Priorities of the NIH Amyotrophic Lateral Sclerosis (ALS) Strategic Planning Working Group

January 17th, 2023

Executive Summary

Background and Priorities. Amyotrophic Lateral Sclerosis (ALS) is a complex, heterogenous disease that poses challenges as we investigate mechanisms that initiate and provoke its rapid progression to motor neuron death. It is noteworthy that scientific discoveries have resulted in the identification of multiple therapeutic targets; three disease-modifying and one symptom-modifying ALS therapies are FDA approved, albeit with modest efficacy. Yet, to develop truly effective ALS treatments, the ALS community must address numerous challenges. The National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS) created this Strategic Planning Working Group to define the highest priorities for ALS research in pursuit of more effective diagnosis, prevention, treatment, and/or a cure. This is the first time such a planning effort has taken place for ALS and the planning committee, which included people affected by ALS, recognizes this as an important document to build and improve on in upcoming years. In addition to individuals living with ALS, people with genetic risk for ALS and caregivers, people involved in this effort included clinicians, researchers and NIH/NINDS staff. Five working groups spanning five focus areas generated a total of 15 priorities to guide ALS research. We consider all of the priorities identified as important and urgent, but also recognize the challenges in defining immediate steps towards putting these priorities in action. Given the rapid timeline of ALS disease progression, there was broad consensus among the working groups and the ALS community that these recommendations need to be addressed without further delay. To facilitate this process and taking into consideration comments on these priorities made by the public, we list the over-arching priorities as follows:

- **Enhance understanding of basic biology of motor neuron disease**. In particular, there is wide consensus that we must do more to understand the cellular and molecular events that underlie non-familial, sporadic ALS (~85% of all cases).
- Translate **novel disease pathways into clinical therapeutic development**.
- **Optimize clinical research** and the design and performance of trials for people living with ALS at all stages of the disease, including pre-symptomatic gene carriers
- Implement comprehensive education and technologies to improve the **quality of life** of people living with ALS and their caregivers.
- Expand and **improve existing collaborations and partnerships between *all* ALS stakeholders, nationally and internationally**: people living with ALS, at risk individuals carrying genetic mutations, caregivers, academic researchers, clinicians, industry partners and philanthropic organizations within the United States and throughout the world.

Discussion and Consensus. There was broad consensus on several interwoven issues. Perhaps most important and uniformly agreed upon is the urgency in putting the recommended priorities in action, as survival in ALS is typically only 3-5 years and the 'ALS Clock' is 'always ticking'. The ALS community established that we must understand the molecular basis of clinical heterogeneity in ALS and improve methods for following the trajectory of the disease course, from pre-symptomatic to late symptomatic phases. A special emphasis was put on decoding non-familial or sporadic ALS (used interchangeably throughout this document), which represents the majority of individuals living with ALS. Also endorsed was the premise that therapies should be initiated as early as feasible,

including at the inflection points when the earliest symptoms appear and/or when molecular and cellular changes are reliably detectable even without clinical symptoms present. There was agreement that the community must develop collaborative, openly accessible research infrastructures, generating synergies that leverage existing resources to build and expand on. These should embrace multi-dimensional data, collected longitudinally, and harmonized to permit data sharing, but should also include repositories of scientific tools, protocols, and resources. Centrally important as well is to ensure that all people living with ALS and caregivers, independent of their geographical location (e.g., urban and rural communities) or socioeconomic status, gain access to information about clinical features of ALS and options for clinical and therapeutic trials, as well as non-pharmacological interventions. Underlying this was the powerful concern that we must understand the impact of ethnic diversity, race, and gender on all aspects of ALS, such as the timeliness and efficacy of therapy. These latter recommendations will enable the community to receive better and more comprehensive education, and consequently care, for all individuals affected with ALS. This in turn will greatly improve the quality of life (QOL) of individuals affected by this disease as well as that of ALS caregivers and family members, especially youth caregivers.

The Path Forward. These strategic priorities will be presented on behalf of the ALS community as urgent recommendations to the National Advisory Neurological Disorders and Stroke Council. Implementation thereafter is expected to entail several approaches; central among these will be the use of existing (and potentially new) funding opportunities through the NINDS and other NIH institutions (Appendix). It is further anticipated that these diverse funding mechanisms will attract individual and collaborative requests from multiple constituencies, including academics, the pharmaceutical industry and patient advocacy groups. Finally, we recommend that in order to maintain momentum of this timely effort, regular follow up meetings with relevant stakeholders are put in place. These meetings will enable the ALS community to discuss progress of the recommended priorities, provide opportunities to adjust the focus areas but also to expand and include additional objectives required to quickly and efficiently reach the goals set for this strategic plan.

Respectfully submitted,

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INTRODUCTION

Background ALS

Clinical Description. Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of motor neurons that begins with subtle focal weakness and progresses to paralysis of most skeletal muscles including the diaphragm. The majority of cases begin insidiously in the limb muscles; in approximately one-third of cases, the muscles of chewing, speaking, and swallowing (bulbar muscles) are initially afflicted. The affected motor neurons typically fall into two groups. Those that actually connect to muscles (spinal cord and bulbar motor neurons) are loosely labelled "lower" motor neurons. By contrast, "upper" motor neurons (corticospinal and corticobulbar motor neurons) are those that allow the brain to communicate with lower motor neurons. Impairment of the upper motor neurons causes weakness with stiffness or spasticity of the involved musculature; by contrast, loss of lower motor neurons causes first muscle twitching (fasciculations) followed by weakness due to muscle atrophy. Motor neurons that innervate eye and bladder muscles are only involved in the late stages of the disease, if at all. Regardless of the type of onset, in most cases of ALS, both upper and lower motor neurons are affected. In up to 50% of cases, there is also degeneration of non-motor neurons in the frontal and temporal regions of the brain; this arises in association with a distinctive type of dementia (frontotemporal dementia or FTD) predominantly characterized by disturbances of behavior and speech. Minor disturbances of cognition are recognized in up to 50% of ALS cases.

Overall survival in ALS is typically 3-5 years but this is dependent on the primary sets of motor neurons implicated in a given case. For example, individuals with predominance of corticospinal tract dysfunction, designated primary lateral sclerosis, may commonly survive more than ten years, while those with bulbar onset may survive less than three years and those with specific mutations in the *SOD1* and *FUS* genes (see page 7) may survive less than one year. Death generally results from respiratory insufficiency.

Therapy. Four drugs are now FDA-approved for use in ALS. These slow or ameliorate some symptoms of ALS, but none arrest the disease process; there is as yet no cure for ALS. Riluzole (Rilutek®) and the drug Relyvrio® (a combination of sodium phenylbutyrate and taurursodiol, labeled Albrioza® in Canada) produce modest increments in survival. Intravenous and oral Edaravone (Radicava®) modestly slows progression; its impact on survival has not been determined. Nuedexta®, a combination of dextromethorphan and quinidine, effectively blunts the exaggerated laughing or crying (pseudobulbar affect) encountered with dysfunction of the upper motor neurons subserving the bulbar muscles.

In the absence of truly effective ALS therapies, there is a major role for symptomatic management in this disease. The mainstays support respiration (initially including positive pressure breathing devices and ultimately requiring tracheotomy and full ventilatory support) and alimentation (feeding tubes) when chewing and swallowing are impaired. A range of effective new computer-based technologies augment speech.

Epidemiology. There are approximately 1-2 new cases of ALS each year for every 100,000 individuals in the population. The total number of cases is ~10/100,000 or ~33,000 overall, and so this qualifies as an orphan disease, with less than 200,000 cases. There is an estimated

lifetime ALS risk of 1/400, which predicts that more than 800,000 individuals now alive in the US will succumb to ALS. While definitive risk factors for ALS have been elusive, it is irrefutable that ALS is age-dependent and, in non-familial forms, more common in males. Many lifestyle traits have been implicated but most are controversial. Smoking appears to be overrepresented in ALS, as does service in the military, which may confer a more than two-fold increased risk of ALS. As reviewed below, genetic factors can confer enhanced susceptibility to ALS.

Available data argue that the incidence of ALS is generally uniform across the globe, although detailed epidemiologic status of ALS in populations of non-European origin is not well characterized. Geographic foci with dramatically increased numbers of ALS cases in Guam (where ALS overlaps with dementia and Parkinsonism) and the Kii peninsula in Japan were discovered several decades ago; Guamian ALS, which was well validated in detailed investigations, is now less common.

Genetics. Over the last three decades, investigations of ALS genetics have provided insight into both familial and non-familial ALS. With the advent of improved technology for DNA sequencing, scores of ALS genes have been identified; it is a fundamental irony that although ALS is a highly cell-type specific disorder of motor and frontotemporal neurons, virtually all of the ALS genes are expressed in all cells, both within and outside of the central nervous system. It has long been recognized that families of people living with ALS have an increased risk of ALS. Moreover, about 10 - 15% of ALS cases are inherited as a dominant trait, which are termed "familial" for this report. ALS individuals with no family history of ALS are said to be "sporadic," a term employed in this report. It should be noted that this definition does not exclude the possibility that "sporadic" patients might, despite a negative family history of ALS, prove to harbor ALS gene mutations.

The most common ALS mutation is an expansion of a six-nucleotide repeat in the *C9orf72* gene. In the United States, this accounts for about 40% of familial ALS and upwards of 10% of sporadic ALS cases. These expansions, which can exceed the normal lengths of 3-30 repeats by 1,000-fold, have multiple adverse consequences. They partially suppress the normal gene function. They also generate intranuclear RNA aggregates of the repeat domains that lead to sequestration of intranuclear proteins. Further, the repeat RNA fragments escape to the cytoplasm where they engage ribosomes and are translated into five toxic dipeptide repeat proteins.

Mutations in the superoxide dismutase (*SOD1*) gene account for about 20% and 1-2% of familial and sporadic ALS, respectively. There is consensus that these mutations exert multiple injurious influences on motor neuron viability not primarily through loss of SOD1 enzyme activity but rather through toxic consequences of the mutations, likely related to instability and misfolding of this highly abundant antioxidant protein.

