Insight

Transforming amyotrophic lateral sclerosis into a liveable disease

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For the **NASEM statement on ALS** see https://nap.nationalacademies.org/catalog/27739/living-with-als

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For more on **clinical trials in ALS** see *Nat Rev Neurol* 2021; **17:** 104–18

For more on **Project MinE** see https://www.projectmine.com/

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that remains incurable, despite decades of basic and clinical research. Key stakeholders—including the US National Academies of Sciences, Engineering, and Medicine (NASEM)—are focusing efforts on advancing ALS research and improving patient outcomes, to make ALS a liveable disease. In collaboration and consultation with people living with the disease, the goals of these efforts are twofold: first, to accelerate therapeutic discoveries for ALS; and second, to individualise approaches to clinical care. Meeting these goals poses challenges to the ALS community and mandates local, national, and global initiatives.

A consensus statement from the NASEM has recently been published that acknowledges and makes recommendations to tackle the complex nature of ALS (appendix p 3). In the report, the NASEM advocates for an interdisciplinary approach to basic and clinical research, combining expertise across multiple scientific and medical disciplines. Furthermore, a novel hub-and-spoke model for clinical care and research is introduced, which is bolstered by a diversified portfolio of funding mechanisms. The crucial essence underpinning the major recommendations from the NASEM is the need for collaboration. Research institutions, industry, patient organisations, and governmental bodies need to collaborate globally, bringing their respective experience and financial support together, to identify and prioritise objectives within the current basic and clinical spheres of ALS research.

With respect to basic research, the multifaceted and complex pathophysiology of ALS—which entails a range of aberrant cellular and molecular pathways—leads to difficulties in developing accurate disease models and identifying a therapeutically targetable biological pathway. Most studies use transgenic mouse models of known genetic variants in ALS (eg, *SOD1*). However, no animal model of non-genetic disease exists, despite genetic variants causing about 20% of ALS cases. Environmental factors also contribute to ALS risk and progression, which should be considered in the development of animal models. Recent advances using patient-derived induced pluripotent stem cells offer new insights into disease mechanisms, but a limitation is that these results are from in-vitro experiments. It is important to remember that in-vitro and animal models do not fully capture human disease because they cannot mimic the complexity of the human neuroaxis, including the key alterations in network connectivity that are observed in ALS. Yet, pharmaceutical companies still mandate animal models as a prerequisite for moving therapies forward, despite their clear limitations. The NASEM report recommends robust investment in basic mechanism-driven discovery at all levels, including federal, pharmaceutical, and foundation support, alongside a necessary shift towards approaches that acknowledge the multiple pathways that drive ALS pathobiology.

The NASEM recommendations come at a time when so-called omics technologies are catalysing breakthroughs in ALS research. These systemwide techniques—eg, genomics, proteomics, metabolomics, and exposomics—can produce comprehensive molecular and environmental insights and are well suited to disentangle the complexity of a heterogeneous disease such as ALS. Artificial intelligence and machine learning approaches could be applied to these techniques to agnostically process and analyse large datasets. Omics platforms might help to pinpoint therapeutic targets and potential drug candidates. Further, omics technologies could be combined with cellular strategies (eg, induced pluripotent stem cells) to identify unique genetic and molecular characteristics of ALS and assess individual patient responses to therapeutic interventions. Moreover, omics technologies could be used to study pathways in new and improved animal models (eg, of non-genetic ALS), to identify underlying mechanisms, understand disease variability, and test new therapies.

With respect to clinical research, omics technologies might help with stratification of ALS trial participants into molecular and genetic subtypes, and could match potential drug candidates to individuals, facilitating personalised approaches to care and increasing the odds of discovering effective treatments. Although our current understanding of ALS is primarily based on research done in individuals with European ancestry, diverse mixed racial groups could teach us a lot about the disease, even though the overall prevalence of ALS might be low in these cohorts. By utilising omics technologies, researchers could more easily analyse and compare data across varied genetic backgrounds. An important and emerging area of clinical research is the targeting of potential treatments to specific subgroups. For example, the antisense oligonucleotide tofersen will be administered to individuals carrying a pathogenic *SOD1* variant in the ongoing ATLAS study (NCT04856982).

Omics technologies might also be able to uncover novel biomarkers to improve diagnostic accuracy and predict disease progression. However, omics techniques are only as good as the data that are gathered and available for analysis, and rigorous collection of clinical data—particularly, longitudinal data—and biological materials can be expensive, time consuming, and difficult. ALS registries linked to clinical and neurophysiological data (eg, banked biosamples) could help to address these challenges. Globally, many such collections exist, such as Project MinE, New York Genome Center's ALS consortium

(NYGC ALS), Answer ALS, Care-MND, Precision ALS, and TRICALS.

The NASEM report emphasises the need to employ omics strategies to identify biomarkers for ALS diagnosis and prognosis, or to identify people most likely to respond to treatment. No biomarkers are available for ALS, although neurofilament light chain (NfL), which is easily measured in blood, is elevated in people with this disease, and this marker has been used as a clinical trial outcome. Yet, NfL is elevated in many other neurodegenerative diseases, which restricts its diagnostic utility. Since ALS is a heterogeneous complex disease, a biomarker panel might better capture disease signatures. Such biomarker panels are being developed based on transcriptomic signatures, and these might be able to molecularly stratify patients for tailoring of treatment. Combining plasma, CSF, and neuroimaging biomarkers might be specific, sensitive, and powerful. However, research into modalities besides MRI is scarce.

