ESTIMATING THE VALUE OF A SUCCESSFUL TREATMENT

The commercial case for investing in ALS

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Foreword

Neurodegenerative disease research is at a turning point, where scientific progress offers the first credible promise of altering the course of some of these devastating conditions. While investment and innovation have surged in large, high-prevalence conditions, such as Alzheimer's and Parkinson's disease (AD and PD, respectively), these spaces have also become increasingly competitive. Hundreds of programs are targeting similar pathways, resulting in limited differentiation and intense competition. Against this backdrop, Amyotrophic Lateral Sclerosis (ALS) represents a significantly different kind of opportunity. Smaller in absolute market size, yet defined by an immense humanistic burden, urgent unmet need and growing scientific momentum. Few neurological conditions impose such a rapid and devastating toll on patients and families. Within a few short years, ALS can take away individuals' independence, mobility and communication, profoundly affecting patients and those who care for them.

Nevertheless, ALS remains one of the most dynamic areas for translational research. Accelerating adoption of newly approved therapies, even those with modest efficacy, illustrates the urgent need for treatment options and the high willingness to pay for incremental benefits. Orphan designation and accelerated regulatory pathways further enhance the opportunity, enabling faster market entry, extended exclusivity and tangible cost advantages. Importantly, ALS trials are smaller, shorter and more targeted with progression endpoints achievable in months rather than years. This creates a development environment that rewards innovation and speed.

Beyond the clinical and commercial rationale, the humanistic impact of ALS amplifies the moral significance of developing a successful therapy. Every intervention that slows decline translates into preserved dignity and measurable improvements in patient and carers' quality of life. These human outcomes are increasingly recognised by regulators, payers and society as legitimate dimensions of therapeutic value. As such, ALS offers a platform for redefining how success is measured in rare, high-severity disease, where time, autonomy and connection carry immense value.

ALS is also emerging as a strategic validation space for next-generation neuro-technologies. Advances in gene therapies and AI-driven drug discoveries are converging in this indication, supported by adaptive platform trials such as HEALEY and EXPERTS-ALS. Success in ALS can de-risk platforms and inform development strategies across related conditions, including frontotemporal dementia (FTD), AD and PD. These markets together represent a cumulative opportunity of hundreds of billions of dollars in potential value. This cross-disease translational potential makes ALS not only a humanitarian imperative, but also a scientific and commercial opportunity.

This report sets out the clinical, humanistic and economic case for greater investment in ALS. While the absolute market estimates are smaller than those in large chronic disease, the risk-adjusted return, societal value, and translational potential are considerable. ALS offers a rare alignment of moral urgency, scientific readiness and commercial viability. This is a space where progress can be both deeply human and highly strategic.

In short, ALS is no longer a niche indication. It is a proving ground for the future of neurodegenerative medicine and a test of how innovation can meet both human and market needs. As the field enters this transformational era, I am excited to play a role in turning scientific progress into meaningful change for patients, families, and the broader scientific community.

Dr. Vishal Gulati, FMedSci
Founder and Managing Partner, Recode Ventures, and Longitude Prize on ALS judge

Executive Summary

Amyotrophic lateral sclerosis (ALS) is a rare, rapidly progressive neurodegenerative disease with devastating clinical and economic consequences. Despite its relatively low prevalence, ALS imposes a disproportionate burden on patients, caregivers, and healthcare systems due to its complex diagnosis pathway, limited treatment options, and high resource utilisation. This report presents a comprehensive commercial case for investing in ALS research and therapeutic development, highlighting the unmet need, socioeconomic burden, and market opportunity across seven major countries: the UK, US, Canada, France, Germany, Italy, and Australia.

Unmet Need and Diagnostic Challenges

ALS is characterised by motor neurone degeneration, leading to muscle atrophy, paralysis, and death, typically within 2-5 years of symptom onset. Diagnosis is often delayed by 10-16 months from symptom onset due to symptom heterogeneity and the absence of reliable biomarkers (Richards, Morren and Pioro, 2020). Only three disease-modifying therapies (DMTs) have been approved to date, each offering modest benefits. The lack of effective treatments and validated biomarkers emphasises the urgent need for innovation in diagnostics and therapeutics.

Opportunities for Strategic Investment

Despite these challenges, ALS research is at a pivotal moment. Key enablers include:

- Rising public and private funding: NIH funding for ALS increased nearly fivefold from 2015 to 2024.
- Use of large-scale datasets: Initiatives like the Global Neurodegeneration Proteomics Consortium support biomarker discovery and provide insights to novel target discoveries.
- Cross-disease potential: Genetic, pathological, and clinical overlap with frontotemporal dementia (FTD) and other neurodegenerative diseases suggests broader therapeutic applicability.
- Platform trials: Adaptive designs like the HEALY ALS and EXPERTS Platform Trials are streamlining drug development.
- AI and in-silico technologies: These tools reduce preclinical costs and accelerate unlocking disease understanding and novel target and biomarker identification and speed up drug discovery and development.

These developments position ALS as a high-impact area for both scientific advancement and commercial return.

Burden of Disease: Socioeconomic and Healthcare Resource Impact

The burden of ALS is particularly stark when expressed in terms of quality-adjusted life years (QALYs) lost. In the UK, an individual diagnosed with ALS may lose approximately 12.6 QALYs over their lifetime, equating to a monetised health loss of $1.2 million per patient. At the population level - given that there are 5,000 prevalent ALS cases in the UK - this translates to $5.9 billion in lost health value across existing patients' lifetimes. Similar estimates across other countries reveal a total monetised health burden ranging

from $1.1 billion in Australia to $34.2 billion in the US, even before accounting for healthcare and broader societal costs.

Furthermore, ALS patients require intensive, multidisciplinary care, with yearly per-patient healthcare costs ranging from $23,039 in Canada to $76,823 in the US. When extrapolated to national populations, these costs represent a significant strain on healthcare systems, reaching $2.5 billion annually in the US alone.

Beyond direct medical costs, ALS imposes substantial non-medical and indirect costs which, when taken into account, approximately triple the cost estimates above. This is because informal caregiving, home modifications, and productivity losses account for up to 64% of the total cost burden, as evidenced by studies in Germany and Canada.

Quantifying the Commercial Opportunity

The report employs three complementary approaches to estimate the commercial value of a successful ALS treatment, the results of which can be compared with the likely investment required to bring such therapies to market:

Approach 1 — Socioeconomic Burden

Monetising the total burden of ALS per year, including QALY losses and healthcare costs (but excluding broader societal costs) of the prevalent population, revealed an upper-bound one-year value of:

- $34.2 billion in the US
- $6.1 billion in the UK
- $1.6-4.4 billion in other markets

Approach 2 — Proxy Pricing via tofersen

Our second approach used the price of tofersen as a benchmark and scaled this price to the full ALS population. We considered this to be a reasonable benchmark, as a recently approved innovative therapy for a genetic form of ALS. We found yearly commercial values of:

- $4.8 billion in the US
- $209 million in the UK
- $139-$347 million in other countries

These values increase substantially over time as incident cases are added, with the US market alone reaching $39.9 billion in cumulative value by year ten.

Approach 3 — Conventional HTA Modelling

A Markov model adapted from Tappenden et al. (2024) evaluated three hypothetical treatment scenarios. Only the most effective scenario, halting disease progression, produced consistently positive value across all countries. We found the yearly value of this hypothetical treatment to be:

- $3.14 billion in the US
- $203 million in the UK
- $137-$3493 million in other countries

Less effective treatments were often deemed not cost-effective, even at price zero, highlighting limitations in current Health Technology Assessment (HTA) frameworks for rare, high-burden diseases, such as ALS.

Spillover Effects and Broader Value

Given the genetic, pathological, and clinical overlap between ALS and Frontotemporal Dementia (FTD), we estimate that a dual-indication therapy could expand the addressable market by up to 2.5-fold. In the US, this would increase the yearly commercial value from $4.8 billion to $12.4 billion. Additionally, broader societal costs, including informal caregiving and productivity losses, are substantial but often excluded from HTA evaluations. Incorporating these could further strengthen the economic rationale for ALS investment.

Conclusion

ALS presents a compelling case for strategic investment. The convergence of unmet medical need, advancing research capabilities, and demonstrable commercial opportunity creates a promising environment for innovation. While current HTA methods may undervalue ALS treatments, alternative frameworks that account for severity, rarity, and societal impact are essential to unlock the full value of therapeutic advances. This report demonstrates that a successful ALS treatment would not only transform patient outcomes but also deliver significant economic and societal returns.

1 Background

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative condition that damages motor neurones in the brain and spine, leading to muscle atrophy, generally followed by paralysis, subsequent respiratory failure and ultimately death (Saini and Chawla, 2024; Wolfson et al., 2023; Ilieva, Vullaganti and Kwan, 2023). Even as the most common motor neurone disease (MND), ALS is still a rare condition. Lifetime incidence of ALS, however, is relatively high, with 1 in 300 people developing ALS in their lifetime (Martin, Al Khleifat and Al-Chalabi, 2017).

The average life expectancy for individuals living with ALS is between 2 to 5 years from symptom onset (Bradford and Rodgers, 2024). However, approximately 20% of patients survive between 5-10 years (Riva et al., 2024), and 5% live 20 years or longer (The ALS Association, 2025). The condition is more prevalent in males and the median age of onset is between 51 and 66 years (Longinetti and Fang, 2019).

The global incidence of ALS is estimated to be 0.78 per 100,000, ranging from 0.26 per 100,000 in Ecuador to 23.46 per 100,000 in Japan. The global prevalence is estimated to be 4.5 per 100,000, ranging from 1.57 per 100,000 in Iran to 11.80 per 100,000 in the United States (US) (Wolfson et al., 2023). The relative rarity of the condition, its rapid progression, and the need for specialised expertise for accurate diagnosis and treatment result in significant variation in published estimates. Similarly, substantial variation in estimated survival may be the result of diagnostic pathways and availability of specialised care in different regions (Wolfson et al., 2023).

ALS management faces numerous challenges, the first of which being the complex diagnostic pathway. The majority of ALS cases have an unknown cause, with only 5-10% having a familial genetic component (Wolfson et al., 2023; Bradford and Rodgers, 2024). This is compounded by the heterogeneity of symptoms, which can mimic a variety of conditions, and a lack of valid diagnostic biomarkers available. As such, clinical diagnosis is based on a "rule-out" approach, often requiring evidence of progressive spread of symptoms, thereby delaying diagnosis often between 10-16 months (Longinetti and Fang, 2019; Bradford and Rodgers, 2024; Richards, Morren and Pioro, 2020).