Also, extremely informative in ALS studies are mutations in the *TARDBP* gene, which provides instructions for making a protein called transactive response DNA binding protein 43 kDa (TDP43), and are detected in ~5% of familial ALS. The mutant TDP43 protein is mislocalized from the nucleus to the cytoplasm and found to be fragmented and hyperphosphorylated. The importance of this gene is underscored by the observation that non-mutant TDP43 protein, also mislocalized and misprocessed, is detected albeit at low levels in most cases of familial and

sporadic ALS, except for SOD1 and FUS ALS. TDP43 is implicated in numerous cellular functions. Among the most important is its role in surveillance and correction of mis-splicing of RNA, a property that is disturbed and highly consequential in sporadic ALS. Another 5% of familial cases arise from mutations in the *FUS* gene, which like TDP43 has protean functions in cells; unlike the TDP43 protein, abnormalities in FUS protein are not at this time identified in typical sporadic ALS.

Several other ALS genes are less common but nonetheless insightful. Mutations in the profilin-1 *(PFN1)* gene support the view that microtubular function and axonal transport are essential elements in motor neuron viability. Mutations in *optineurin* and *TBK1* genes underscore the importance of non-neuronal cells and events, such as neuroinflammation and autophagy, in ALS pathophysiology. Importantly, there are genetic variants that do not by themselves cause ALS but nonetheless augment ALS risk (e.g., intermediate expansions of the CAG repeat in the gene *ATXN2*) or influence clinical features such as survival (e.g., variants in the *UNC13A* gene.).

Fortunately, knowledge of the broad set of mutant genes has permitted generation of new rodent ALS models. Thus, transgenic SOD1 and profilin mice develop age-dependent, ultimately lethal motor neuron disease; while transgenic *C9orf72* mice do not demonstrate progressive paralysis, they recapitulate the predominant molecular and pathological attributes of *C9orf72* cases. Analogously, it has been possible to generate pluripotent stem cells and subsequently human motor neurons with ALS mutations. These authentic human models demonstrate some of the same pathological and molecular defects found in patients. Together, these diverse models have been pivotal both in further investigation of cascades of events initiated by the mutant genes and in preclinical development of ALS therapies.

Pathology. The pathological hallmark of ALS is progressive degeneration of motor neurons in the brain, brainstem and spinal cord. As brain motor neurons deteriorate, there is scarring (sclerosis) along the length of the corticospinal tract. Death of spinal cord motor neurons and resulting denervation of muscle underlie muscle wasting (amyotrophy). As above, in many types of ALS (but not *SOD1* or *FUS* gene cases) there is cytoplasmic deposition of filamentous TDP43 with concurrent loss of nuclear TDP43. In *C9orf72* ALS cytoplasmic deposits of dipeptide repeat proteins are detected. Other hallmarks in many cases include the deposition of aggregated proteins, which are sometimes ubiquitinated, and filamentous swelling and disruption of axons.

At the ultrastructural level, many findings are described including mitochondrial abnormalities. A range of pathologies mediated by mutant ALS genes are reported in cultured cells, including the presence of stress-induced, non-membrane bound granules (stress granules) and disruption of the nuclear membrane pore complexes with disturbance of nuclear-cytoplasmic gradients of a range of substances. A salient aspect of ALS pathology is the role of non-neuronal cells in the disease; with progression, there is activation of microglia, aberrant function of astroglia and degeneration of oligodendroglia. Many studies support the concept that these cell types can, with advanced disease, adopt cytotoxic profiles.

ALS is a complex and heterogenous disease, based on its clinical, genetic, and pathological features. This complexity poses equally complex, parallel challenges as researchers attempt to understand mechanisms that trigger ALS and provoke its spread and progression to motor neuron dysfunction and cell death. Most knowledge about these mechanisms has been garnered from the analysis of genetic forms of ALS and both cellular and animal models of the disease. These

approaches have disclosed multiple, sometimes overlapping cellular and molecular processes that are dysfunctional in ALS. These include abnormal regulation of RNA biogenesis and metabolism, neuroinflammation, disturbances in mitochondrial function, altered synaptic transmission, protein dyshomeostasis, and disturbances in subcellular structures such as the nuclear pore complex among others.

Scientific discoveries have resulted in the identification of numerous novel therapeutic targets – processes in the disease mechanisms that can be manipulated genetically or pharmacologically to ameliorate the cellular degeneration and potentially slow or even stop ALS disease progression. As noted, these efforts have led to the approval of 3 disease-modifying therapies for people living with ALS. It is encouraging that, in addition to those approved treatments, numerous promising clinical trials are underway exploring different, innovative therapeutic options.

While these efforts are promising, we still do not have therapies that stop or reverse ALS. To achieve genuine therapeutic advances, the ALS community must overcome numerous unresolved challenges. These are elaborated in detail in this report, but several major hurdles may be summarized here. Among the most important is understanding causation in the approximately 85% of cases that do not have an identified genetic trigger, i.e., sporadic ALS cases. Closely related is establishing more sensitive and reliable methods to diagnose people with ALS earlier, thereby facilitating earlier therapy. This goal is important for sporadic ALS and potentially also as an inroad to pre-symptomatic therapy in familial ALS. In addition, it is critical to determine if disease subgroups can be further sub-stratified based on their molecular characterizations and if such stratification would influence therapeutic treatment.

The ALS community must consider how to optimize collective infrastructure to serve both pre-clinical research and ALS trials, and to transition rapidly from the preclinical to the clinical trial realms. The journey from a lab petri dish to a drug trial is arduous, lengthy, and costly. Can the process be improved and accelerated? This report, which reflects the consensus of multiple clinicians, scientists, and people living with or at risk for with ALS, summarizes the major therapeutic challenges in ALS and prioritizes research options.

Charge

Identify the highest priorities for research that will lead to the discovery of effective interventions for the diagnosis, treatment, management, prevention, or cure of ALS.

Process

In January of 2022, the NINDS, the lead institute for ALS research within the NIH, initiated a strategic planning process to identify the highest priorities for research that will lead to the discovery of effective interventions for the diagnosis, treatment, management, prevention, or cure of ALS. NINDS began by releasing a Request for Information soliciting public input on research priorities for ALS (NOT-NS-22-056) and by soliciting nominations for people affected by ALS, including people living with ALS, caregivers, and people at genetic risk for developing ALS, to participate in the strategic planning process. NINDS established a steering committee (Appendix 2: Rosters) that included researchers and people affected by ALS to oversee the strategic planning process. This steering committee helped form five working groups of

researchers, clinicians, advocates, and people affected by ALS (Appendix 2: Rosters) to develop research priorities for:

1) accelerating research on the biology behind ALS,
2) translating fundamental research into potential ALS therapies,
3) optimizing ALS clinical research,
4) optimizing the quality of life of people living with ALS and their caregivers, and
5) identifying opportunities for collaborations and partnerships.

These working groups were charged with using the responses to the public request for information (Appendix 1: Summary of Responses to Request for Information (RFI): Soliciting Input on Research Priorities for ALS) along with their own knowledge of the research landscape, to develop up to three priorities within their focus area. NINDS staff helped to facilitate and coordinate the working groups, and representatives from other NIH institutes and federal agencies (Appendix 2: Roster) served as *ex officio* members to learn from the discussions and to answer questions as needed.

The working groups presented their findings at a public meeting on October 26 and 27, 2022, which provided opportunities for public input on the priorities. The meeting was free and open to the public. Registration for the workshop was through https://als-strategic-plan.com/, and the workshop was videocast and archived at https://videocast.nih.gov/. After the meeting, the steering committee and working groups were able to modify the research priorities to reflect the public input. The research priorities were posted online for public comment before their presentation to National Advisory Neurological Disorders and Stroke Council for approval.

Summary and Vision of ALS Research and Care

This strategic plan describes the strategic steering committee's and the working group members' vision for what is needed to solve current challenges surrounding ALS research and treatment, with the ultimate goal of providing new therapies, and hopefully cures, for ALS. In addition to contributions from the working group members, this plan also integrated comments and suggestions posted by the public either during the workshop or via comments on the draft made available online before and after the public workshop. The top three recommendations from each working group are shown summarized in ***Table 1*** and are described in greater detail below. Presented here is a brief outline of the major priorities that the members of the five working groups put forward. The summary below indicates that there are overlapping recommendations which rose to the top.

One top priority is to enhance understanding of basic biological properties that underlie motor neuron degradation in ALS. There is wide consensus that we must do more to understand the cellular and molecular events ***that underlie sporadic ALS***, which represents ~85% of all cases. In this pursuit, it will be important to dissect multiple mechanisms that explain clinical ***heterogeneity*** in both familial and sporadic ALS. It will also be compelling to ***define novel factors, including genetic, that enhance both the risk of ALS and, in other instances, improve resilience to the disease.*** Finally, ALS researchers need to uncover and ***implement emerging and innovative technologies*** and initiate collaborations across scientific disciplines to identify new disease pathways and/or to revisit known existing ideas with constructive new approaches.

A second priority is implementing measures to facilitate the translation of newly discovered disease pathways into clinical trials and therapeutic development at ALS clinics throughout the United States. Toward this end, it is recommended that the NIH create ***ALS Centers of Excellence*** with appropriately selected sets of expertise to coordinate and implement the translational research efforts. These represent a ***centralized and standardized infrastructure*** that improves access to critical care, high quality clinical research data, samples from people living with ALS, and other resources to optimize trial development. While these Centers were deemed critical, the ALS community stressed that the creation of these Centers shall not undermine the importance to providing accessibility to the services for rural communities, which otherwise will be left behind. There was a suggestion to model this effort based on the previous successes in the field of pediatric oncology. There, the community created a 'cooperative group' composed of oncology programs from around the country. This 'ALS Cooperative Group' could then serve as a resource to all ALS clinics including those with limited resources to e.g., use newer technologies such as virtual appointments and telehealth to address currently existing geographic challenges. Finally, it is recommended that these Centers facilitate collaboration with industry at early stages of therapeutic discovery. Efforts must be made to overcome impediments (e.g., intellectual property issues) in order to yield ***productive public-private partnerships***.

Fortunately, biomedical research has benefitted in recent years from new concepts in the design and operation of clinical trials. The third focus considered in this strategic plan is capitalizing on these exciting advances to optimize design and performance of ALS trials. One cornerstone in this effort is to develop a better definition of ***the natural history of ALS,*** encompassing the full disease spectrum from preclinical, at-risk individuals through late-stage disease, with the mandatory inclusion of phenotypically, genetic, socioeconomic, and racially/ethnic diverse group of participants. From this, a corollary effort should involve development of ***new, sensitive biomarkers as well as improved outcome measures***. Optimized trial methodologies must also address the ***challenge of heterogeneity***, both in clinical status and in genetic stratification. There is growing agreement in the ALS community that early treatment intervention is desirable; toward this end, another high priority is better knowledge of the early signs of disease, permitting new opportunities to ***identify and treat people at risk***.

