing authorisation[133] **USA:** FDA Fast Track designation[134], Accelerated Approval[135] and Priority Review[136]
iii	Work towards advancing existing regulatory pathways via adaptive-type processes to better foster innovation and allow for faster approval of promising new treatments, for example with the implementation of rolling regulatory submissions and by allowing to supplement traditional evidence requirements (e.g., real-world evidence)	**USA:** FDA Rolling Review[134]

Policy recommendation 10

Provide timely access to new treatments targeting life-threatening diseases with extremely high unmet need via fast-track and conditional reimbursement processes, that consider the holistic value of medicines

Policy actions		Best practice examples
i	Where consistent with national policy, encourage consistent processes and implement best practice nationally funded early access programmes in all EU member states for new treatments targeting life-threatening diseases with high unmet need, covering the periods between pre- and post-marketing authorisation until P&R decision and considering appropriate financial risk-sharing where required	**FR:** AAP programme[137] **IT:** Law 648[138]

Policy actions		Best practice examples
ii	Ensure that the urgency, extent of unmet needs, rapidly progressive and life-threatening nature of ALS is recognised, warranting national access via early access and/or fast-track pricing and reimbursement channels to expedite decisions	**IT:** Faster access through innovative status need[139] **DE:** Automatic added benefit assumed for orphans; immediate access while price being negotiated[140] **ES:** Lower mandatory discount[141] **FR:** Fast-track evaluation for innovative medicines by HAS[142] **FR:** Upcoming implementation of direct access (1-year free pricing commercialisation period) for medicines with SMR of major or important and ASMR I to IV[143]
iii	Consider in the value assessments of new medicines targeting life-threatening diseases with high unmet need such as ALS: a) broader impacts of treatment (e.g., caregiver burden, quality of life, costs to health and social care systems, socioeconomic impact, etc.) and b) the sustainability of OMP innovation (e.g., risk of failure and level of unmet need, value of incremental innovation and contribution to disease knowledge, etc.)	**SE:** Societal impact considered in HTA evaluations[144] **UK:** HTA evaluation process considers evidence on carers[145] **Scotland:** Patient and carer evidence considered in the initial HTA evaluation by SMC[146] and Patient and Clinician Engagement (PACE) meetings in event of negative reimbursement decision[147]
iv	Allow for the implementation of managed access agreements with formal evidence collection plans to further evaluate effectiveness of medicines in the real world	
v	Standardise measures, as defined by ALS clinical experts and patient advocacy groups, used in the collection of real-world evidence and leverage recent technologies (e.g., health-monitoring mobile apps), to reduce administration burden and harmonize data collection	**TRICALS:** PRECISION ALS[110]

Conclusions

People living with ALS have no time to wait. Diagnosis must be optimised, a proactive model of care must be adopted and collectively we must work towards achieving a better prognosis for all PLWALS in Europe. We must continue to progress European initiatives focused on increasing disease understanding, sharing of knowledge, and advancing treatments for ALS, including PRECISION ALS and ERN EURO NMD. While looking forward is crucial and appropriately funded research must continue, immediate policy change focused on improving the daily lives of PLWALS, their families and caregivers is critical. The ten policy recommendations outlined in this paper serve as a roadmap for policymakers at European and national level, providing an opportunity to tangibly improve the diagnosis, care, and prognosis for PLWALS in Europe today. As with all policy change, appropriate funding is essential and wherever possible, EU funding should be leveraged (e.g., via EU Horizon Programme and EU4Health Progamme). Policy action for ALS today will not only pave the way for a better future for PLWALS, but also for the many thousands of people across Europe diagnosed and living with similarly complex conditions. If we solve the challenges in ALS, we can tackle other severe and complex neurological disorders!

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