In addition to a complex diagnostic process, drug development for ALS has seen limited success. Only one medication, riluzole, has been approved for the treatment of ALS in Europe and the United States since the 1990s. Riluzole is a disease-modifying therapy (DMT) that modestly slows disease progression, extending survival by only a few months without substantially improving functional decline (Tappenden et al., 2024; Khamaysa and Pradat, 2022). The other commonly used DMT, edaravone, which is currently not approved in Europe, acts by modestly slowing disease progression. However, its role as an ALS therapy remains a subject of debate due to limited evidence of long-term efficacy (Ilieva, Vullaganti and Kwan, 2023; Carroll et al., 2025). Another intervention, tofersen, was approved by the US Food and Drug Administration (FDA) in 2023 for the treatment of adults with a SOD1 gene mutation, which is responsible for 20% of familial and 1-2% of sporadic ALS cases (Saini and Chawla, 2024). Tofersen was approved by the European Medicines Agency (EMA) in 2024 and by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) in July 2025. Additional therapeutic agents are currently undergoing clinical trials as the knowledge of the pathophysiology of ALS deepens (Khamaysa and Pradat, 2022).

2 Study objectives

The aim of our study is to investigate the existing unmet need in ALS and demonstrate its burden of illness. By quantifying the patient health impact and the economic impact on healthcare systems, our objective is to show the potential value of effective treatments for ALS, and the commercial opportunity associated with their development. We focus on seven markets: Australia, Canada, France, Germany, Italy, the UK and the US.

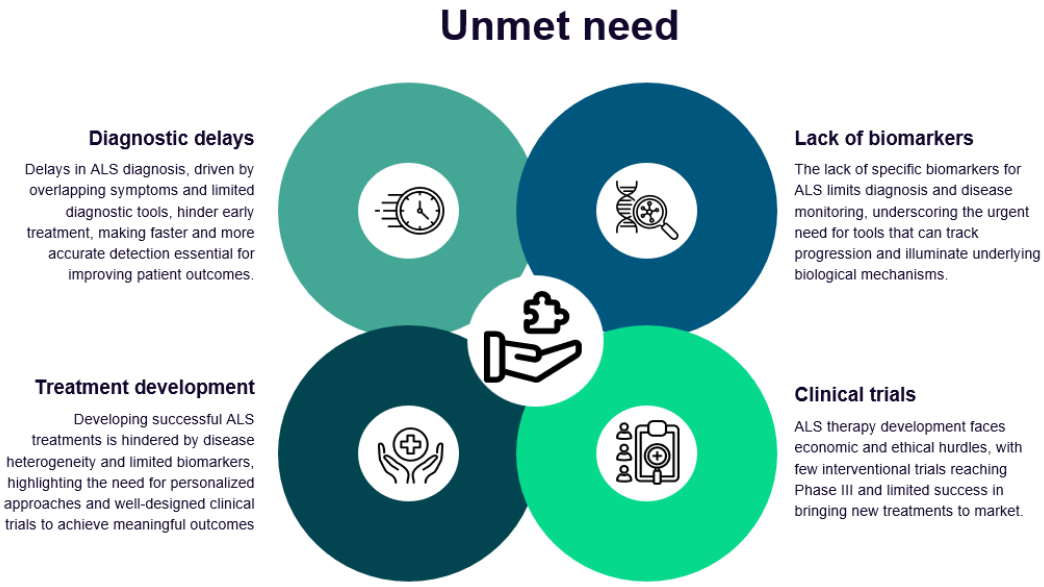
We complement this analysis with a discussion of forthcoming advances that could improve our understanding of ALS and, thus, give rise to new treatments that might radically change patient prognoses and pathways, like the hypothetical treatments included in this report.

Finally, we include as a sub-analysis an estimate of the potential market expansion if an ALS treatment were to be effective for diseases with genetic links to ALS, such as Frontotemporal Dementia (FTD).

3 Motivation

The following section describes the current challenges to ALS care, such as diagnostic delays, difficulties in treatment development, and lack of biomarkers (Figure 1). In addition, we discuss developments in ALS and pharmaceutical research to showcase how these advances create an opportunity for strategic investment in ALS research, with the potential to accelerate successful therapies (Figure 2).

Figure 1. Challenges for ALS management



3.1 Challenges to ALS management

The first key challenge in successfully managing and treating ALS is the diagnostic delay, with the time between symptom onset and diagnosis averaging nine to twelve months (Tzeplaeff et al., 2023). Reasons for the delay are multifaced, but the main problems arise from late referral to neurologists, misdiagnoses, and erroneous investigations. These are generally driven by the overlapping clinical presentation of ALS with other conditions, especially in its early stages, and a lack of accurate diagnostic tools (Gwathmey et al., 2023). Given the rapid progression of ALS, delayed diagnosis often means patients are only identified in the later stages of the disease. Early initiation of treatment, particularly when combined with multidisciplinary care, is widely recognised to improve outcomes (Gwathmey et al., 2023). As such, avoiding delays in diagnosis could lead to timely interventions and in some cases significantly improved outcomes.

Another significant hurdle is the development of successful therapies. Drug development is a lengthy process that hinges on efficient clinical trials, robust progress monitoring tools and reliable biomarkers to guide therapeutic strategies. ALS is a heterogenous disease, with several genes affecting various neural processes. Therefore, focusing on a single mechanism of action without considering the heterogeneity of ALS is unlikely to produce meaningful clinical endpoints in therapeutic trials. A better understanding of disease pathology is needed to allow for patient stratification and use of personalised medicine for more efficacious and targeted trial designs (Bradford and Rodgers, 2024).

Additionally, advancing the use of specific biomarkers for both diagnostic and progress monitoring purposes is needed to accurately assess disease progression and gain deeper insight into the underlying biological mechanisms (Khamaysa and Pradat, 2022). The current lack of specific biomarkers presents a significant limitation for ALS management, reflected in the extensive ongoing efforts in the research for suitable biomarkers (Riva et al., 2024). Continued research in this area could guide therapeutic development by improving diagnostic accuracy, monitoring progression and evaluating treatment efficacy.

Lastly, ALS faces challenges in terms of clinical trials; indeed, only a small fraction of people with ALS participate in clinical trials — usually due to the clinical heterogeneity of ALS conflicting with investigators' desires to enrol homogenous patient populations (van Eijk et al., 2019; Wong et al., 2021). In addition, the lengthy duration of such trials can pose ethical concerns, as patients with a condition marked by rapid progression and limited life expectancy understandably seek faster access to novel therapies (Khamaysa and Pradat, 2022). At the time of this research, 20 clinical trials related to ALS were actively recruiting patients on clinicaltrials.gov, yet only eight were interventional. This limited progress is further reflected in the scarcity of economic evaluation studies published over the last two decades. Moreover, the recent market withdrawal of AMX0035, following negative clinical outcomes, highlights the persistent obstacles in bringing effective ALS treatments from development to clinical practice (Bradford and Rodgers, 2024; Tappenden et al., 2024). These challenges emphasise the urgent need for innovative trial designs, sustainable funding strategies, and collaborative efforts to accelerate the development of safe and effective therapies for ALS.

3.2 Opportunity

In spite of the challenges facing ALS diagnosis, clinical trial design and treatment development, there are several opportunities that put ALS at the forefront of innovation. The convergence of increased funding, large-scale collaborative initiatives, and an ageing population, meaning a growing at-risk population, creates a rich environment for transformative discoveries in ALS and related conditions. These factors position the field as a priority for scientific innovation and strategic investment, with the potential to accelerate the development of diagnostics, therapies, and preventive strategies.

Neurodegenerative disease as a new frontier

There has been an increase in funding for neurodegenerative disease drug discovery in recent years. Notably, in the US a significant milestone was in 2016 when Congress directed National Institute of Health (NIH) to allocate designated funding of $3.5bn towards Alzheimer's research (Giani and Sohaib, 2022). Interest in ALS has been steadily expanding, with NIH funding rising from $49m in 2015 to $234m in 2024 (NIH, 2025). In Europe, the Innovative Medicine Initiative, a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA), has dedicated over €380m to neurodegenerative research since its launch in 2008 (O'Rourke et al., 2022). Beyond government support, the funding ecosystem is multifaced, including private investors, pharmaceutical companies, non-governmental organisations and charities. At market level, the global neuroscience sector was estimated to be worth $612bn in 2022, and is projected to grow to $721bn by 2026 (Nuno Perez, Le Bars and Suarez, 2023). These trends reflect sustained momentum in neurodegenerative research funding and scientific discovery, highlighting the growing recognition of the field as pressing economic challenge and a high-potential area for impactful returns. The increased investment, and resulting expansion of research and data, has led to a stronger foundational understanding of the disease.

Improved understanding of ALS

Although the exact mechanism of neurodegeneration in ALS remains unclear, significant advances in pathophysiology and disease management tools have been made in recent years (Riva et al., 2024). The first gene linked to ALS, SOD1, was identified in 1993 and is thought to be responsible for 20% of familial ALS and 1-2% of non-familial ALS cases. Since then, more than 200 different mutations of the SOD1 gene have been reported, and more than 40 different genes have been identified to contribute to the risk of disease development (Saini and Chawla, 2024; Riva et al., 2024). The link between the SOD1 gene and ALS ultimately informed the development of tofersen (MHRA, 2025), highlighting how an improved understanding of the mechanisms of ALS can be leveraged to discover innovative therapies. The advent of next generation sequencing in the 2010s and whole-genome and exome sequencing technologies more recently has led to the detection of more than 250 new genetic associations each year, creating a new knowledge base that could inform and motivate drug discovery (Riva et al., 2024).

Increased understanding of the underlying pathology of ALS has been significantly advanced by the discovery of TAR DNA-binding protein 43 (TDP-43) aggregates in affected individuals (Jo et al., 2020). Under normal physiological conditions, TDP-43 is a commonly expressed nuclear protein involved in RNA processing, transport, and stability. However, in ALS, pathological TDP-43 is characterised by misfolding, chemical modification and aggregation - features observed in more than 90 % of ALS cases (Jo et al., 2020). Recognising TDP-43 pathology as a central hallmark of ALS has provided crucial insights into disease mechanisms, enabling the identification of novel molecular targets and biomarkers and opened new avenues for therapeutic interventions.

Advances have also been made in the development of diagnostic and prognostic biomarkers as well as neuroimaging techniques, aiming to improve diagnosis and drug development. For one, neurofilament light chain and phosphorylated neurofilament heavy chain have been recently identified having potentially promising diagnostic and prognostic capabilities (Riva et al., 2024). Moreover, recent improvements in assistive technologies have been a cornerstone for supporting patients overcome functional limitations and preserve autonomy (Riva et al., 2024). These ongoing advancements highlight the significant progress being made in understanding and managing ALS, signalling a clear opportunity and urgent need for increased investment.