In line with this strategic plan's focus on people affected by ALS, current gaps in how we perform research to ***improve the quality of life of people living with ALS and their caregivers*** was addressed as the fourth major area for consideration. For this, we need to ***better understand how quality of life is defined, how it can be improved and how we can successfully implement these efforts, specifically regarding symptom management*** (such as pain control and respiratory involvement), function including mobility and communication, and access to education and resources for people living with ALS and their caregivers.

Finally, the fifth focus area corresponded to the unanimous view that the above priorities will be expedited by more ***collaborations and partnerships between all stakeholders, including people living with ALS, caregivers, people with genetic risk of ALS, researchers, clinicians, and industry partners.*** One approach is to organize the ***collection and distribution of patient data, biofluids and biospecimens, along with multimodal data, to be shared by other federal and state agencies, academic laboratories, and industry.*** It is already evident that such agency-academic-industrial collaborations bring complementary resources to ALS investigations. Also recognized was the value of a different kind of repository, a virtual warehouse that ***collects and***

shares research relevant tools, protocols, and other experimental resources. It was emphasized that recent transformational methods in artificial intelligence might powerfully interrogate and interpret huge compendia of information collected in this way, enabling better modeling of systems and themes in each of the focus areas: disease pathogenesis, clinical progression, or new modes of clinical trials.

Table 1: Recommended Priorities as presented by the working groups

Accelerating Research on ALS Biology

1. Dissect causes of sporadic ALS to identify therapies across diverse ancestries
2. Define molecular basis of heterogeneity in familial and sporadic ALS
3. Employ new technologies for ALS research

From Research to Therapy

1. Establish ALS Centers of Excellence to support ALS translational research
2. Enhance infrastructure for biosample and data acquisition and storage
3. Enable trials and foster industry/academic collaboration

Optimizing Clinical Research

1. Define ALS natural history across clinical spectrums from pre-symptomatic stages through disease
2. Develop more powerful assessments of treatment across the disease spectrum (pre-symptomatic to late stage) within diverse sets of participants
3. Define earliest manifestations of ALS

Optimizing ALS Quality of Life

1. Improve understanding of how physical, psychological, cognitive, and behavioral symptoms impact QOL to facilitate and implement the development of pharmacological and non-pharmacological management approaches
2. Optimize function
3. Identify evidence-based best practices and resources for ALS care

Improving Collaborative Partnerships

1. Establish multi-modal data platform including multidimensional clinical and non-clinical information; define standards for data structure and sharing, enable use of AI to define subgroups of ALS
2. Develop platform (repository) of research tools, protocols, and resources
3. Establish framework for ALS research collaboration across academia, government, industry, and organizations for people affected by ALS

STRATEGIC PLAN PRIORITIES DEFINED BY THE INDIVIDUAL WORKING GROUPS

Accelerating Research on the Biology Behind ALS

Non-technical Summary

Understanding what is happening in cells to cause ALS is crucial for developing therapies tailored to different forms of the condition. Advances in human genetics have led to insights on the causes of familial ALS. These discoveries have opened opportunities for creating animal and cell-based models of genetic forms of the disease, and these can be used for laboratory experiments to better understand ALS and identify potential therapies. In contrast, our understanding of what happens in sporadic ALS, remains limited. Because of this gap, a top priority is to learn from studies in people with sporadic ALS to guide research in animal and cell-based models, which until now have always been based on genetic forms of ALS.

The initial manifestations of ALS can vary. The disease might start with walking or swallowing difficulties, progress rapidly or slowly, start when the person is young or old, or might be associated with changes in thinking. This variability even happens in people with the same genetic cause A second priority is therefore to understand why there is such variability, and what makes some people relatively resistant to ALS while others are not, including what determines why and when someone will convert from pre-symptomatic to symptomatic ALS. A third priority is to encourage the use of new technologies from other fields of research through collaborations and training to expand ALS researchers' areas of expertise.

Introduction

Understanding the molecular and cellular mechanisms leading to ALS is crucial for the development of therapeutic approaches tailored to different forms of ALS. Advances in human genetics have provided major insights on the molecular causes of familial ALS and have opened opportunities for modeling genetic forms of the disease. In contrast, our understanding of the mechanisms leading to non-familial, sporadic ALS remains limited. Hence, a major priority for the field is to develop clinically informed basic research aimed at defining the molecular pathways of all forms of ALS across ancestries, and to develop preclinical model systems that encompass diverse mechanisms of sporadic ALS. A second priority is to determine the molecular basis underlying clinical heterogeneity by investigating the mechanisms leading to ALS versus FTD and determine the factors that confer resilience to disease or lead to conversion from pre-symptomatic to symptomatic ALS. A third priority is to encourage the adoption of emerging technologies from other fields through multidisciplinary collaborations and training efforts to expand ALS researchers' areas of expertise.

Priorities for Accelerating Research on the Biology behind ALS

1. Unlock sporadic ALS to identify new therapeutic targets across ancestries.

In this priority we emphasize the urgent need to characterize the molecular and cellular events occurring in ALS forms for which no genetic cause is identified. We note that the widely used

term of "sporadic ALS" means the absence of a family history but does not exclude a genetic cause of the disease. It will be crucial to determine whether disease subgroups resulting from distinct mechanisms can be identified and to generate cellular and animal models that would enable the development of new therapeutic targets to benefit the vast majority of people living with ALS. Better characterization and modeling of TDP43 disruption is crucial since it represents a common denominator in the vast majority of ALS. The field should also determine whether yet un-identified mechanisms underly non-familial, sporadic ALS. ***To achieve this unlocking of sporadic ALS, we propose four approaches:***

i. *Clinically informed basic research to define molecular pathways of all forms of ALS and to determine if subgroups can be defined through unique or converging mechanisms*

Classifying ALS into subgroups will be crucial for the targeted application of potential therapies but remains a challenge. Indeed, the definition of different forms of sporadic ALS based on distinct molecular mechanisms leading to neurodegeneration would allow the identification of new candidate therapeutic targets and the development of approaches tailored to specific ALS forms. To identify unique and converging mechanisms, close collaboration between basic and clinical researchers should be prioritized, and the integration of clinical features to the interpretation of mechanistic studies should be further developed. Clinical endophenotypes, longitudinal data matched to biospecimens, multimodal questionnaire and geospatial data should be harnessed. Epidemiological and similar approaches, exploring the exposome of both endogenous and exogenous risk factors should be pursued. Such data can then be used to understand the relationship between molecular pathways, phenotypic and molecular subgroups, and disease mechanisms, which may be unique to a subgroup or converge from more than one.

ii. *Develop infrastructure for multimodal datasets that enables interoperability across data*

Collection of phenotypic, clinical, epidemiological and omics data, requires accessible, affordable, user-friendly data infrastructure that protects confidentiality, has clear lines of responsibility and ownership, but is consistent with a harmonized open data architecture. Such an infrastructure would greatly accelerate ALS research by allowing interoperability across datasets and improving access to researchers who might not otherwise contribute to the field. Recognizing that ALS and FTD are overlapping clinical disorders that, in many cases represent one pathobiological disease, it is important to prioritize the collection of rich datasets that include longitudinal clinical assessment of motor, behavioral and cognitive functions and are consistent across countries with inter-operability at a global scale. To achieve this harmonization rather than standardization of data, major efforts are necessary to share methodologies and develop a central repository for protocols and a common data dictionary while maintaining flexibility to allow local practices. Quality control is critical and should be at the core of all data collection.

iii. *Perform studies across ancestries and under-represented groups*

Nearly all current knowledge of ALS is based on data from people of European ancestry, with emerging data from people of East Asian ancestry. We therefore lack knowledge of ALS in multiple ancestries and under-represented groups, despite the significant insights this is likely to provide, both because of comparisons between such groups and because

of statistical techniques that leverage ancestral differences. It is essential therefore that initiatives prioritize ALS studies in all ancestries and groups, including under-represented groups.

iv. *Develop model systems that encompass diverse mechanisms of sporadic ALS*

Understanding the mechanistic relationship between familial and sporadic ALS is key to designing accurate models and faithfully translating lessons from these models into therapeutic gains. Current practice is to assume that a genetic model based on familial ALS is generalizable to all ALS, but this should be challenged. There are currently difficulties in reverse translating from clinical observation to laboratory models of ALS where no large effect genetic cause has been identified. There is therefore an unmet need to develop model systems for sporadic ALS that are predictive of the human disease. Emerging repositories of cells from individuals with sporadic ALS should be harnessed to generate human cell-type specific models of the disease. It is also important to recognize the limitation of any model and to encourage studies integrating multiple models across species. Notably, TDP43 represents a target that is central in most forms of familial and sporadic ALS, highlighting an example of shared biology between sporadic and genetic forms of the disease. While numerous models of TDP43 proteinopathy have been developed, innovative approaches avoiding an overexpression paradigm should be prioritized. In addition, modeling downstream targets of TDP43 that are emerging as contributors of disease may provide crucial platforms for therapeutic development.

2. Understand the molecular mechanisms underlying clinical heterogeneity in ALS.

Both familial and sporadic ALS are characterized by a tremendous clinical heterogeneity with important disparities in the age and site of onset, the rate of progression, and the presence or absence of a cognitive deficit. Even individuals harboring the same genetic mutation may convert from pre-symptomatic to symptomatic stages at widely different ages. Some gene carriers may even be completely resilient to disease, defining the incomplete penetrance of mutations as observed for the hexanucleotide expansion in the *C9orf72* gene. Understanding the molecular and cellular mechanisms underlying clinical heterogeneity may inform the development of therapeutic approaches and should be prioritized. ***To achieve this understanding, we propose addressing the following questions:***

i. *What are the molecular and cellular mechanisms leading to ALS as opposed to FTD when risk factors are shared?*

Genetic risk factors such as hexanucleotide repeat expansion in the *C9orf72* gene can lead to ALS or FTD or both. Since a central mystery in neurodegenerative diseases is the cell-type specific nature, an understanding of how the different clinical phenotypes arise is likely to be of great importance in understanding disease mechanisms and the development of new therapies. As with sporadic ALS, harnessing large datasets and samples from biorepositories that include both ALS and FTD may provide crucial insights on the mechanisms of clinical heterogeneity. There is also a need to expand research efforts to better understand and monitor the contribution of cortical neurons including upper motor neurons and other circuits affected in ALS and FTD.