While new technologies and registries offer a strategy to accelerate ALS research, goals for shorter clinical trials and for treating the most people living with ALS still must be addressed. New and creative aspects of trial design could meet these demands. One solution could be to generate so-called digital twins from large-scale datasets, which would simulate how patients would be likely to progress without treatment, substantially reducing (or, even, eliminating) the need for a traditional placebo arm. Another idea is to conduct a platform trial that simultaneously assesses multiple drugs against a shared placebo arm, using a single master protocol. This trial design increases the rate of candidate testing and augments the chances of randomising a participant to a treatment arm. An additional approach is to run an adaptive trial, flowing seamlessly through phases 1, 2, and 3, reducing bureaucracy and streamlining workflow. Platform and adaptive designs could be combined to maximise the benefits of each—eg, the MND-SMART trial and the Healey-ALS platform trial. However, until patients can be categorised into specific subgroups based on underlying biological mechanisms, these studies will still encounter challenges because a one-size-fits-all approach to testing drug efficacy has, to date, proven ineffective, underscoring the importance of identifying the molecular mechanisms driving ALS.

The NASEM report expands the recommendations for novel trial designs by proposing a US-centric hub-and-spoke clinical care and trial network for ALS. Clinical care occurs throughout the USA in community-based clinics, which provide patients with access to centres for clinical research. A network of clinics and research centres (ie, the spokes of the proposed model) would be coordinated by a few large ALS centres of excellence—the hubs. If implemented, this new ALS network would transform and improve ALS patient care and participation in clinical research. Global consortia providing similar networks include ENCALS in Europe, NEALS in North America and PACTALS in Asia–Pacific. Collaboration between these groups could accelerate the discovery of effective therapies. However, obstacles remain, particularly the varying regulations on privacy and data-sharing across regions and countries. The 2023 EU–US Data Privacy Framework attempts to reconcile regulatory differences, but its practical effectiveness is unknown. A potential solution could involve establishing funding initiatives aimed at harmonising data collection processes, which would enable data sharing or facilitate the replication of analyses.

To make progress in both basic and clinical research, new approaches to research funding are also required, according to the NASEM report. Ideally, funders should partner with industry and the ALS community to develop specific research programmes focused on unique and unmet needs (eg, at-risk individuals with gene mutations). Linked to such programmes, large-scale, prospective, natural history studies of populations at-risk of ALS should inform key priorities. Greater alignment of government funding with regulatory authorities will also help to establish and accelerate programmes that provide targeted therapies to current patients and future at-risk individuals. In the USA, such government initiatives are underway for ALS, with a focus on enhancing coordination for basic research and drug development. The Accelerating Access to Critical Therapies for ALS Act (ACT for ALS), was enacted in 2021, and Section 3 of ACT for ALS authorised a public–private partnership for rare neurodegenerative diseases, which includes the US National Institutes of Health (NIH) and the US Food and Drug Administration. The NASEM report was commissioned by the NIH after ACT for ALS, and the Access for All in ALS (ALL ALS) consortium was initiated to organise the ALS clinical research landscape in the USA. Similar international initiatives for research funding and prioritisation include the European Precision ALS programme, the community-orientated Australian MiNDAUS partnership, and the UK MND Research Institute, as well as international philanthropic efforts.

The NASEM report presents recommendations to make ALS a liveable disease, and emerging technologies and innovative clinical trial strategies are opportunities to address these recommendations. To transform ALS into a chronic disease, it is crucial to prioritise and translate scientific discoveries into effective therapies, with the ultimate objective of improving ALS patient care. Continued investment, and collaboration by researchers, clinicians, and stakeholders, will be essential to overcome challenges and seize opportunities in ALS research. By working together, we can accelerate the development of life-changing treatments, improve patient outcomes, and ultimately, bring hope to those affected by this devastating disease. Now is the time to act and make ALS a liveable disease.

Author affiliations, contributions, declarations of interest, and acknowledgments are available in the appendix (pp 1–2).

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For more on **NYGC ALS** see https://www.nygenome.org/science-technology/collaborative-research-programs/neurodegenerative-disease-research/als-consortium/

For more on **Answer ALS** see https://www.answerals.org/

For more on **Care-MND** see https://www.care-mnd.org.uk/

For more on **Precision ALS** see https://www.precisionals.ie/

For more on **TRICALS** see https://www.tricals.org/

For more on **molecular stratification of ALS patients** see *Acta Neuropathol Commun* 2023; **11:** 208

For more on **adaptive platform trials in ALS** see *Ann Neurol* 2022; **91:** 165–75

For more on the **MND-SMART trial** see https://mnd-smart.org/

For more on the **Healey-ALS platform trial** see https://www.massgeneral.org/neurology/als/research/platform-trial

For more on **ENCALS** see https://www.encals.eu/

For more on **NEALS** see https://neals.org/

For more on **PACTALS** see https://pactals.org/

For more on the **EU–US Data Privacy Framework** see https://www.dataprivacyframework.gov/Program-Overview

For more on **ACT for ALS** see https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/accelerating-access-critical-therapies-als-act-act-als

For more on the **ALL ALS consortium** see *Muscle Nerve* 2024; **70:** 1140–50

For more on the **MiNDAUS partnership** see https://www.mindaus.org/

For more on **philanthropy and ALS** see **In Context** *Lancet Neurol* 2023; **22:** 204–05