Use of platform trials

The emergence of Platform Trials, such as the HEALY ALS Platform Trial signifies a step towards streamlined clinical research and drug development. The platform enables testing multiple treatments simultaneously, resulting in faster enrolment, increased patient participation, and reduced costs (Bradford and Rodgers, 2024; Khamaysa and Pradat, 2022). Furthermore, the platform incorporates innovative features such as an early stopping feature for success or futility and a model that estimates treatment effectiveness by integrating both function and survival.

EXPERTS-ALS, a UK-led project providing a platform to rapidly test drugs for their potential to slow progression in ALS is another example. The technology can be used to prioritise the choice of drugs to proceed to Phase 3 clinical trials in less than 6 months, which is a significant reduction in the timeframes for assessing the viability of drug candidates (Experts-ALS, 2025).

Platform trials have been successfully used in oncology, neurology and infectious disease, and are especially useful for a condition with high unmet need and large investigational pipeline (Quintana et al., 2023). A recent paper proposes using adaptive platform trials as a new approach to funding drug development (Cho et al., 2025). Platform trials could represent a transformative approach for ALS research, offering a faster, more efficient pathway to identify effective treatments by streamlining drug development and harnessing innovative trial designs.

Availability of large datasets

Broader interest in neurodegenerative disease is further mirrored by the recent private-public partnership led by philanthropist Bill Gates, pharmaceutical company Johnson & Johnson and several academic institutions. The result — the Global Neurodegeneration Proteomics Consortium (GNPC) — is one of the world's largest harmonised proteomic databases, demonstrating the appeal of international collaboration in the field (Imam et al., 2025). The availability of such large databases could enable researchers to uncover early biomarkers, identify novel therapeutic targets, and accelerate the translation of research findings into clinical interventions. By providing a shared, high-quality resource, the GNPC fosters cross-disciplinary collaboration and reduces duplication of effort, ultimately speeding progress in understanding and treating neurodegenerative diseases (Imam et al., 2025; Peel, 2025). Beyond proteomics, there are additional valuable cohorts for studying the impact of genetics, for example, on the risk or rate of progression (Baxi et al., 2022).

Opportunity to expand into other neurodegenerative disease

Increasing evidence of the shared mechanism between ALS and other neurodegenerative diseases presents a compelling opportunity for cross-disease research and therapeutic development. Recent studies demonstrate that ALS and frontotemporal dementia (FTD) show substantial overlap, noting that both disorders can occur in the same individual and have significant genetic similarities (Abramzon et al., 2020). Moreover, similar proteinopathies observed across ALS, FTD and Alzheimer's Disease, particularly the misfolding and aggregation of TDP-43, highlight the potential for broader therapeutic applications. (Jo et al., 2020). Insights from TDP-43 pathology have positioned the protein as a promising molecular target for cross-disease drug discovery. By focusing on pathways regulating TDP-43 stability, clearance, and function, future therapeutic strategies could

yield benefits that extend beyond ALS, offering a unified approach to tackling multiple neurodegenerative conditions (Jo et al., 2020).

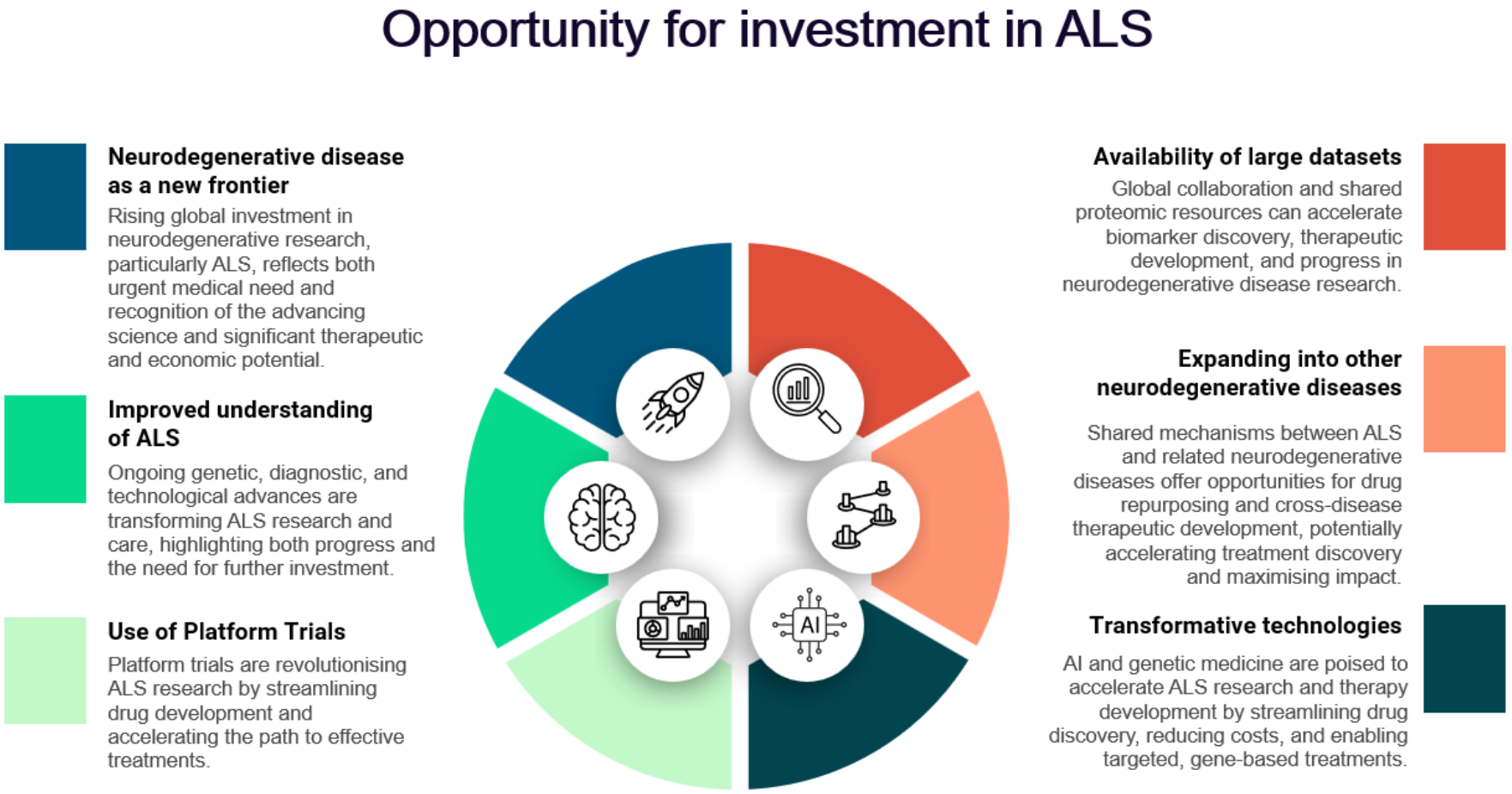
Furthermore, drug repurposing, such as edaravone, originally used to treat stroke, was thought to help ALS by reducing oxidative stress. Despite modest and mixed clinical results, edaravone was later approved for ALS treatment in Japan and the United States, though recent trials of its oral formulation have failed to meet efficacy endpoints (Carroll et al., 2025). These findings emphasise the potential of leveraging shared mechanisms across ALS and related neurodegenerative diseases to drive therapeutic innovation. By identifying common pathways and repurposing drugs, there is an opportunity to accelerate treatment discovery and broaden the impact of therapeutic advances across multiple disorders.

Transformative technologies

Leveraging the capabilities of AI could accelerate research and drive significant innovation in drug discovery. Indeed, McKinsey estimates that generative AI could produce more than $28 billion in annual value across the clinical development and research and early discovery phases of R&D (2024). Key enablers include reduced time and cost, strengthened probability of success, and identification of innovative targets and therapies (Wellcome Trust and BCG, 2023). A recent study estimated that AI-driven drug development can reduce time and cost in the preclinical stage by more than 25%. Approximately 70% of AI-related investment in the last five years have focused on oncology, neurology and COVID-19 (Wellcome Trust and BCG, 2023). Despite rapid advances in disease understanding, drug development continues to be slow and costly. AI offers a powerful means to bridge this gap by using large datasets to streamline development, improve efficiency and lower costs (McKinsey & Company, 2024). Furthermore, AI could play a crucial role in advancing personalised treatments, an increasingly important factor in improving patient outcomes (McKinsey & Company, 2024). These factors position AI as a transformative opportunity to accelerate therapeutic breakthroughs in ALS, where innovation is urgently needed.

The emergence of genetic medicine is opening new therapeutic pathways in ALS, moving beyond traditional small-molecule and biologic drugs to target the disease at its genetic roots. In particular, gene-silencing therapies have shown growing promise, exemplified by the encouraging results of tofersen (Suzuki et al., 2025). Tofersen is an RNA-based therapy that reduces production of the SOD1 protein in individuals with SOD1-mutation ALS. It works by infiltrating nerve cells and blocking the faulty genetic instructions that produce the harmful protein, thereby protecting the neurones and lowering levels of a key marker of nerve damage (Saini and Chawla, 2024). Another emerging therapy, jacifusen, targets mutations in the FUS gene, which are associated with particularly aggressive forms of ALS. Early studies suggest that jacifusen can effectively silence FUS gene expression and reduce the resulting pathology caused (Suzuki et al., 2025). Although still in the early stages, these developments provide cautious optimism that gene-based technologies could fundamentally change the trajectory of ALS treatment.

Figure 2 Opportunity for investment in ALS



4 Methods

To inform our research, we conducted a targeted literature review to identify relevant studies exploring the socioeconomic burden of ALS, current unmet need and future opportunities for innovation. After identifying an initial set of sources, we applied the snowballing technique, reviewing their reference lists and citations to uncover additional relevant sources.

We employed three different approaches to estimate the commercial value of an ALS treatment — all of which are described in Section 4.2. We conducted two semi-structured interviews with field experts to validate our methods and ensure the relevance of our modelling to a hypothetical ALS treatment.

4.1 Burden of ALS

We used the literature identified in our targeted literature review to collect data on the burden of ALS across seven markets: Australia, Canada, France, Germany, Italy, the UK and the US. Specifically, we gathered data on the health burden of disease, measured in quality-adjusted life years (QALY)[1] lost due to ALS and the health system cost, as measured by the resource use associated with medical management of ALS. We used the most recent studies to identify country-specific healthcare costs. Where data was not directly available, we used estimates of healthcare resource utilisation from a pan-European database of ALS patients (Tappenden et al., 2024), alongside the relevant healthcare unit costs in the respective countries. To provide an overview the total burden of ALS, we also scanned the relevant literature in each country to capture indirect costs, including carer burden and productivity losses, and non-medical costs, such as home renovations and transportation costs, for instance.