What are the resilience factors and mechanisms underlying incomplete and age-dependent penetrance of genetic forms of ALS?

Deep analyses of samples from individuals with resilience to a fast progression of disease or complete resilience to a genetic form of ALS may uncover molecular pathways that confer resistance to neurodegeneration and would represent attractive therapeutic targets.

ii. *What molecular mechanisms underly conversion from the pre-symptomatic stage to ALS?*

An understanding of why ALS has a delayed onset when a gene mutation is carried and expressed from birth will help prevent ALS in gene carriers and may allow therapies in individuals with sporadic ALS. It is important to uncover the molecular and cellular events precipitating the emergence of symptoms and to determine whether monitoring such events may accurately predict conversion. Broad analyses of samples collected from clinical studies in pre-symptomatic gene carriers will be crucial to achieve this goal. In addition, researchers should leverage animal models as pre-symptomatic tools to explore biomarker trajectories.

iii. *What are the modifiable genetic and environmental risk factors, including epigenetic factors and those influencing genomic instability?*

Studies grounded in human-based epidemiology studies with the collection of samples from people living with ALS as well as their family members are needed to identify genetic and environmental risk factors. Molecular factors that may modulate the pathogenicity of a mutation such as epigenetic changes and factors influencing genomic instability should also be investigated.

3. Harness emerging technologies to uncover new disease mechanisms of ALS.

ALS researchers should embrace technological advances from other fields to generate new hypotheses and revisit older concepts. ***To harness emerging technologies, we propose two main strategies:***

i. *Adopt emerging technologies to identify new pathways and revisit older concepts*

Emerging technologies and ideas from any other fields (molecular and cellular biology, neuroscience, imaging, biophysics...) should be implemented by ALS researchers to discover new disease mechanisms. For example, state-of-the-art genetic screens, spatial transcriptomics, or new imaging technologies may uncover unanticipated pathways. In addition, it may be helpful to revisit older concepts that may have been abandoned prematurely but might be useful given parallel advances in detection hardware, computing, machine learning and artificial intelligence.

ii. *Facilitate effective collaboration and training to expand expertise in the ALS field*

Implementation of new technologies is vital but requires expertise from other disciplines. Indeed, adoption of any new technology means that, by definition, most people will have no experience, and a few will have very limited knowledge. Collaboration is needed to bring the expertise into ALS research, and training is essential to embed it in a new

generation of researchers. Dissemination of the expertise, sharing of resources and protocols, and educational activities such as workshops should be encouraged to enable broad use of emerging approaches. Funding strategies should emphasize the importance of building teams with individuals from various disciplines and broad perspectives.

Translating Fundamental Research into Potential ALS Therapies

Non-technical Summary

Translating advances in understanding the fundamental biology behind ALS into new therapies will require a coordinated approach that includes sustained NIH support for collaborative research, centralized resources for sharing biological samples (such as blood or tissue) and clinical data, and robust and open collaboration with industry and nonprofit partners. The first priority is to establish "Centers of Excellence" that support collaborative research to identify new targets for future ALS drugs and core facilities to oversee collection of tissue, fluid, and genetic information. The second priority is to establish large-scale repositories for biological samples and clinical data from people living with ALS. These samples and data would be broadly available to academic and industry researchers to facilitate the development of therapies that are tailored to individuals. Finally, the third priority is to encourage industry investment in ALS therapy development by supporting early development of therapeutics for novel targets, developing effective and efficient clinical endpoints for ALS trials, and funding clinical testing of novel therapeutics.

Introduction

To accelerate the translation of fundamental research into effective ALS therapeutics, there are some key areas where additional investments could have a major impact. Fundamentally, the field needs to continue to build a comprehensive molecular understanding of the underlying pathophysiology of ALS, out of which will come prioritized ALS targets. Translating this understanding into potential therapeutics will require long-term investment to ensure resources and information are durable and maintained at scale to enable multiple stakeholders to gain insight. Learnings from efforts in related neurodegenerative disorders will allow this to be accomplished quickly in ALS.

As in these related cases, success in ALS requires sustained support, particularly in infrastructure development and execution, led by an evergreen organization with mission alignment to ALS. NIH fits this bill and has executed as a leader and convener for similar efforts in other areas. With NIH leadership, public/private partnership should be prioritized and leveraged to unify the ALS field and amplify resources, drawing on the relative strengths of industry and academic investigators to enable progress that benefits ALS patients and families. A fundamental principle is that access to all data, samples, and other resources should be equally available to researchers in academia and industry as it will take both groups working together to successfully translate fundamental research into therapeutics.

Therefore, it is important for the NIH to facilitate collaboration between industry and academia by encouraging greater access by researchers in the biotech/pharma sector to public resources, and the sharing of data from industry-sponsored trials with the broad ALS research community.

Draft Priorities for Translating Fundamental Research into Potential Therapies

1. Establish a network of ALS Centers of Excellence to support ALS translational research.

In other neurodegenerative diseases, the NIH has established **Centers of Excellence** programs to translate research advances into promising therapies while also immediately improving patient care. These include the NIA-funded Alzheimer's Disease Research Centers (ADRCs), the NINDS-funded Morris K. Udall Centers of Excellence in Parkinson's Disease Research, and the Paul D. Wellstone Muscular Dystrophy Specialized Research Centers (MDSRCs). In each case, these centers of excellence work together to foster collaboration, support research in basic science, develop sample and data repositories, engage and support the patient community, and support clinical trials. Establishment of a network of ALS Centers of Excellence will provide a foundation upon which coordinated research can be conducted at scale. These centers will also accelerate and enhance existing efforts for providing access to data, patient samples, and other patient resources.

Proposal: Establish a **Centers of Excellence Program in ALS Research** as a key step in developing a translational research infrastructure for ALS. These Centers should collaborate with NIH resources/programs for related neurodegenerative diseases so as to (1) take advantage of existing structures and experience to quickly establish an ALS program, and (2) integrate data among disorders to identify common underlying biology, breaking down silos that currently exist. Working from the various available models, ALS Centers of Excellence will each have their own area of emphasis, but will be organized as a network of interactive/collaborative sites that comprise:

- A Program Project Core to study basic (genetic, molecular, cellular) mechanisms underlying the pathogenesis of ALS and related disorders, including FTD. Building on the strengths of each center, the program will support team-based, interdisciplinary research projects to elucidate disease mechanisms, identify key pathways and therapeutic targets, and to develop strategies to alter the disease course in ALS patients with and without causal mutations.

- A Clinical Core to oversee ALS biofluid/tissue collection with deep clinical phenotyping at each ALS Center of Excellence, drawing on the well-established ALS multi-disciplinary ALS care clinics at each site serving a large and diverse ALS patient population. These Centers will be nodes of a larger network of ALS programs providing longitudinal, ALS biofluid and tissue samples to a centralized/organized ALS biorepository along with demographic, clinical and other data for the purpose of biomarker development and the elucidation of disease mechanisms to enable novel therapeutic discovery (see Priority 2). The Clinical Core would also enhance the clinical trial infrastructure of each Center, providing administrative support for interventional trials, including expanded access and research programs involving investigational therapeutics.

- A Genetic Core to provide comprehensive genetic characterization of all ALS research participants, including predictive testing to individuals from ALS families at risk as carriers of pathogenic mutations.

- An Administrative Core at each Center to support the overall management of the Center and provide the leadership necessary to achieve the goals of the program, ensure operational efficiency and relatedness among the individual Cores. Responsibilities of the Administrative Core will include organizing and directing regular meetings, overseeing diversity and inclusion programs, community outreach and education initiatives for ALS patients and families. In addition, the Administrative Core will collaborate with the clinical, data and biomarker cores to ensure the timely disbursement of data and biospecimens to academic and clinical ALS investigators.

2. Enhance and expand ALS biosample and data infrastructure.

The most significant advances in the field of ALS over the last 30 years have come from the identification of pathogenic mutations in a large number of genes that cause motor neuron disease and FTD. From the elucidation of the complex genetics of ALS have come insights into disease mechanisms and pathways that have enabled rational drug development efforts in ALS based on a growing understanding of the biology of the disease. Because of the availability of experimental models of familial/genetic forms of ALS, these relatively rare forms of the disease have been a major focus of study in the field, and the most promising of ALS therapies are gene-based approaches, possibly relevant only to a small minority of ALS patients. This approach is justified by the common biology of the disease suggested by the shared clinical phenotype and pathology of familial and sporadic forms of ALS. However, there remains a critical need in ALS to bridge the divide between forms of disease with and without causal genetic mutations, and to identify markers and mechanisms that distinguish various subtypes of ALS across the broad spectrum of ALS-FTD.

Key to this challenge is to establish **large-scale repositories of ALS biofluid and tissue samples** from clinically well-characterized patients, collected longitudinally from diagnosis (or earlier) through the late stages of disease, and including postmortem samples. As important as the collection, storage, and distribution of biosamples is to ALS research, it is equally critical to establish a **centralized and standardized infrastructure to store and share integrated individual-level data** from diverse sources, including clinical trials, longitudinal observational studies, patient registries and real-world data (e.g., electronic health records). It is also critical that such resources are supported by stable and sustained funding. The ALS Centers of Excellence described in Priority I will be excellent sources for many of the samples and data for such repositories.