4.2 Commercial value of a hypothetical ALS treatment

There are several ways in which one can conceive the commercial potential of a treatment for ALS — that is, what could be obtained as revenue by an innovator in ALS therapeutics. We capture three approaches in this report: one capturing the (monetised) socioeconomic burden of ALS across countries; one method using the price of a recently approved innovative ALS treatment; and one approximating the value of a hypothetical treatment for ALS given various assumptions around treatment efficacy, and how it would be evaluated using conventional health technology assessment (HTA) methods that are used to assess the value of new medicines. For all three approaches, we present the year-one value that could be captured by a hypothetical treatment, and we also present the present value[2] of such a treatment after 10 years.

For each approach, we present the values of hypothetical treatments as if they were available in the present day. Though not realistic, this approach allows us to illustrate

[1] The quality-adjusted life year (QALY) is a commonly used measure in health economic assessment which combines length of life with quality of life into a single metric. A year lived in less than perfect health is given a weight (utility) between 0 (equivalent to death) and 1 (perfect health). For example, one QALY could be one year lived in perfect health, or two years with a health utility of 0.5. We can use this metric to summarise disease burden (i.e. how many QALYs are lost due to a disease's impact on quality and length of life), as well as to consider the benefits of a treatment that improves quality or length of life compared with current practice.

[2] To calculate present value, we apply a discount rate of 3.5% to future value.

future market potential, assuming the ALS population today is similar to what it would be when such a treatment could be brought to market. In addition, we assume full market penetration in year one. This is a simplifying assumption that also could be interpreted as the potential yearly value if such penetrance was realised. When estimating the cumulative values of a hypothetical treatment after 10 years, we employ additional simplifying assumptions — pivotally, that all patients with ALS receive care through the healthcare system, that such a treatment does not substantially alter the size of the ALS population (a conservative assumption), and that pricing pressures and competing medicines do not affect future value.

The outputs of these estimations represent different ways that one can capture and describe the potential value of a successful ALS treatment, i.e. what it would be worth given various assumptions we can make around the diagnostic/treatment context, treatment success, and the perspective of the payer/decision-maker. This top-line commercial value can then be considered against the likely investment in R&D required to bring such a treatment to market, along with the costs associated with its production, commercialisation and delivery within the healthcare system.

Approach 1: Using the total country-specific burden

First, our calculation of the (monetised) socio-economic burden of ALS in each country can be interpreted as an estimation of the 'upper bound' of the societal value of a potential ALS treatment.

That is, by quantifying the size of ALS' impact on patients and healthcare resource utilisation, we are generating an estimate of the societal value of eradicating ALS. Therefore, this approach assumes a fundamental shift in our understanding of ALS, as we are essentially representing the value of a pathway that includes effective predictive screening tools and a curative therapy that reverses disease progression.

Taking this approach serves to demonstrate the total burden that ALS places on society, and, therefore, the benefits that would be associated with eradicating this burden. It is thus reflective of the high unmet need in this space.

In order to reflect a more realistic view of what an actual treatment might achieve in the medium-term, Approaches 2 and 3 focus on treatment prices realised (Approach 2) or hypothesised (Approach 3, which sets out various scenarios for treatment efficacy and how existing HTA frameworks would value them).

Approach 2: Using a current treatment price

Our second approach estimates the commercial value of a potential ALS treatment using the existing price of tofersen, a recently approved innovative ALS therapy. Tofersen represents an important step forward in treatment, and is authorised for patients with ALS caused by mutations in the SOD1 gene - about 2% of all ALS patients (Biogen, 2023; MHRA, 2025; European Medicines Agency, 2024).

This approach uses the price of tofersen as a proxy for the price that could be achieved by a new hypothetical ALS treatment (or treatments) that could serve a wider population base. It is worth noting that tofersen is a type of gene-targeted therapy called an antisense oligonucleotide (ASO). Such precision therapies are expensive to develop and deliver and generally command relatively high prices. Therefore, a new treatment that falls into another drug category could command a different price level. We considered tofersen to be a reasonable benchmark, as a recently approved innovative therapy for a genetic form of ALS, reflecting current pricing expectations, delivery complexity, and payer precedent in this disease area. However, it should be noted that the ability/willingness to pay for tofersen is likely to be impacted by the fact that it is to be used for an ultra-rare

indication (a small subset of the full ALS population). This being the case, payers (such as NICE in the UK) are willing to pay higher prices. Another way to consider the commercial value estimate generated by this approach is for it to represent the cumulative value of several specialist treatments which, like tofersen, are developed for a subset of the ALS population.

To determine the total commercial value of such a treatment, we scale this price by the prevalence of ALS in each country, thereby assuming that such a treatment(s) would be available and effective for all people with ALS across all disease stages. This result provides us with the initial commercial value of a treatment in its first year of use. We also predict the cumulative value of a treatment after five and ten years. Assuming the mortality and incidence rates have the same effect on prevalent cases and that all patients continue to use the treatment throughout their lifetime, we project the treatment's total value by scaling its estimated price according to prevalence over five and ten years and convert to a present value.

As the price of tofersen in most of the markets under study has not yet been negotiated or published, we base our estimates on the reported US list price, and scale this to discounts that are typically achieved across the markets considered. We determined the list price of tofersen in the US using pharmaceutical pricing data from the Veterans Affairs National Acquisition Center programs (Office of Procurement, Acquisition and Logistics, 2025), and we estimated the net price using Beinfeld et al.'s (2025) estimates of the proportional differences between list and net prices for orphan drugs in the US. To determine country-specific estimates of the discounted price of tofersen, we relied on a Mulcahy et al. (2021) paper, which describes the differences in list prices between US branded medicines and the same medicines in other OECD countries; we assumed that the relationships between net prices were proportionally equal to the relationships between countries' list prices.

Approach 3: Using conventional HTA methods

Finally, our third approach uses conventional HTA methods to approximate the value of hypothetical ALS treatments. To do so, we used an adapted Markov model originally developed by Tappenden et al. (2024) — courtesy of the authors — wherein they conducted an economic evaluation of hypothetical treatments for ALS in the UK. Model details and assumptions can be found in the Appendix.

As the Tappenden et al. (2024) paper focuses on the value of hypothetical treatments in the UK, we adapted it to include the other countries in this analysis. Specifically, we used the stage-specific disease management costs that we found while capturing the burden of ALS in each country to provide estimates of how the hypothetical treatments used in this analysis would alter disease-management costs on a country-by-country basis. Otherwise, we assumed the model's other parameters, such as its transition probabilities and utility values, would apply for patients in each of the countries we included in this analysis, which we viewed as reasonable given that the model is informed by pan-European ALS registries.

For the purpose of this report, we estimated the value of three hypothetical treatment profiles with the aim of representing a range of possibilities for potential treatment outcomes. Consistent with Tappenden et al. (2024), we modelled the relative effects of these treatments through two mechanisms: slowing the rate of disease progression by applying a relative risk reduction (RRR), and/or including beneficial health-related quality of life (HRQoL) effects in each stage beyond the equivalent utility values for patients receiving current care, by applying a utility gain for patients receiving treatment.

Table 1 describes the hypothetical treatments we assessed and the parameters we inputted for each.

Table 1. Hypothetical treatment parameters

TREATMENT	RELATIVE RISK REDUCTION (RRR)	UTILITY GAIN	REASONING
MEDICINE 1	0.39	0.14	Parameters are informed by clinical trial results for tofersen (Joint Nordic HTA-Bodies, 2025), which suggested a hazard ratio of 0.61 and an additional utility gain of 0.14.
MEDICINE 2	0.5	0.14	The RRR parameter was used by Tappenden et al. (2024) as an input for one of the hypothetical treatments they evaluated in their analysis. This input was validated by clinical experts. We assume the same utility gain as tofersen, as described by the Joint Nordic HTA-Bodies (2025).
MEDICINE 3	1	0.14	This medicine represents the upper bound of what a potential ALS treatment could achieve: completely stopping (but not reversing) disease progression, meaning patients stay in the disease stage they are in when they begin treatment, and assuming life expectancy is returned to the population average. We assume the same utility gain as the previous medicines.

To determine the full value of these treatments, we aggregated the change in healthcare costs and the change in QALYs resulting from medicine use. To sum these values, we assigned a monetary figure to QALY gains, based on each country's implied or explicit willingness to pay for a QALY (e.g. the cost-effectiveness threshold used in drug reimbursement decisions). These values can be found in the Appendix of this report.

By combining and aggregating the information collected, including the estimated treatment value and market size data (using countries' incidence of ALS, as we assume patients enter the model at disease diagnosis), we estimated the commercial value of a successful treatment (total addressable market) across the seven countries.

4.3 Estimating potential spillover effects

As there are substantial links between ALS and FTD, we also consider the 'spillover' effects an ALS treatment could yield if it were also able to target this neurodegenerative disease. This dual indication could significantly expand the commercial opportunity for such a treatment.

To illustrate this potential, we modify Approach 2 by incorporating a combined prevalence estimate that includes both ALS patients and the relevant subset of FTD patients. Using data from the Global Burden of Disease Study and established estimates of FTD's proportion within total dementia cases (Global Burden of Disease Collaborative Network, 2024; Hogan et al., 2016; 2024 Alzheimer's disease facts and figures, 2024), we focus our analysis on the US market to demonstrate how this expanded patient population could increase a treatment's yearly commercial value.

5 Results

5.1 Burden of illness in ALS

People living with ALS require complex, multi-disciplinary care, which varies by disease stage. ALS progression can be measured by several staging methods, which vary by geographical region or physician preference (Stenson et al., 2023). In this study, we use the King's staging system, which consists of five stages that reflect the central nervous system regions involved in the disease (Balendra et al., 2019). King's stages 1-3 describe the number of clinical regions involved, stage 4 indicates the involvement of nutritional or respiratory failure, and stage 5 represents death (Tappenden et al., 2024). As staging reflects changes in diseases severity, later King's stages are generally associated with increased healthcare resource utilisation and a lower health-related quality of life.

Beyond medical care, people living with ALS rely heavily on informal caregivers such as family and friends. Due to the progressive worsening of motor function, those living with ALS may need support with a variety of day-to-day activities, including eating, mobility and medical care (de Wit et al., 2018). Caring for someone living with ALS can become all-consuming: studies report that carers face physical and emotional distress as well as financial burden as a result of disruptions in professional careers (Schischlevskij et al., 2021; de Wit et al., 2018). Summary results are presented in this section; full tables including references can be found in the Appendix.

Epidemiology and prognosis

Epidemiology and prognosis data (Table 2) were collected from the literature and validated by an expert in the field during an online interview.

Table 2. Country-specific epidemiology and prognosis for ALS

	UK	USA	CAN	AUS	FRA	ITA	GER	EUROPE	WORLD-WIDE
INCIDENCE (Per 100,000)	1.61	1.44	2.00	2.73	3.5	2.12	3.10	2.13	0.78
PREVALENCE (Per 100,000)	7.35	9.67	6.98	8.70	11.0	8.87	8.00	6.22	4.50
PREVALENCE (per country population)	5,000	32,893	2,800	2,094	7,331	5,233	6,662	46,000	710,000
LIFE EXPECTANCY (Years)	1.5-3 After diagnosis	3 From onset	3 From onset	2.5 After diagnosis	2.3 From onset	3-5 From onset	3.5 From onset		
MEDIAN AGE OF DIAGNOSIS	63	64.8	61.8	64	68.4	72	61.4		

Incidence, representing new cases of ALS per year, typically ranges between 1-3 cases per 100,000 in most countries and at the European level. Prevalence, representing existing cases of ALS, is less consistent across countries, averaging approximately 8 cases per 100,000 people, and slightly lower at 6.22 cases per 100,000 people in Europe. On a global level, incidence and prevalence are lower, 0.78 and 4.50 per 100,000 respectively, likely due to variations in diagnosis, estimated survival and measuring methods in different regions (Wolfson et al., 2023).

Prognostic life expectancy estimates are generally consistent across regions, aligning with figures reported for other regions in the literature, ranging from 1 to 5 years. For the UK and Australia, estimates are based on time from diagnosis, which could explain why they are slightly lower than those from other countries, where estimates are based on symptom onset. Notably, diagnosis can take up to two years to complete (Richards, Morren and Pioro, 2020). The median age at diagnosis was similar between countries and compared with other regions not included in this analysis. The average age of onset was 65 years. Notably, Italy and France had a slightly higher median age of diagnosis, at 72 and 68.4 respectively.

Disease burden

For ALS, the burden of disease is particularly stark when expressed in terms of QALYs lost due to disease. On average, in the UK, an individual diagnosed with ALS may experience a QALY shortfall of around 12.6 QALYs compared to the age-matched general population, reflecting both shortened survival and a lower quality of life. When valued using the Treasury's Green Book willingness-to-pay-threshold value of a QALY - which is what the Government and Department for Health and Social Care (DHSC) use to value the costs and benefits of policies - of £70,000 per QALY (2020/21 prices), this equates to a quantified health loss of approximately £879,193 per patient. At the population level, with around 5,000 people currently living with ALS in the UK, the aggregate shortfall rises to an estimated 62,800 QALYs, translating to nearly £4.4 billion in lost health value. We have used this approach to estimate the QALYs lost and costs in the other countries of interest (Table 4).

Framing ALS burden in monetary terms highlights the urgency of investment in research, innovation, and therapies that could alleviate this substantial loss, ensuring resources are directed toward conditions where the health and economic stakes are most profound.

Table 3. QALY shortfalls due to ALS

	UK	USA	CAN	AUS	FRA	ITA	GER
QALY SHORTFALL per person	12.56	9.65	15.02	15.34	12.63	9.27	15.55
QALY SHORTFALL ALS population	62,800	317,335	42,049	32,131	92,570	48,522	103,588
MONETISED BURDEN per person	£ 879,193	$ 964,748	CAD 750,874	AUD 767,220	€ 351,630	€ 306,003	€ 528,637
MONETISED BURDEN per person (USD)	1.2 million	964,748	542,383	508,260	411,938	358,485	619,303
MONETISED BURDEN ALS population	£ 4.4 billion	$ 31.7 billion	CAD 2.1 billion	AUD 1.6 billion	€ 2.6 billion	€ 1.6 billion	€ 3.5 billion
MONETISED BURDEN ALS population (USD)	5.9 billion	31.7 billion	1.5 billion	1.1 billion	3.0 billion	1.9 billion	4.1 billion

Healthcare resource utilisation

Healthcare resource utilisation represents the use of healthcare staff time, facilities and consumables (including medicines). ALS is characterised by rapid functional decline, requiring a plethora of medical services including multidisciplinary care, assistive support and palliative care. Capturing these elements is essential to understand and quantify the economic burden imposed by the condition and therefore demonstrate the potential value of a successful therapy that could reduce these costs.

The healthcare costs per person per year living with ALS (Table 4) are estimated to range from CAD 32,064 ($23,039) in Canada to $76,823 in the US. When extrapolated to national level, these costs represent a considerable economic impact and substantial pressure on the healthcare system. The costs per ALS population per year span from $64.6 million in Canada to $2.5 billion in the US. It should be noted that the reported figures are based on average weighted costs per disease stage, which inevitably mask the wide variation in real-world spending. In practice, the range of costs is likely to be considerably larger, as individual patients differ in the disease progression and care needs resulting in heterogeneity in timing and extent of supportive interventions.

Table 4. Healthcare resource utilisation estimates across countries

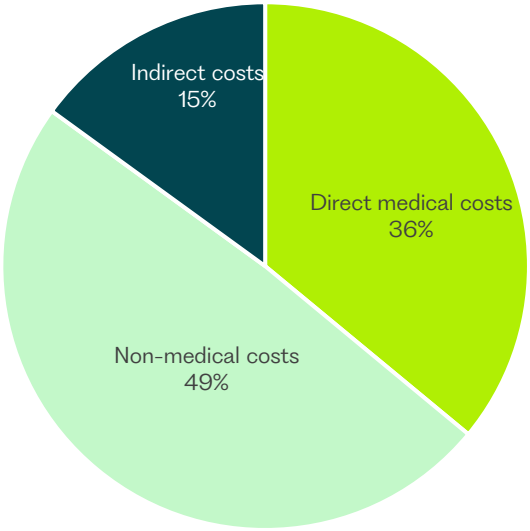
	UK	USA	CAN	AUS	FRA	ITA	GER
HEALTHCARE RESOURCE UTILISATION (PPPY)	£ 26,576	$ 76,823	CAD 32,064	AUD 103,684	€ 20,165	€ 33,193	€ 32,611
HEALTHCARE RESOURCE UTILISATION (USD PPPY)	35,635	76,823	23,039	66,536	23,384	38,492	37,817
HEALTHCARE RESOURCE UTILISATION (USD PWPY)	178. 2 million	2.5 billion	64.6 million	139.3 million	171.4 million	201.4 million	251.9 million

PPPY: per person per year; PWPY: (ALS) population-wide per year

Broader societal costs

Beyond the immediate healthcare system expenditure, ALS imposes a wide range of additional costs that stress the need to consider its broader societal value when evaluating potential treatments. Evidence from a recent German study illustrates this imbalance (Figure 3): direct medical costs accounted for only 36% of the total cost of illness, while non-medical costs represented 49% and indirect costs an additional 15% (Schönfelder et al., 2020). The largest share of non-medical costs was attributed to informal caregiving, supplemented by expenses such as travel, legal support, and home modifications to accommodate progressive loss of function. Indirect costs capture the significant productivity losses experienced both by people living with ALS and by family members who reduce or leave employment to provide informal care (Schönfelder et al., 2020).

Figure 3 Distribution of costs in ALS



Data on the true cost of a disease beyond direct medical costs are challenging to capture in a systematic way, and this information is lacking across the countries under study. However, we used the findings above to speculatively consider the total broader cost burden of ALS, by scaling the known direct medical costs by country (presented in the previous section) assuming ratios of direct medical to non-medical and indirect costs equivalent to the German study described above. We demonstrate the findings — which should be considered indicative only — in Table 5.

Table 5. Broader societal cost estimates across countries (indicative only)

	UK	USA	CAN	AUS	FRA	ITA	GER
HEALTHCARE RESOURCE UTILISATION (USD PWPY)	178. 2 million	2.5 billion	64.6 million	139.3 million	171.4 million	201.4 million	251.9 million
ESTIMATED NON-MEDICAL COST (USD PWPY)	242.5 million	3.4 billion	87.8 million	189.6 million	233.3 million	274.2 million	342.9 million
ESTIMATED INDIRECT COST (USD PWPY)	74.2 million	1.1 billion	26.9 million	58.1 million	71.4 million	83.9 million	105.0 million
ESTIMATED TOTAL COST (USD PWPY)	494.9 million	7.0 billion	179.2 million	387.0 million	476.2 million	559.6 million	700.0 million

PPPY: per person per year; PWPY: (ALS) population-wide per year

Another study exploring the economic burden of ALS on patients and their families in Canada, a government-funded healthcare system, estimated that out-of-pocket expenses account for 61% of all direct payments. The largest contributors were home renovations, mobility aids, and privately funded medical services such as physiotherapy (Gladman, Dharamshi and Zinman, 2014). The same study suggests that ALS patients have significantly higher annual out-of-pocket costs compared to other neurological conditions (Gladman, Dharamshi and Zinman, 2014). Applying this range to the direct medical costs estimated here suggests that the overall societal cost could be two to three times higher than the figures reported in Table 5. While these extrapolations are illustrative and depend on regional differences in healthcare systems, they provide a benchmark for understanding the full scale of ALS-related costs and highlight the need for more comprehensive burden-of-illness studies.

According to these studies, the true economic and societal burden of ALS is borne largely outside the formal healthcare system. By overlooking these broader societal costs, assessments risk underestimating the full impact of ALS on patients, families, and society. Incorporating them into value frameworks would ensure that potential treatments are evaluated in a way that reflects not only their clinical benefits but also their capacity to reduce caregiver strain, preserve productivity, and mitigate profound non-medical costs.

5.2 Commercial value of an ALS treatment

Approach 1: Using the total country-specific burden of ALS

Our results capturing the total burden of ALS in each country also lend insight into what the upper limit of a treatment's commercial value could be. Indeed, as treatment value is quantified using the costs avoided and monetised health benefits owed to a new therapy, Section 5.1 demonstrates the value of a treatment capable of eradicating and/or preventing ALS altogether.

Table 6 summarises the population-wide healthcare costs owed to ALS in each country alongside our estimates of the monetary value of the QALY shortfalls due to ALS across each market, thus providing the total monetised burden of ALS.

Table 6. Total monetised burden of ALS per year (millions of USD) [Approach 1]

	UK	USA	CAN	AUS	FRA	ITA	GER
POPULATION-WIDE HEALTHCARE COSTS	178.2	2,500	64.6	139.3	171.4	201.4	251.9
MONETISED HEALTH LOSSES DUE TO ALS POPULATION	5,900	31,700	1,500	1,100	3,000	1,900	4,100
TOTAL MONETISED BURDEN	6,078	34,200	1,565	1,239	3,171	2,101	4,352

Evidently, this approach suggests that a treatment with the capacity to completely eradicate ALS would be worth several billions in each of the relevant markets in this analysis, even ignoring the societal costs outside the healthcare service which, as shown in the previous section, are significant and would nearly triple the "cost" element of the monetised burden. However, such value realization would require fundamental changes to the current ALS landscape: effective predictive screening to identify at-risk patients before symptom onset, and a curative therapy that both halts and reverses progression.