Proposal: In conjunction with the ALS Centers of Excellence proposed in Priority I, sustained support should be provided to create and maintain large-scale repositories of ALS biofluid and tissue samples, and it is recommended that existing infrastructure for related diseases be leveraged to maximize the usefulness of these resources. There are many great examples of resources that could be leveraged for such repositories. Examples include the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), NINDS Human Cell and Data Repository (NHCDR), The Accelerating Medicines Partnership (AMP) program (e.g., AMP-PD), the Answer ALS iPSC cell line collection, and Target ALS cores. It is essential that access to the repositories be available, on like terms, for both academic and industry investigators, enabled by appropriately broad consent, and that there be sharing and collaboration across diseases. As these samples will be a limited resource, sharing of data from

studies that come out of using these resources should be encouraged, utilizing sharing platforms that exist for other areas (e.g., the Terra Platform at the Broad Institute or the Alzheimer's Disease Data Initiative (ADDI). These platforms could also house clinical data generated within the ALS Centers of Excellence and beyond. In addition to tissue and biofluids, the Clinical Cores within the ALS Centers of Excellence could provide specialized resources made broadly available to academic and industry-based ALS investigators, including induced pluripotent stem cell (iPSC) generation, custom antibody production, cellular models (e.g., fibroblast, peripheral blood mononuclear cells), and a genetics database.

3. Increase the biotherapeutic pipeline by enabling clinical trials and fostering academic/industry collaboration.

The establishment of safe and effective therapeutics for ALS will require several key phases of support by the NIH. While much of the actual drug development can be supported by industry, there is much that an organization like the NIH can do to enable faster and more efficient clinical trials. Federal support to validate novel targets and show feasibility of novel therapeutic approaches and demonstrate potential for clinically meaningful impact is needed to de-risk programs sufficiently for industry investment. Encouraging industry involvement at earlier stages of therapeutic development would also be helpful and efforts must be made to overcome impediments (e.g., intellectual property issues) to productive public-private partnership. These efforts will also be supported by the proposals in Priorities 1 and 2.

Proposal: Sustained investment in the following three priority areas would help to catalyze biotherapeutic development.

- Early development of therapeutics for novel targets: Central to the advancement of new biotherapeutics for ALS is the strategic investment of new therapeutic strategies for novel targets, concepts, and treatment modalities that have the highest likelihood for impacting ALS. Antisense oligonucleotides, RNAi-based gene silencing methods, genome editing and transcriptome editing technologies, cell therapy-based methods, antibody- or antibody-like-based biologics, and small molecule therapeutics are all promising approaches for neurodegenerative disorders including ALS. The application and optimization of these and any emerging modalities for existing and novel ALS targets is of the upmost importance. Support for the validation and initial characterization of a modality against an existing or novel target for ALS would be extremely impactful and could be supported by NIH programs dedicated to early stage translational research, including the Innovation Grants to Nurture Initial Translational Efforts (IGNITE) Program and SBIR/STTR funding for small US biotech companies.

- Development of effective and efficient clinical endpoints for ALS trials: The ALS Centers of Excellence and the biorepositories created from and within them will provide invaluable resources for generating information on markers of disease progression that will be essential for developing both diagnostic and theragnostic biomarkers. Investment in the development of markers as enrollment criteria, clinical endpoints, and specific theragnostic markers will significantly enable all researchers seeking to develop a novel therapeutic. In addition, the development of strategies for overcoming the genetic heterogeneity characteristic of familial ALS and overall disease heterogeneity would be enabled by further biomarker work.

- Clinical trial support: Support for clinical testing of novel therapeutics within the proposed Centers of Excellence Program will significantly leverage the investment in the infrastructure and expertise of these centers. These Centers would have investigators advancing therapeutics against a single or multiple targets, providing an element of synergy that would benefit drug development. Furthermore, active engagement of the ALS community as well as the resources and novel methods to measure outcomes could be significantly leveraged by industry partners seeking to advance the development of a novel therapeutic.

For all these efforts, data sharing will be key to enabling the entire ALS research community and will also potentially foster valuable collaboration between academia and industry.

Optimizing ALS Clinical Research

Non-technical Summary/Introduction

The symptoms, age of disease onset, speed of progression, and underlying genetic and environmental causes vary widely among people living with ALS. Understanding this variability and designing clinical trials that account for this variability among people will be crucial for identifying therapies to effectively prevent, slow, or stop all forms of ALS. The first priority for optimizing clinical research for ALS is to conduct studies in which researchers record and measure various aspects of the disease, including pulmonary function, but do not test a therapy (also called natural history studies) to improve our knowledge of how the disease initiates and progresses over time in diverse individuals living with and at risk for ALS. These studies should measure how symptoms change over the course of the disease and seek to identify biomarkers (objective measures such as a blood test, pulmonary function tests or a brain image, that will improve diagnosis, monitor disease status, and facilitate developing therapies for ALS that are tailored to the individual). The second priority is to effectively use clinical trial resources through innovative clinical trial designs, improving how disease progression is assessed, developing methods for considering the variability between people, engaging a diverse group of clinical trial participants, and openly sharing data and resources. The third priority is to improve our understanding of the earliest stages of the disease so that treatments can be developed to slow or stop ALS early in the disease process, perhaps even before symptoms appear.

Draft Priorities for Optimizing ALS Clinical Research

1. Define the natural history of ALS from the at risk, pre-symptomatic, and disease states.

An in depth understanding of ALS across its complex pathogenesis is necessary to inform its natural history during complex stages including at risk, pre-symptomatic, and disease. Such knowledge will facilitate recognizing the earliest manifestations of ALS, developing more sensitive and specific diagnostic tools and biomarkers, and identifying new disease outcome measures. This important knowledge will provide insights into the biological basis of ALS and aid in planning more innovative clinical trials that can be implemented in earlier disease stages. All the above will accelerate the identification of new disease modifying therapies and prevention efforts. While the NIH and other organizations currently support small, focused natural history studies, these small studies are insufficient to address the unmet scientific needs for ALS community. In addition, access to participation and access to the data is limited.

In **Table 2** below, we outline strategies to ensure the effectiveness of such a study.

Table 2. **Principles for a large, comprehensive ALS natural history study**	
Category	**Criteria**
Study Design	Given the need for an acceleration in ALS advancements, retrospective studies of those with ALS, with or without a control population, are needed to continue hypothesis generating research. In parallel, additional emphasis should be placed on funding prospective cohorts for those with increased disease susceptibility--either due to a genetic mutation, family history, or other exposures and environmental and lifestyle factors—and those at all spectrums of ALS—including pre-symptomatic and symptomatic. Opportunities for data integration with other large cohort studies is recognized as an important opportunity as well.
Inclusion criteria	Individuals at risk of, pre-symptomatic with, or with ALS. Pre-symptomatic studies will likely require very large cohort studies of the general population to identify those at risk for sporadic disease.
Access	These studies must be inclusive, enabling enrollment of all individuals with ALS regardless of age, sex, race/ethnicity/gender, primary language, or cognitive status. Additionally, expanding clinical research sites involved in such studies not only improves geographic access, but also helps to engage and train the next generation of clinical researchers.
Content	Any subset of the following: past medical history, medical history including genetic data, digital data, biomarkers (fluid or otherwise) and other (both standard and novel outcome measures), risk factors, environmental exposures
Data Sharing	Follow NIH new guidelines
Governance	Should include a Team Management Plan recognizing contributions from early investigators and community partners. Should have a plan for valuing diverse perspectives and include those impacted with ALS in the planning of the study.

2. Efficiently use all resources (participants, data, infrastructure, etc.) for clinical trials in individuals living with ALS and those at risk of developing ALS to provide more informative and powerful assessments of treatment response within a diverse group of participants.

Priorities in clinical trial methodology highlight a more efficient use of all resources within ALS (participants, data, infrastructure, etc.) to provide more informative and powerful assessments of treatment response within a phenotypically, genetic, socioeconomic, and racially/ethnic diverse

group of participants. This includes the identification of better outcome measures across the entire disease spectrum, broader clinical trial enrollment (including early symptomatic and pre-symptomatic), identification of factors explaining disease heterogeneity, as well as inclusion of diverse populations, and more generally, innovative clinical trials. New methods and approaches to include participants from rural communities or from diverse ethnic populations are imperative to increase clinical trial participation and representation across ethnic groups.

Making the most efficient use of patient resources for clinical trials starts with the development of better outcome measures that span the entire disease spectrum including the investigation of preclinical measures. Such measures might include pharmacodynamic and disease related biomarkers, as well as improved measures of disease state, function, and quality of life. This includes, but is not limited to, measures of all symptoms that occur in ALS, including speech, swallowing, breathing function, limb strength and cognition. The FDA framework for the development of biomarkers should be used as a point of reference. While the revised ALS functional rating scale (ALSFRS-R) is an accepted outcome of disease progression, its use is limited to individuals with clinical ALS, focuses only on motor manifestations of the disease, and cannot distinguish between disease progression in the central nervous system vs spinal and bulbar motor neurons. Several limitations to its sensitivity to detect meaningful clinical changes have been identified. It is also far more sensitive to changes in the extremities than bulbar or respiratory progression. Thus, new measures are required to evaluate the spectrum from pre-symptomatic to late-stage disease. Identification of measures that are more sensitive to progression at earlier or later stages of the disease would allow for the inclusion of participants within clinical trials across a wider range of disease stages. Disease progression models that differentially assess those at different stages of disease might allow for broadly inclusive designs that employ different outcome measures depending on disease burden. Novel models of ALS disease progression that utilize multiple measurement approaches (clinical, biomarker, radiological) in individuals at different stages of disease to identify common and separate disease trajectories and develop progression indexes for use as outcomes in clinical trials are needed.

To address heterogeneity, a disease progression approach can be used to "situate" ALS patients (according to case severity) within a universe of trajectories and develop the methods for analyzing these longitudinal data together. This approach would facilitate the description of common and distinct trajectories and the development of outcome measures based on these trajectories, such as disease progression scores.

The inclusion of a broader range of ALS participants within clinical trials will also help to address heterogeneity in disease manifestations and potential heterogeneity in treatment effects. This approach may lead to insights into the causes of this heterogeneity and links to the value of natural history studies to identify such heterogeneity. As was hypothesized in other neurodegenerative diseases, treatments given early in the disease course or pre-symptomatically may provide better outcomes. Understanding how to best include early symptomatic or pre-symptomatic populations within clinical trials will allow for this hypothesis to be tested. FDA approved medications for symptomatic ALS should be considered for testing in pre-symptomatic population. In addition, specifically including those who are later in their disease course offers opportunities to identify classes of therapies that might not otherwise be recognized.

More generally, innovations within clinical trial designs should be considered that include sharing of information across multiple sources and platforms (ex. sharing within a single study across regimens in a master protocol, or use of information from outside the trial via access to EMR data, use of wearable and other digital data sources, and other approaches), frequent updates based on accumulating data with trial adaptations, and more powerful and robust analysis methods. These innovations may result in clinical trials that are more efficient and have more statistical power. There may be many approaches to improve and accelerate how therapies are developed and it is critical to encourage and allow multiple approaches. Given the added complexities often associated with new trial innovations, design choices must be guided by evidenced-based clinical trial simulation and developed in close collaboration with all involved parties including sponsors, regulatory agencies, patient advisory groups and trial investigators. It is important to include specialists from many areas who have knowledge and interest in the many facets of ALS. Development of an innovative clinical trial requires investment and time upfront to make these evidence-based decisions and to get approval of an often-unfamiliar approach from a diverse set of stakeholders. This development should be guided by extensive data collection in natural history studies and historical patient-level databases and development of disease progression models.

3. Improve our understanding of the earliest manifestations of ALS.

ALS involves both neuronal and non-neuronal cells, and pathologic changes are not restricted to the motor system. Further, ALS shows genetic overlap with other non-motor diseases, such as FTD. Determining how to detect the earliest manifestations of ALS and whether they are confined to the motor system is important for identifying individuals early in disease when treatments may be most effective. Currently, people are diagnosed approximately 12 months after first symptom onset, meaning that we are intervening with treatments late in the disease process. It is also critical to understand these early changes to be able to conceive of and run studies to prevent or delay symptomatic onset. We recommend detailed studies in two broadly defined groups:

a. At-risk due to genetics
    i. Monogenic carriers
    ii. Those with a family history, but no identified genetic cause
b. At-risk due to environmental, lifestyle, and other clinical exposures

To understand what happens biologically and clinically in the years and decades before clinical diagnosis of ALS, it is critical to study people at the highest risk for developing ALS. These are people with known monogenic genes associated with ALS, such as mutations in *SOD1* or *C9orf72* and others. These types of studies have been done in other neurodegenerative disorders and yielded great insights into disease biology and natural history data crucial for designing and running prevention trials. For example, studies in people at high risk for Alzheimer's disease have informed imaging and fluid biomarker changes that start decades prior to overt clinical symptoms. This has led already to trials earlier in the illness. Studies of people at high risk for Parkinson's disease have provided information about changes in skin, the retina and in sleep patterns prior to overt clinical signs. It is critical to take a similar approach in ALS.

We currently have very little knowledge of what the earliest changes are with the exception of work by Dr. Michael Benatar and colleagues in SOD1 ALS who showed increased in neurofilament levels approximately a year prior to clinical symptoms, and work coming from the ARTFL-LEFFTDS Longitudinal FTD (ALLFTD) initiative. Discoveries in this high-risk population will likely yield critical insights also in the biology that happens in people with the non-monogenic forms of ALS and allow earlier diagnosis and intervention.

To understand the earliest changes in people with sporadic disease will take more creative, novel approaches using big data sets and analytics. Even incremental improvements leading to earlier diagnosis could lead to earlier use of disease modifying treatments, all predicted to improve long-term patient outcomes. In parallel, it would also decrease unnecessary testing and procedures, physician visits and stress associated with delayed diagnosis. There are some large datasets that follow people without disease for long periods of time (Framingham Heart Study, Physicians' and Nurses' Health Study, etc.) where some number of people have developed ALS. These provide an opportunity to go back in time to look at changes in blood, CSF, or medical history. There are some countries that have very detailed health care records that might yield important information. Examples of potential creative approaches for studying sporadic ALS include 1) leveraging existing large prospective longitudinal datasets for ALS cases, especially those with banked samples, 2) examining cases/controls in large datasets such as insurance databases or Medicare, 3) leveraging data available in Veteran's Affairs system and the Department of Defense, if feasible, and 4) other creative records review, digital app approaches, etc.

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Optimizing the Quality of Life of People Living with ALS and Their Caregivers

Non-technical Summary

Given the widespread effects of ALS on physical function, mental health, and cognitive/behavioral function, quality of life (QOL) becomes a critical concern for people living with ALS and their caregivers. In developing a strategic plan for research directed at optimizing QOL, responses to a request for information were reviewed and three areas identified as recurring themes: 1) symptom management; 2) optimizing activities of daily living, particularly communication and mobility; and 3) education, including both the development of resources and the identification and sharing of existing resources. Through these themes, this working group recognized that health disparities exist in ALS that directly impact QOL. A critical element of each priority is to foster research that reduces those health disparities and thus contributes to the best possible QOL for people living with ALS and their caregivers. These priorities are considered equally crucial.

Introduction

QOL depends on several factors, including symptoms and function, which can overlap. A person's ability to participate in activities serves as a guide to function, while the level of impairment can be considered a symptom. Importantly, QOL is determined by factors much broader than physical symptoms and physical function. Psychological and existential factors, as well as emotional support, all play major roles. Further, it is critically important to recognize that QOL for people living with ALS is often underestimated by others and should be assessed by people living with ALS themselves. For those people living with ALS who maintain high QOL over time, factors critical to QOL evolve from those based on physical function (for example, exercise, travel, sports) to existential matters and those that provide support (such as interpersonal interactions and appreciating the beauty of their surroundings).

Environmental, cultural, and personal factors affect QOL, highlighting the need for an inclusive and equitable research approach to optimizing QOL. By utilizing a health equity lens, it is critical that evidence-based resources are identified and accessible across diverse constituent backgrounds, especially for historically underrepresented and underserved ALS populations.

QOL metrics specific for ALS exist but there is lack of data and an absence of agreement regarding the optimal instruments and the settings in which they should be used. Health-related QOL measures reflect health status and are relatively tightly coupled to physical function. Global QOL assessments, in contrast, are relatively independent of physical function, and more reliant on psychological, existential, and support factors. Additionally, there are generic as well as ALS-specific QOL instruments within each of these two categories. Every study in which QOL is used as an outcome measure should define QOL as precisely as possible so that the most appropriate instrument(s) can be chosen.

Draft Priorities for Optimizing the Quality of Life of People Living with ALS and Their Caregivers

1. Improve our understanding of how physical, psychological, cognitive, and behavioral symptoms impact QOL in people living with ALS and their caregivers to facilitate the development of meaningful pharmacological and non-pharmacological management approaches. These include not only traditional approaches (approved prescription drug, counseling, respiratory care, cognitive-behavioral therapy, etc.), but also assistive technologies with machine learning/artificial intelligence capabilities, and complementary and alternative therapies.

Physical symptoms are diverse and may be widespread or localized. People living with ALS have identified a number of key areas of concern as impacting their QOL, including, but not limited to, fatigue, pain, mobility limitations, poor sleep quality, respiratory dysfunction, and loss of motor speech. Research on instruments for assessing these symptoms, assessing risk of complications such as falls and pneumonias, preventative measures, and pharmacological and non-pharmacological interventions for treatment should be pursued. Respiratory function is of particular importance because of the benefits of noninvasive ventilation in improving survival and QOL. Research is needed on identifying best practices for monitoring respiratory function, initiating device use, and optimal respiratory management. Interdisciplinary collaboration between neurologists, allied health care professionals, and pulmonary medicine specialists is essential.

Psychological symptoms impact QOL in people living with ALS. Gaps in the assessment and management of the mental health of people living with ALS should be explored, including access to care. Pharmacological and non-pharmacological management strategies should be evaluated. Mental health care should be initiated early in disease and should include caregivers as well as children and youth in the family.

At least 50% of people living with ALS demonstrate cognitive and/or behavioral dysfunction. Best practices for the type and frequency of cognitive and behavioral screening are needed. Equally or even more important are guidelines for management since the behavioral and cognitive symptoms of FTD can affect the implementation of standard care guidelines in ALS.

Advance care planning and end-of-life care need further research. Many people living with ALS have concerns about specific end-of-life symptoms such as choking, pain, dyspnea, and psychological concerns such as helplessness/dependency and burden to caregivers. Studies of those factors that people living with ALS consider most important for maintaining QOL at the end of life and guidelines for administering end-of-life care to people living with ALS are needed. Adequate training in end-of-life care for neurologists specializing in ALS is lacking and would be a valuable area of research development.

Finally, suboptimal symptom management impacts QOL not only of people living with ALS, but of their caregivers and family members, including children. Furthering the science of systematic assessment and management of caregiver distress and burden, with the goal of optimizing caregiver QOL, is a pressing need.

2. Identify interventions that promote maximal function and daily participation through adaptation during the course of neurodegeneration. Functional needs include mobility, environmental control, context-dependent communication (both face-to-face and remote speech and writing), and all activities of daily living.

Research related to function is needed in the areas of needs assessment, interventions including durable medical equipment (DME) development and evaluation, and new innovative measurements all guided by input from the ALS community (i.e., people living with ALS, caregivers, family members, physicians, therapists, DME manufacturers and representatives, rehabilitation engineers and those who are integral to people living with ALS). Proposed interventions should be based on needs assessment, which should include continuous monitoring of needs and environments (i.e., wearable technologies). DME development and testing should leverage current technologies that are available to the general public (i.e., smart home technologies), as well as design specific interventions (i.e., brain-computer interfaces) that extend function in novel ways.

In the case of new emerging technology or DME research and development, three fundamental datasets acquired over time with use should be considered and included – user performance, device performance, and adaptation and customization through machine learning. This latter is important as functional capabilities will change over the course of the disease. Furthermore, as part of the goal of maximizing function, resultant reduction of caregiver responsibilities must be considered.

For all research directed at improvement of function there need to be measurement of the effect. Outcome metrics should include QOL, ease of use, flexibility including automatic adaptation and customization, and the short- and long-term effectiveness of the intervention as applicable. Patient-reported outcome measures are critical to assessing these outcomes and should be part of all outcome assessments.

3. Identify evidence-based best practices and resources for the care of people living with ALS by caregivers (including youth), people living with ALS themselves, clinicians, allied health professionals, and researchers.

Access to education and resources about ALS is currently not equitably available to all those impacted by ALS. Improving access to best practices will contribute to optimizing the QOL of people living with ALS and their caregivers. This will be achieved by compiling and equitably disseminating proven best practices and resources for people living with ALS themselves, caregivers, family members (including youth), at risk individuals carrying genetic mutations, clinicians, allied health professionals, and researchers.