Spinal muscular atrophy (SMA), another MND, provides a successful precedent. Researchers identified SMA's genetic cause, enabling infant screening programs, and developed disease-modifying therapies that stop or significantly slow progression (Nishio et al., 2023). This comprehensive approach has helped significantly reduce SMA's burden — the same outcome required to achieve the commercial valuations projected in this approach.

Approach 2: Using a current treatment price

We used the price of tofersen as a proxy for the price of a hypothetical ALS treatment. Whereas tofersen is authorised for approximately 2% of the ALS population, we use ALS population size estimates to extrapolate the market size and value for an equivalent hypothetical drug (sold at the same price) but indicated for all ALS patients.

From pharmaceutical pricing data from the Veterans Affairs National Acquisition Center programs, we found that tofersen has a yearly price of $204,077 in year one of use, and $189,500 in subsequent years (Office of Procurement, Acquisition and Logistics, 2025).[3] Assuming that US payers achieve a 23% discount, in line with the median discounts achieved for orphan drugs in the US, we estimate the yearly price of tofersen to the US healthcare system to be $145,915.

A Mulcahy et al. (2021) report provides the relationship between the prices of branded medicines in the United States and other OECD countries. We used these values, alongside the post-year-one price of tofersen in the United States, to estimate the price of tofersen (and by implication our hypothetical ALS treatment, as we assume the same price can be achieved) in the other countries in this analysis. Details of our price estimations and assumptions can be found in the Appendix.

Table 7 provides the results of this approach, showing the total aggregate commercial value of a hypothetical treatment in years 1, 5 and 10 after market availability. Notably, the year-1 values reflect the potential of a treatment that were to be provided to all current people living with ALS, and the values in years 5 and 10 reflect the expanded value if such a treatment were to continue being given to the prevalent populations in all subsequent years.

Approach 2 highlights that, across all the markets in this report, the commercial value of a hypothetical treatment that could be used by all ALS patients could be worth hundreds of millions per year in each of the relevant countries.

[3] Note: we estimate the price of tofersen based on the citation provided, which is similar to that noted in other news outlets (e.g. FDA Approves Biogen and Ionis' Qalsody as Fourth-Ever ALS Therapy - BioSpace). However, we cannot verify this price, and we note that other sources provide very different estimates. For example, the price used to support the Canadian Drug Agency's appraisal of tofersen was 50% time higher, at CAD 425,560 for the first year.

Table 7. Estimated commercial value of treatment at years 1, 5 and 10 [Approach 2]

	ESTIMATED COMMERCIAL VALUE OF TREATMENT IN YEAR 1 (IN MILLIONS, USD)	ESTIMATED TOTAL CUMULATIVE COMMERCIAL VALUE OF TREATMENT AFTER YEAR 5 (IN MILLIONS, USD)	ESTIMATED TOTAL CUMULATIVE COMMERCIAL VALUE OF TREATMENT AFTER YEAR 10 (IN MILLIONS, USD)
UK ($USD)	209.0	943.8	1,738.5
USA ($USD)	4,799.6	21,670.4	39,916.2
CAN ($USD)	139.0	627.4	1,155.7
AUS ($USD)	143.4	647.7	1,193.0
FRA ($USD)	250.9	1,132.6	2,086.3
ITA ($USD)	242.4	1,094.5	2,016.0
GER ($USD)	347.2	1,567.5	2,887.3

These estimates rely on some key assumptions. First, that our estimations of the price achieved for tofersen are correct. While we have tried to account for typical levels of discount that drive a wedge between list-to-net price, and typical differences between US and international prices, these assumptions are highly speculative. Tofersen itself is still being considered for reimbursement in many countries, and we cannot observe what the net price achieved will be in reality, and/or whether tofersen will be considered cost-effective (i.e. achieve positive reimbursement decisions) at this price in all countries. Further, by considering that the new hypothetical treatment could attract a similar price as tofersen, we imply that the hypothetical treatment would have equal treatment efficacy. A treatment with greater therapeutic benefits than tofersen could, in theory, attract higher prices and result in greater commercial value across these markets.

It is also important to note that tofersen's achievable price is likely to be influenced by the fact it is a highly specialised gene-targeting therapy for an ultra-rare condition (subset of ALS). If a new treatment falls into another drug category or is indicated for the full ALS population (thus not qualifying for certain concessions reserved for ultra-rare conditions), it may not achieve the same price. Another way to consider the commercial value estimate generated by this approach is for it to represent the cumulative value of several specialist treatments which, like tofersen, are developed for a subset of the ALS population.

Approach 3: Using conventional HTA methods

Table 8 presents the country-specific values of the various treatment profiles we analysed in this report using conventional HTA methods.

Table 8. Country-specific treatment values per patient (all costs presented in USD) [Approach 3]

HYPOTHETICAL TREATMENT PROFILE		UK	USA	CAN	AUS	FRA	ITA	GER
MEDICINE 1 [RRR = 0.39; UTILITY GAIN = 0.14] $USD	Cost Increase	55,217	86,215	29,861	40,703	25,196	45,882	50,005
	QALY Increase	45,861	119,608	43,673	39,465	36,051	42,727	44,017
	Total Value	**-9,356**	**33,393**	**13,812**	**-1,239**	**10,855**	**-3,155**	**-5,988**
MEDICINE 2 [RRR = 0.50; UTILITY GAIN = 0.14] $USD	Cost Increase	83,120	133,099	47,957	61,757	40,803	73,773	77,041
	QALY Increase	62,547	163,127	59,563	53,825	49,168	58,274	60,032
	Total Value	**-20,573**	**30,028**	**11,607**	**-7,932**	**8,365**	**-15,499**	**-17,008**
MEDICINE 3 [RRR = 1.00; UTILITY GAIN = 0.14] $USD	Cost Increase	169,008	273,360	70,353	117,663	82,778	101,581	146,344
	QALY Increase	350,726	914,710	333,992	301,813	275,703	326,761	336,622
	Total Value	**181,718**	**641,350**	**263,639**	**184,145**	**192,925**	**225,180**	**190,278**

Refer to the Appendix for the values that were used to monetise QALY gains

As described in the methods section, for each drug profile we assume a positive utility gain for patients on treatment of 0.14, with each drug having a different impact on relative risk reduction (RRR)[4], from 0.39 for medicine 1 (the estimated RRR of tofersen), to 0.5 (hypothetical) for medicine 2, and 1 for medicine 3 (the upper-bound of treatment efficacy, assuming medicine halts progression entirely but does not reverse it).

As evidenced by the results above, the treatment yielding the highest value is Drug 3, which is characterised by a RRR of 1 and an additional utility gain of 0.14. This treatment represents a disease-modifying treatment that completely halts progression, maintaining patients at their initial King's stage throughout their treatment period, while simultaneously improving patient's HRQoL.

The results also indicate that the primary source of value from ALS treatments comes from the QALY gains owed to a medicine prolonging a patient's life or providing additional utility in each stage. This finding reflects two critical factors related to the model structure and ALS as a disease. Specifically, the current framework assumes that patients experiencing treatment benefits, as expressed in our model by a RRR, continue to

[4] Relative risk reduction (RRR) refers to how the risk of progression to the next stage of disease is reduced for patients on treatment, compared with baseline. In the disease model, this has the effect of slowing progression of patients along the (increasingly severe) disease stages, each being associated with worse health and higher costs.

consume equivalent healthcare resources per stage, thereby extending resource utilisation duration rather than reducing intensity. And more, ALS' progressive nature means that slowing or stopping decline generates substantial value through prolonged time in higher-functioning states, but also leads to higher healthcare resource utilisation when compared with the existing situation where progression is rapid and life expectancy is short.

Though RRR increases from Medicine 1 to Medicine 3, the total value of each medicine does not increase in the same way. This ultimately reflects the fact that from Medicine 1 to Medicine 2, patients spend an increased amount of time in more expensive disease stages, resulting in greater increases in healthcare resource utilisation compared to the increased QALY gains that are yielded as a result of the RRR. Medicine 3, however, completely stops disease progression, meaning that patients spend more time in the least-expensive disease stage (i.e. King's stage 1); as a result, the balance between QALY gains and healthcare resource utilisation is more favourable, resulting in greater overall treatment value of Medicine 3.

To estimate the commercial value of these treatments, we scaled individual patient values by country-specific incident rates. Table 9 presents the aggregate commercial value for each treatment scenario across the different national markets, representing the total returns achievable if treatments were universally accessible to the entire ALS population.

Table 9. Yearly commercial values of treatments (in millions of USD)

	UK	USA	CAN	AUS	FRA	ITA	GER
MEDICINE 1 ($USD)	-10.4	163.5	11.4	-0.9	26.0	-3.9	-15.5
MEDICINE 2 ($USD)	-22.9	147.1	9.6	-5.9	20.1	-19.4	-44.0
MEDICINE 3 ($USD)	202.5	3,141.1	217.7	136.8	462.7	281.6	492.6

These results, put into context with the other findings highlighted in our report, serve to demonstrate the tremendous challenges associated with existing HTA methods, when used to evaluate innovative therapies in rare and under-served populations like ALS. While each of the three medicine profiles elaborated above improve health and extend life, some of the scenarios in some of the HTA contexts demonstrate *negative* treatment values, even before the cost of the medicine is accounted for. That is to say, the monetary value ascribed to the gains in health are not sufficient to compensate for the higher (non-drug related) medical costs associated with providing care to ALS patients. In other words, the intervention would not be cost-effective even at price zero. This counter-intuitive result highlights methodological challenges that are well known (Mladsi et al., 2023), and the reason that most HTA bodies have special provisions in place when it comes to the evaluation of treatments for severe and life-limiting diseases, as well as for drugs serving rare diseases. While we have not attempted to incorporate those into our analysis, these results serve to highlight their importance, as well as the need to keep under review how well those adjustments reflect society's true valuation of such treatment advances.

5.3 Estimating spillover effects

A treatment for ALS might also yield benefits for patients with other neurodegenerative diseases. In particular, there is compelling clinical overlap between FTD and ALS, with up to 50% of ALS patients developing FTD-associated cognitive impairment, while approximately 30% of FTD patients experience ALS-related motor dysfunction (Abramzon et al., 2020). This clinical convergence suggests that effective ALS therapies may demonstrate therapeutic value across the ALS-FTD spectrum, thereby dramatically expanding the potential patient population.

The financial implications of this overlap are substantial. Using Approach 2, capturing 30% of the FTD population would expand the addressable market by 2.5-fold. With equivalent pricing to tofersen, this potential to treat beyond ALS would increase the projected year-one commercial value of a hypothetical treatment from $4.8 billion to $12.4 billion for the US market alone. Similar market expansion potential exists across international markets, highlighting how treatments developed for ALS could generate considerably greater commercial value through their applicability to related conditions.