The compiled information should address all aspects of care for people living with ALS and those who carry genetic mutations within affected families. For example, some of the best practices may involve multidisciplinary care by health care providers (e.g., sharing information across the spectrum of disease care from a prompt initial diagnosis to end-of-life care) and others may be specific for individuals living with ALS and caregivers (e.g., nutrition and personal home care practices). There is an unmet need for consistent and accessible information relevant to both health care providers and people living with ALS (e.g., how to access telehealth, how to identify specialty ALS multidisciplinary care centers, and how to recruit for and participate in

research studies). Additionally, information should be made available about ALS genetics to those with familial ALS and to at-risk relatives and pre-symptomatic mutation carriers.

The compilation should be assembled through systematic and inclusive review to ensure health equity for all affected groups. Resources for medical professionals should be directed at both specialist and non-specialist physicians given that non-specialists are the entry point for most people into the health-care system. Resources for people living with ALS and caregivers should be accessible, inclusive, and equitable to all people living with ALS, especially for those communities that have been historically underrepresented: (1) rural; (2) English as a second Language; (3) non-male; (4) younger; and (5) Black, Indigenous, People of Color (BIPOC). The information should be updated regularly with ongoing assistance in navigating the educational resources available. Resources, suggestions, and best practices should clarify what social, cultural, racial-ethnic, or economic barriers may exist when accessing and using the resource. A diverse group of people impacted by ALS should be engaged in the development of the compilation thus improving the depth and breadth of effective patient care, reducing the inequities in access to diagnosis, treatment, and participation in research, and facilitating broad representation in ALS research databases.

Progress in this priority will be bolstered by the National Academies of Science, Engineering, and Medicine (NASEM) study commissioned by NIH to recommend actions for the public, private, and nonprofit sectors to make ALS a livable disease within a decade. NASEM should assess the range and types of care and services needed to optimize the QOL, health, and well-being of those affected by ALS. Towards this aim, NASEM should address the need for such an educational resource as described above.

Identifying Opportunities for Collaborations and Partnerships

Non-technical Summary/Introduction

Over the past decade, there has been dramatic progress in accelerating ALS research into clinical trials, in stark contrast to the prior 140 years since the disease was discovered. That progress occurred on three dimensions – bringing new investigators and technologies into the field; new discoveries of the genetic and biological pathways that cause motor neurons to die; and engagement on the part of the biotech and pharmaceutical industries. Much of that was catalyzed by increased public and private funding focused on ALS along with a greater degree of collaboration and effective partnerships among all the constituencies that are necessary to bring effective treatments to patients, including academia, industry, venture capital, ALS non-profits, clinicians, patients, and government. The ALS community is now at a critical juncture in ALS research. There is a growing consensus among all parties that over the next ten years one could see viable therapies that will extend, if not save, lives and that ten years from now we could look forward and see the day when every person with ALS's life will be saved. Nevertheless, it is imperative that we keep in mind the urgent needs of people living with ALS and the ALS community when decisions are made, and prioritization are set.

The goal of the Collaborations and Partnerships Working Group of the NIH ALS Strategic Plan is to identify the most important potential synergies across governmental and non-governmental organizations and to leverage shared resources to accelerate translation of ideas from the lab to the clinic and care models. Input from the ALS community highlighted urgency, access, and coordination of research efforts as the highest areas of priority for partnerships and collaboration. With that in mind this working group has highlighted three priority areas: (1) Standardized approaches to expanding collection and use of data and biosamples; (2) Providing accessible tools and resources to the research community; (3) Developing a framework for ALS research collaboration through public-private partnerships.

Our working group also supports the development of information and education for the entire ALS community with the goals of increased and equitable access to best practices in ALS clinical care as well as diversification of population in ALS research databases. There is a need for greater collaboration with research communities focused on other neurodegenerative disorders to bring new ideas and new people into the field.

Draft Priorities for Identifying Opportunities for Collaborations and Partnerships

1. Establish multi-modal data platform to include multi-dimensional clinical data (including longitudinal respiratory data, genomes, imaging, biofluids, biospecimen, blood repository, induced pluri-potential stem cells) with a focus on aggregating available data sets and defining standards for future data collection that will promote open data sharing, ensure diversity, equity, and inclusion, and enable application of AI and machine learning to discover the sub-groups that comprise ALS.

The past 10 years have brought tremendous advancements in human genome sequencing, exponential computing power, enhanced big data storage capabilities, artificial intelligence and machine learning, and the ability to create patient derived induced pluripotent stem cells (iPSCs)

differentiated to motor neurons, among other major breakthroughs. Collection of additional novel data types, such as novel digital data reflecting clinical status, can continue this positive trend of discovery.

The goal of this priority will be to systematically capture a large reservoir of data and biological samples to enable the application of AI and machine learning to discover the sub-groups that comprise ALS, and, therefore, identify targeted treatments. The federated system for multi-modal data would include multi-point clinical data, genomes, imaging, biofluids, biospecimen, blood repository, iPSCs, etc. Key to success are common data elements (CDE), standardized consent on data collected prospectively and retrospectively, common data standards for emerging data types, and a consistent process for data collection at clinics with an emphasis on diversification of the population in research databases. The next steps for this priority should include identification of data elements to be captured, benchmarking of existing data elements, and creation of data-sharing mechanisms. The NIH should require all NIH-funded bio sample and data generation initiatives to submit to this shared data platform and should provide dataset creation/collection guidelines and resources across studies.

2. Develop a platform (repository) of research tools, protocols, and resources to interrogate the disease (e.g., biological materials, reagents, animal models, antibodies, molecular constructs, viral vectors) including descriptors of associated data, in order to accelerate ALS research and to identify gaps related to diversity, equity and inclusion representation to be prioritized for future scientific efforts.

Critical to developing potential targets for ALS is lowering the barriers to entry for researchers who may not have engaged in ALS research as well as investigators, from both industry and academia, who have research underway. One major opportunity is to have research tools and resources for the research community that are easily accessible at low cost. A lack of awareness about the tools and resources, as well as inefficient processes in place to access them, contribute to low usage across the research community. Another contributor is a lack of standardization of protocols and methodologies to create/collect and use research tools and resources. With the development of cloud-based data platforms that enable integration of diverse information and easy access worldwide, it is conceivable to centralize information on available research tools and resources, protocols for their generation, methodologies for use, associated datasets and a process to access them, ensuring availability for all researchers and help avoid duplication of efforts.

Formation of a committee that includes representation from academia, industry, nonprofits and government funding agencies and people living with ALS would focus on the goals of this priority to integrate research tools and resources from diverse categories (biosamples, animal models, antibodies etc.) along with associated protocols and methodologies for their generation and use. Additional effort will identify gaps in the suite of tools and resources available and compare the quality of data generated from use of research tools (especially in cases where multiple versions of the same tool are available).

Key future steps include creating consensus on specifications for the proposed open-source, centralized platform and considerations for access that allow investigators to fully retain rights to the data and intellectual property generated from use of information on the centralized platform.

Policy that requires all NIH funded efforts to load historical and new information and outreach to encourage foundations and industry to share information to the platform will significantly improve these shared resources.

3. Establish a framework for ALS research collaboration across academic, industry, government and organizations for people affected by ALS that will ensure all ongoing and future collaborative efforts emphasize diversity, equity, and inclusion with a goal to accelerate research and authorization for effective treatments.

Despite a substantial research and development investment for ALS including several independent large-scale collaborations, advances in our understanding of disease pathogenesis have not yet translated into safe and effective treatments. There is a need to better coordinate how the academic, biopharmaceutical, and government sectors that participate in ALS research and therapy development generate, share, and use knowledge to propel development of critically needed therapies. This is especially important in a rare disease like ALS and especially for patients that are often not as well represented in research such as minority groups and patients in peripheral sites with limited ALS clinics.

Incentivizing ALS research stakeholders to coordinate work across all stages of evolution of a target, from discovery to validation and development will focus efforts and accelerate translation of ideas from the lab to the clinic to people with ALS. A comprehensive collaborative framework for ALS requires planning and resources to be effective, as well as clear goals and objectives, timeframes, and metrics to measure the effectiveness of such a collaboration. One such partnership recently launched by FDA and NIH, the Critical Path for Rare Neurodegenerative Diseases (CP-RND), will bring together experts across rare neurodegenerative diseases with a focus on identifying novel strategies and approaches to therapy development and clinical testing. Another model, the Accelerating Medicines Partnership (AMP) Program, is an example of a public-private partnership between NIH, FDA, multiple biopharmaceutical and life science companies, and nonprofit organizations that enables rapid sharing of data and analytical tools through the centralized data infrastructure managed by NIH.

The goal of this priority is for NIH to serve as a natural home for better coordination and building on successful ongoing partnerships by integrating both individual research efforts and existing collaborations such as Target ALS (which funds collaborative consortia as well as multiple core scientific tools and resources), Robert Packard Center, Answer ALS (longitudinal clinical, genetic, biofluids, induced pluripotential stem cells, multi-omics) and Everything ALS (early diagnosis).

The next steps for this priority should include a review from ongoing AMP programs and independent ALS collaborations about learnings related to improving overall impact and speed, as well as the current state of resources and specific research questions best addressed by such frameworks. Key topics could include a detailed evaluation of regulatory issues regarding sharing patient data/biologicals across institutions and industry and consideration of mechanisms to support and encourage additional data sharing by smaller data sources as well as by patients, to increase participation and inclusiveness, while maintaining data standards. Potential specific areas for collaboration (identified in other sections of this document) could include assistive technologies, home-based outcome measures, new patient reported outcomes and functional

scales, diagnostics, and biomarkers. Leveraging NIH funded biosample and data generation initiatives to add novel data and samples, involvement of "big data" partners to develop needed tools and algorithms, and the development of a comprehensive research landscape will also be important.

APPENDICES

Appendix 1: Summary of Responses to Request for Information (RFI): Soliciting Input on Research Priorities for ALS

To gather broad input from people living with ALS, people who are at genetic risk of developing ALS, families, caregivers, advocates, scientists, clinicians, and the broader community, the NINDS issued a Request for Information (RFI) (NOT-NS-22-056) that was open to all members of the public from January 4, 2022 to February 11, 2022. There were 312 total responses, from people living with ALS, caregivers, people with genetic risk for ALS, ALS advocates, academic/non-profit researchers, healthcare providers, industry representatives, and other interested parties. Complete RFI responses and this summary will assist and facilitate the ALS Strategic Planning Working Group discussions and help identify the highest priorities for research that could lead to the discovery of effective interventions for the diagnosis, treatment, management, prevention, or cure of ALS.