This example is illustrative and considers only one potential disease area that might benefit from a treatment discovery for ALS. As researchers' understanding of ALS evolves, links between other neurodegenerative diseases are likely to emerge. For instance, pathological TDP-43 characterises 97% of ALS cases and 50% of FTD cases; however, it has also been found in up to 57% of Alzheimer's disease (AD) cases. Therapies with mechanisms that address this underlying shared pathology could, thus, have huge market potential beyond what is suggested in this report.

5.4 Summary of results

We present a summary of our findings across all three approaches in Table 10. In this, we include both the year-one commercial value estimates using each approach, along with the cumulative value such a treatment would yield after 10 years. To estimate the present value of the cumulative total over 10 years, we applied a discount rate of 3.5%.[5] Ultimately, these 10-year values are reflective of the total value that a treatment could be worth over time, as they incorporate the current population that would benefit from such a therapy, as well as future patients.

We also aggregate the commercial values across all seven markets, noting that the most optimistic of our approaches yields a cumulative value of $142.6 billion after 10 years, while the other approaches point to a cumulative value around $40-50 billion. Considering that the countries under study only contribute approximately 17% to the global ALS population, these value estimates could substantially increase if we were to capture a larger proportion of people with ALS.

[5] Note, that while a 3.5% discount rate is that typically applied to future costs in health economic assessments, a more appropriate rate for investors considering commercial returns could be the cost of capital, which differs by company, its capital structure, and market conditions.

Table 10. Summary of year 1 and cumulative 10-year commercial values for each approach (millions of USD)

	APPROACH 1 ***Monetised total ALS health & healthcare burden***		**APPROACH 2** ***Proxy pricing via tofersen***		**APPROACH 3 (MEDICINE 3)** ***HTA Modelling***	
	Year 1 Value	10-Year Cumulative Total	Year 1 Value	10-Year Cumulative Total	Year 1 Value	10-Year Cumulative Total
UK ($USD)	6,078	17,346	209	1,739	203	1,684
USA ($USD)	34,200	76,550	4,800	39,916	3,141	26,123
CAN ($USD)	1,565	5,402	139	1,156	218	1,811
AUS ($USD)	1,239	4,895	143	1,193	137	1,137
FRA ($USD)	3,171	13,713	251	2,086	463	3,848
ITA ($USD)	2,101	6,278	242	2,016	282	2,342
GER ($USD)	4,352	18,416	347	2,887	493	4,097
Total ($USD)	**52,707**	**142,600**	**6,131**	**50,993**	**4,935**	**41,042**

6 Discussion

This study explored the commercial rationale for investing in ALS research by outlining the disease burden, the unmet clinical need, and the potential value of advancing research and treatments.

Currently, long diagnostic delays, driven in part by the absence of reliable biomarkers, pose significant threats to early identification and management of people living with ALS. The lack of such biomarkers also limits effective treatment monitoring. Combined with the requirement for lengthy clinical trials, these barriers slow therapeutic development, reinforcing treatment innovation as the most critical unmet need in ALS.

In spite of these challenges, ALS stands at a pivotal moment, with unique opportunities to drive both innovation and impact in research and investment. Rising levels of funding, scientific advancements in disease understanding, expanding large-scale collaborations, and a growing at-risk population have created appealing grounds for breakthrough discoveries in ALS and related neurodegenerative diseases. These factors make the field a priority for scientific advancement and strategic investment, opening the door to faster progress in diagnostics, therapies, and prevention.

With global populations rapidly aging, the prevalence of neurodegenerative disease is projected to increase substantially. Age itself is a significant risk factor and increasingly recognised as a driver of neurodegenerative disease (Hou et al., 2019). The combination of demographic pressure and biological vulnerability should encourage sustained investment in neurodegenerative research. Given that the benefits of such research are likely to unfold over decades, the global trend of population aging provides both a pressing rationale and strong support for long-term commitment in this field. Furthermore, a growing ALS population will substantially expand the societal value (and therefore commercial opportunity) of finding viable treatment solutions.

The research study in the literature that came closest to our research question was the model-based economic evaluation of hypothetical treatments for ALS by Tappenden et al. (2024). The results from this study show that disease-modifying therapies, acting by delaying ALS progression were unlikely to be cost-effective when compared to standard of care in the UK, however, symptomatic therapies were more likely to be cost-effective. Ultimately, this is in line with our finding from Approach 3 of this analysis, wherein only Medicine 3, the most optimistic of the medicine profiles we considered in that approach, produced positive values across all the countries in this report. These themes are also highlighted in the Canadian Drug Agency review of tofersen, where the committee noted the hugely significant role of non-drug related costs in the challenging cost-effectiveness profile of the treatment, as well as the hurdles to obtaining sufficient data to provide evidence of the broader societal impacts (Canada's Drug Agency, 2025).

These results can be understood as reflecting deficiencies that exist in conventional HTA methods when evaluating medicines for rare and progressive diseases such as ALS. This report has highlighted the significant burden that ALS places on society. ALS generates considerable direct medical and non-medical costs, leads to substantial quality-of life decrements and reduced life expectancies for patients, and decreases productivity for both patients and their informal caregivers.

This analysis, along with Tappenden et al. (2024), demonstrate how traditional HTA frameworks may systematically undervalue treatments for progressive and severe diseases such as ALS, due to the high healthcare resource utilisation paired with existing unmet need, thereby creating inadequate commercial incentives for pharmaceutical innovation in these areas. This challenge provides a useful case study for how alternative or broader value frameworks are necessary to overcome these challenges that diseases like ALS face

in order to appropriately reflect the value that medicines in these disease areas could have.

With this in mind, this report presented two complementary approaches (Approaches 1 and 2) that demonstrated potential treatment value. Approach 1 quantified the total disease burden of ALS, essentially providing the maximum commercial value that could be justified for a hypothetical treatment capable of completely eradicating the disease. Approach 2 used the price of tofersen as a proxy for the hypothetical treatment's price, to reflect the potential commercial value that could be expected from real-world ALS treatments. Ultimately, all three of our approaches considered a spectrum of therapeutic benefits. Complete disease eradication, while captured in Approach 1, represents an unlikely short-term outcome; however, treatments that slow disease progression could capture a significant portion of the value that we describe. Both Approaches 1 and 2 produced values well into the hundreds of millions of US dollars; thus, these findings demonstrate that advances in ALS treatment research represents a substantial societal opportunity despite it being a rare disease. Together, these approaches provide a comprehensive understanding of the environment for ALS therapies.

The findings of our study should be considered in light of some limitations. First, throughout the report we refer to a 'hypothetical ALS treatment', and we scale up this treatment value to the entire ALS population. In reality, the commercial value to which we refer more likely points to the aggregate impact that several ALS therapies could have. Ultimately, this is due to the fact that ALS is a disease with heterogeneous causes, and researchers have identified several genes that share a link to the disease. As such, therapies addressing different underlying mechanisms may need to serve distinct patient subpopulations, each capturing a portion of the total commercial opportunity we have outlined. Thus, our valuations reflect the collective commercial opportunity available across multiple therapeutic approaches targeting the various mechanisms that may contribute to ALS onset.

Moreover, we report the value of a therapy, or therapies, that would be made available at present. Realistically, such a treatment would not be available for several years, meaning that current patient populations would not benefit. We also apply simplifying assumptions of full market penetrance from the outset, which may not be realistic in practice and also does not account for the impact of pricing pressures or competing market entrants. Still, quantifying the present-day value of reaching all those that could benefit demonstrates the substantial future market opportunity and potential value of successful therapeutic development.

It is also important to remember that, in capturing the total value, we estimate the returns that could be achieved if therapies are priced to value, assuming all of that value could be appropriated by the developer. However, if significant health care costs are associated with delivery of the treatment(s), then these should be accounted for within that value window. These estimates of commercial returns (value net of delivery costs) can then be compared with the likely investment required in bringing such therapies to market, including the cost of R&D and commercialisation as well as production. Comparing projected returns with projected costs of development can aid an understanding of return on investment, critical for commercial development decisions. While we recognise that, in practice, investment decisions are complex and encompass many different factors (including competing opportunities, and returns on investment elsewhere), this value assessment offers an important insight into the size of the problem and therefore the size of the opportunity to address it.

Additionally, while we consider the various impacts that ALS has outside of direct healthcare costs and QALY gains, we do not include these quantified values in our aggregate commercial value figures. This ultimately reflects traditional HTA remit and methods; however, when considering the productivity losses incurred by patients and their caregivers, the non-medical costs patients face to improve accessibility and quality-of-life,

and the healthcare resources that are used as patients navigate the long, costly diagnostic pathway for ALS, the total socioeconomic burden of this disease becomes much larger. Including these broader impacts would substantially increase the commercial value estimates for ALS treatments, suggesting that the economic case for ALS therapeutic development may be even more compelling when the full disease burden is considered.

Our third approach also faces significant limitations. Specifically, the structural assumption that all patients enter the model at King's stage 1 and age 63 simplifies the considerable heterogeneity observed in real-world ALS onset and progression. Second, the restriction that patients cannot regress to an earlier disease stage excludes the possibility of stabilisation or functional improvement observed in some subgroups, potentially underestimating treatment benefit. In addition, applying transition probabilities and utility values uniformly across all countries assumes homogeneity in disease course and patient experience, which may not hold true in diverse healthcare contexts. Lastly, as previously outlined in this paper, ALS is a highly heterogenous condition, which the current model does not fully capture. By applying a single relative risk reduction to all patients, the model oversimplifies the complexity of real-world disease trajectories. Emerging evidence suggests that certain treatments may halt progression in a subset of patients, highlighting the importance of incorporating subgroup analyses in future research to generate more accurate and meaningful insights.

In addition, the value of the treatment from Approach 3 is likely to be understated because the model does not take into consideration and modifiers, which are used by several HTA bodies in their decision making (Radu et al., 2024). Formal frameworks utilised by HTA agencies have considered either qualitatively or quantitatively severity, unmet need, rarity, innovative treatments and end-of-life (Radu et al., 2024). This means that a potential therapy for ALS, which would meet at least one of those criteria would likely benefit from higher thresholds applied to treatment benefits, which could greatly increase the value-based price of such treatments.

Finally, as the analysis is based on hypothetical treatments, the findings are illustrative rather than predictive, and should be interpreted as indicative of potential value rather than precise estimates for a potential treatment. Further, the scenarios we explore in this analysis assume that our health systems can successfully identify and treat all ALS patients that could benefit from the hypothetical treatment, and that they can do so rapidly. Thus, our analysis implicitly captures value that would accrue from several R&D outcomes, such as the development of reliable biomarkers that could facilitate more efficient clinical trial design, identification of at-risk populations, and evaluation of treatment efficacy. As noted in our introduction, this requires strong health system improvements to overcome the diagnostic delays that currently exist, alongside scientific advances in the identification of biomarkers.

7 Conclusion

The aim of this report was to quantify the market size and potential economic value of a hypothetical ALS treatment across various markets. While the treatment landscape for ALS is still extremely limited and the disease faces substantial challenges in other ways, including, for instance, in terms of diagnostic delays and a lack of biomarkers, our analysis suggests that there are several opportunities that could place ALS at the forefront of innovation. Indeed, with advances in AI and in-silico technology, platform trials, and large datasets, researchers are equipped with unprecedented tools to accelerate ALS research and transform the treatment landscape.

This report used three approaches to quantify the value of a successful hypothetical ALS treatment. Two approaches demonstrated substantial commercial viability: one examining tofersen's pricing revealed significant values when scaled to the entire ALS population, while the other quantified ALS' total socioeconomic burden to illustrate the maximum commercial opportunity for a transformative therapy. Our third approach, using traditional HTA methods, yielded mixed results that highlight fundamental deficiencies in current HTA frameworks for diseases like ALS.

The numbers in our report are significant, but do not tell the whole story. Most meaningfully, they fail to do justice to the enormous and devastating human toll of ALS, and the commensurately fierce hope associated with finding treatments. The numbers also represent just one (albeit important) factor in commercial investment decisions, which are influenced by many other factors, across which ALS could represent an attractive investment prospect.

While the market size estimates presented in this report are meaningful, they remain smaller than some of the larger, highly competitive indications such as the GLP obesity and metabolic space. However, ALS is less crowded, making successful market entry more feasible, even when patient populations are small. The economics and policy levers in place for orphan diseases further help: higher willingness to pay by reimbursement agencies, additional regulatory incentives (market exclusivity, tax credits, fee waivers), and regulatory pathways that can accept progression-slowing data from single trials improve commercial risk-adjusted returns. Clinically, ALS's rapid progression also enables smaller, shorter, and therefore lower-cost Phase II proof-of-concept trials and reduces the number of patients needed to show meaningful endpoints. Further, the development of a therapy that treats the underlying disease pathology has significant potential for cross-disease utility, which would hugely inflate the commercial opportunity. Taken together, ALS stands out as a compelling and scalable investment opportunity for developers and investors.

Overall, our research demonstrates that a successful ALS treatment is likely to have significant societal and economic value. The convergence of substantial unmet medical need, demonstrated commercial opportunity, and advancing research capabilities creates an environment ripe for ALS drug development.

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9 Appendix

9.1 Methods

Approach 3: Model assumptions and details

The model utilises data from the ALS-CarE research programme, a pan-European Joint Programme in Neurodegeneration Disease (JPND)-funded initiative launched in 2014. This project used data from European ALS registries and national services to develop a care pathway for ALS patients, tailored to their individual disease characteristics, cognitive function, disease progression, and prognosis (Tappenden et al., 2024). As such, the ALS-CarE programme has produced data with a wealth of information on European ALS patients, which were used to inform the parameters of the model used in the original Tappenden et al. (2024) paper and, therefore, this report.

Structurally, the model uses King's staging classification, which was informed by data availability from the ALS-CareE database and is consistent with other ALS models (Stenson et al., 2023). King's staging classification includes five disease stages, where stages 1-3 describe the number of clinical regions involved, stage 4 indicates the involvement of nutritional or respiratory failure, and stage 5 represents death (Tappenden et al., 2024). We assume that all patients enter the model in King's stage 1 and at age 63 - a value informed by the mean age at patients' first clinical visits in the ALS-CareE dataset (Tappenden et al., 2024). Additionally, the model restricts the disease pathway such that patients cannot regress to an improved health state - this is a conservative assumption but is ultimately consistent with other ALS models. Within the model, a patients' disease stage determines their mortality risk, HRQoL, and disease management cost. That is, a patient in King's stage 1 generally has a lower mortality risk, higher HRQoL, and lower disease management cost compared with patients in later disease stages.

Approach 3: Monetary valuations of QALYs in each country

Table 11. Country-specific monetary valuations of QALYs

	MONETARY QALY VALUE	SOURCE
UNITED STATES	$100,000*	(ICER, 2019)
UNITED KINGDOM	£30,000 or £100,000**	(Strohmaier and Zechmeister-Koss, 2024)
GERMANY	€34,000***	(Gandjour, 2023)
CANADA	CAD 50,000	(Balijepalli et al., 2024)
AUSTRALIA	AUD 50,000	(Xia et al., 2025)
ITALY	€33,004**	(Russo et al., 2023)
FRANCE	€27,847 - €112,586***	(Tehard et al., 2023)

**The US threshold is often reported as 100,000-150,000; we took the lower bound for this analysis.*
***NICE uses a threshold of approximately £30,000 for its standard technology appraisals but uses a much higher threshold of approximately £100,000 for highly specialised technologies for ultra-rare diseases. To provide a conservative approach, we used the £30,000 figure for our calculations.*
****Germany, Italy, and France do not use explicit willingness-to-pay thresholds; thus, these values are based on calculated estimates of each country's (revealed) willingness to pay for a QALY based on previous HTA decisions. Ranges reflect the lower and upper bounds of what these estimates might be. For France, we used the €27,847 to monetise QALYs.*

9.2 Results
Epidemiology and prognosis

	UK	USA	CAN	AUS	FRA	ITA	GER	EUROPE	WORLD-WIDE
INCIDENCE (Per 100,000)	1.61	1.44	2.00	2.73	3.5	2.12	3.10	2.13	0.78
SOURCE	(Opie-Martin, et al. 2021)	(Mehta, et al. 2025)	(Hodgkinson, et al. 2018)	(MND in Australia, 2021)	(Corcia, et al. 2025)	(Bacigalupo, et al. 2024)	(Schönfelder, et al. 2021)	(Brown, et al. 2021)	(Wolfson, et al. 2023)
PREVALENCE (Per 100,000)	7.35	9.67	6.98	8.70	11.0	8.87	8.00	6.22	4.50
SOURCE	(Opie-Martin, et al. 2021)	(Mehta, et al. 2025)	(Hodgkinson, et al. 2018)	(MND in Australia, 2021)	(Corcia, et al. 2025)	(Bacigalupo, et al. 2024)	(Schönfelder, et al. 2021)	(Brown, et al. 2021)	(Wolfson, et al. 2023)
PREVALENCE (per country population)	5,000	32,893	2,800	2,094	7,331	5,233	6,662	46,000	710,000
LIFE EXPECTANCY (Years)	1.5-3	3	3	2.5	2.3	3-5	3.5		
	After diagnosis	From onset	From onset	After diagnosis	From onset	From onset	From onset		
SOURCE	(Burchardt, et al. 2022)	(Thakore, et al. 2020)	(Hodgkinson, et al. 2018)	(MND in Australia, 2021)	(Corcia, et al. 2025)	(Bacigalupo, et al. 2024)	(Schönfelder, et al. 2021)		
MEDIAN AGE OF DIAGNOSIS	63	64.8	61.8	64	68.4	72	61.4		
SOURCE	(Tappenden, et al. 2024)	(Engelberg-Cook, et al. 2024)	(Hodgkinson, et al. 2018)	(Wei, et al. 2025)	(Corcia, et al. 2025)	(Bacigalupo, et al. 2024)	(Schönfelder, et al. 2021)		

Disease burden

Health utilities by ALS King's stage were directly available for the UK (Tappenden et al., 2024), US (Thakore et al., 2020), and Germany (Schönfelder et al., 2020). For France, and Italy, utilities were obtained from a pan-European study (Stenson et al., 2023). No country-specific data were found for Canada and Australia - therefore, values from the US and UK studies were applied, respectively.

Age-matched general population utilities were assumed based on the entry age for each country. Sources included: UK (McNamara et al., 2023), US (Jiang, Janssen and Pickard, 2021), Canada (Yan et al., 2024), Australia (Redwood et al., 2024), France (Gautier et al., 2023), Italy (Meregaglia et al., 2023), Germany (Grochtdreis et al., 2019).

Life expectancy data on all countries was obtained from the World Bank, at: https://data.worldbank.org/indicator/SP.DYN.LE00.IN and the willingness to pay thresholds used are as described in Table 11 , apart from for the UK where we utilised the Treasury's £70,000/QALY, as described in the report. For France, we take the lower bound of the estimated range provided in Table 11

Healthcare resource utilisation

Healthcare resource utilisation data, including unit prices (i.e., cost per GP appointment) where applicable, was obtained from sources including: UK (Tappenden et al., 2024), US (Thakore et al., 2020; Stenson et al., 2023; Obermann and Lyon, 2015; Larkindale et al., 2014), Canada (Canadian Institute for Health Information, 2022; Amoozegar et al., 2022; Employment and Social Development Canada, 2024; University of Calgary, 2021; Gladman, Dharamshi and Zinman, 2014), Australia (Delloitte, 2015), France (Corcia et al., 2025), Italy (Pöhlmann et al., 2020) https://www.agenas.gov.it/images/agenas/monitoraggio/spesa_sanitaria/tariffe/specialistica_ambulatoriale_tariffe.pdf, Germany (Schönfelder et al., 2020).

Costs were extracted directly from the referenced studies for the UK, the US, Australia, and Germany. For Canada, France and Italy, time spent in each King's stage was assumed to follow proportionally that reported in (Tappenden et al., 2024) model, with unit costs extracted from the corresponding studies cited above.

Healthcare resource utilization costs comprised a varying set of elements, depending on data availability. These included: GP appointments, nurse visits, therapies (occupational, physiotherapy, speech, dietician, psychiatrist), social care, palliative care, counselling, clinic outpatient visit, overnight stays, accidents and emergency attendance, any aids, medication.

Estimated country-specific prices of tofersen

Table 12. Estimated country-specific prices of tofersen

	US BRAND-NAME ORIGINATOR DRUG PRICES AS A % OF OTHER-COUNTRY PRICES, 2018	ESTIMATED YEARLY PER-PATIENT PRICE OF TOFERSEN (USD)	ESTIMATED COMMERCIAL VALUE OF TREATMENT, YR 1 (IN MILLIONS, USD)
UNITED STATES	100%	$145,915	$4,799.6
UNITED KINGDOM	349%	$41,809	$209.0
CANADA	294%	$49,631	$139.0
FRANCE	349%	$41,809	$250.9
GERMANY	280%	$52,112	$347.2
ITALY	315%	$46,322	$242.4
AUSTRALIA*	213%	$68,505	$143.4

*Australia was not included in the Mulcahy et al. analysis, so we used the results of a paper cited by Mulcahy et al. (2021) that estimated the relationship between branded medicines' prices in the US and Australia (Kanavos et al., 2013).

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