The below summary includes the most commonly mentioned topics and responses. Not all the topics or suggestions listed in this summary fall within the mission of NINDS or lie within the scope of the ALS Strategic Planning process. However, they were included in this summary because these are the issues that were commonly cited as important to the ALS community.

Among the diverse 312 responses representing people living with ALS, caregivers, people with genetic risk for ALS, ALS advocates, academic/non-profit researchers, healthcare providers, industry representatives, and other interested parties, **urgency and access were the most pertinent and unifying factors**. With respect to urgency, respondents conveyed frustration with delayed and/or misdiagnoses. With respect to access, respondents often cited lack of ability to participate in clinical trials as well an inability to access certain medications and treatments. Related to both urgency and access, many respondents, people living with ALS and caregivers in particular, mentioned accelerated drug approvals and increased funding for development of new treatments. In particular, respondents stressed the importance of therapeutics that slow the progression of disease as well as reverse disease symptoms and tissue damage. Additional topics included development of new genetic models; identification of biomarkers; longitudinal studies; natural history studies; reevaluation of clinical endpoints; standardization of care, practices, and diagnostics; and data/resource sharing.

Summary of Responses by Topic

Increased Accessibility of Clinical Trials. Respondents often cited the lack of access to clinical trials in certain geographic locations such as rural communities with limited clinics and healthcare centers. Several respondents suggested increasing the number and reach of clinical trials through the creation of an inclusive and expansive network. Respondents requested greater equity in patient participation in clinical trials, noting that socioeconomic status should not limit access to these resources. Respondents also urged broader eligibility criteria so people with more advanced disease can participate in clinical trials. Additionally, many respondents would like improved communication and education for people living with ALS and caregivers on how to identify and participate in clinical trials. Lastly, many respondents called for an increase in funding to support accessibility to clinical trials.

New Therapeutics. Many respondents urged the development of new therapeutics that slow progression, reverse damage and symptoms, or prevent disease. A wide variety of approaches such as stem cells, pharmacological agents, gene therapy, immunotherapy, and novel drug delivery technologies such as focused ultrasound were suggested as new therapeutics. To reverse damage and symptoms, a few respondents suggested focusing on therapeutics that facilitate regrowth or reactivation of affected motor neurons. Similarly, some respondents asked for the development of therapeutics that promote blood-brain-barrier repair. To slow progression of disease symptoms, a few respondents called for therapies that help preserve the integrity and function of axons, pericytes, and neuromuscular as well as neurovascular junctions. In a few cases, comments advocated for combinatorial therapeutic approaches in treatment of people living with ALS as well for use in clinical trials.

Accelerated Approvals. To facilitate therapy development, many respondents emphasized the need to accelerate approval of new therapies. Several respondents noted specific therapies that they would like to see approved such as NurOwn or PrimeC.

Non-Traditional Therapies. A few respondents asked for better guidance on how to navigate available non-traditional therapies such as herbal remedies, vitamins, and other supplements. Additionally, these respondents asked for more research to be carried out to identify which types of non-traditional therapies might provide the best outcomes.

Quality of Life. Many respondents called for improved symptom management for people living with ALS and support for managing everyday life, including new symptomatic treatments and new or improved assistive technologies or devices. The ability to communicate was frequently cited as a critical issue for people living with ALS, and many respondents urged for the development of assistive technologies to aid communication, such as brain-computer interfaces or improved speech-to-text software. Respondents also identified the need for technologies to improve breathing and swallowing. There was a call for financial support for the many technologies and house modifications necessary for a person living with ALS to maintain as much independence and dignity as possible. Some suggested that financial support to people living with ALS and caregivers of people living with ALS should be mediated through increased funding to ALS foundations. Others called for the development of a comprehensive resource guide for people living with ALS, caregivers of people living with ALS, families, social workers, and healthcare providers to direct them to services such as voice banking, advocacy groups, clinical trial registrations, and comprehensive scientific information in plain language. A few respondents noted a lack of hospice care for military veterans, even though veterans are at an increased risk of developing ALS.

People with Genetic Risk for ALS. Many respondents highlighted the need to increase research on those with pre-manifest ALS, those with a family history of ALS or known gene mutations but no current symptoms. Specifically, respondents called for longitudinal studies of this population involving repeated biomarker sampling throughout the entire disease course, facilitated by remote sample collection and non-invasive or less invasive biomarker development. Respondents urged for proactive data sharing across all familial ALS studies via the use of globally unique identifiers. With a better understanding of disease trajectory, respondents noted, pre-symptomatic therapeutics can and should be developed to treat pre-manifest ALS before symptom onset to prevent ALS.

Clinical Trial Design. Many respondents called for patient-centric clinical trial designs (PaCTD), often citing the PaCTD rating criteria established by I AM ALS (see here). To summarize, PaCTD means that access to investigational therapies is broad (open-label extension, expanded access, minimized placebo usage), disease heterogeneity is considered, eligibility criteria are scientifically justified, one or more biomarkers are investigated, interim efficacy is considered by an independent, unblinded review panel, travel burden is reduced, and a run-in observation period is included. In addition to calling for PaCTD, respondents highlighted the need for clinical endpoints beyond the revised ALS functional rating scale (ALSFRS-R), which was described as subjective and limited. Suggestions for endpoints included biomarkers, data from digital technology (e.g., wearable devices) and other remote monitoring tools, patient-reported outcomes, and an updated functional scale. Respondents urged the development of patient stratification tools to better identify populations of participants who respond to the clinical intervention. Some respondents proposed the use of basket trials, a type of clinical trial design that tests a treatment in people who have the same underlying disease mechanisms (e.g., disease causing mutation or molecular alteration) but who may have different clinical diagnoses. In addition, platform trial designs were proposed to allow more patients access to therapies. Specifically, several respondents cited the Healey ALS Platform Trial as a well-designed, patient-centric clinical trial to be used as an example for clinical trial design going forward. Finally, many respondents called for clinical trial recruitment to focus more heavily on including diverse communities of color and women. [See **Increased Accessibility of Clinical Trials**]

Data and Data Sharing. Many respondents cited the need to create a better system for data sharing and standardization to drive ALS research forward. These comments included calls for gathering more comprehensive data including multiple "omes" (multi-omics) such as the genome, proteome (proteins), microbiome (microbes living in a person's digestive system and on their skin) to help identify potential known and unknown causes of ALS. These data as well as environmental, and/or lifestyle information can then be shared between researchers, institutes, and clinical centers. A few respondents advocated for data-sharing to be a required component of funded research grants and to build off existing common data elements already in use at the NIH. In conjunction, many of these comments also advocated for a registry to connect researchers to people living with ALS and to capture data from these individuals. Respondents suggested supporting grant programs to promote the use of currently available databases and to conduct validation studies for targets that were identified using shared data resources.

Collaboration/Synergy. Several respondents called for increased collaboration between federal agencies, academic institutions, medical centers, non-profits, and the private sector. Several responses made calls for greater research consortia that bring together clinicians, people living with ALS, and scientists with wide-ranging expertise and familiarity with ALS. Responses often cited the need for increased communication lines, shared resources, and decreased redundancy of efforts. A few respondents also called for the creation of grants at every level (e.g., R01s, P01s, U01s) that incorporate more industry partners.

Natural History. Many respondents called for a comprehensive natural history study for people living with ALS and genetic mutation carriers aimed at collecting real-world clinical and genetic data. Respondents noted that natural history studies should be fully accessible and should not only target those people living with ALS enrolled in clinical trials. As part of this effort, respondents urged widespread whole genome sequencing (WGS) for people living with ALS and

those at risk to be analyzed by the research community and widely distributed. In addition to WGS, a few respondents called for multi-omics research to be included in the study, along with tissue sampling through a pre- and post-mortem biorepository. Respondents noted that the data generated through the natural history study could identify genetic, environmental, and lifestyle factors that impact disease onset and progression, distinguish between those who progress quickly and slowly in the disease course, and further define subsets within the heterogenous population of those living with ALS. A better understanding of the ALS disease course and heterogeneity will be a key resource in guiding effective therapeutic development.

Epidemiology. Many respondents pointed out the lack of knowledge surrounding causes of ALS beyond known genetic predispositions. Several respondents specifically called attention to the higher incidence of ALS among veterans and called for greater investigation of this correlation. Many of these comments also included calls to broadly investigate environmental and/or risk factors that might predispose individuals to ALS. Some factors mentioned by a few respondents included trauma/injury, shingles, Lyme's disease, nutrition, and viral and bacterial infections. Related to comments regarding collaboration [see **Collaboration/Synergy**], many comments suggested that partnerships between the NIH and different federal agencies like the EPA, OSHA, and the ATSDR can help to explore ALS clusters (such as geographic areas with unusually high prevalence of ALS) identified by the ALS community.

Biomarkers. Many respondents emphasized the need to identify new biomarkers (measurable indicators of a condition, such as neuroimaging tests, quantitative muscle function tests, or tests for specific proteins in blood, urine, sweat or cerebrospinal fluid) for enhanced diagnostics and assessment of disease prognosis. This includes establishing biomarkers that allow for early detection of neurological symptoms and rapid intervention. Respondents stressed the need to identify a variety of biomarkers that capture the variability in disease progression within different people living with ALS as well as at different time points. Respondents often suggested that diverse biomarkers could help to determine the mechanisms driving disease progression in a case-by-case basis manner and could be used to determine suitability of treatments and participation in clinical trials. Additionally, the need for less invasive biomarkers that do not involve cerebral spinal fluid or blood samples was often mentioned. Some respondents advocated for development of novel technologies that could facilitate wearable devices that detect digital biomarkers. In several instances, respondents suggested that more accurate and real-time digital markers could replace outdated rating scales for disability progression such as the Revised ALS Functional Rating Scale (ALSFRS-R) or other clinical endpoints. Wearable devices were suggested as a more proactive approach to tracking and treatment of disease, enabling robust metrics between visits with healthcare professionals. Lastly, a few respondents suggested that identification of new biomarkers could serve to codify "types" of ALS, correlating unique markers to specific symptoms and time points in disease progression. A combinatorial approach could also be employed in this process (e.g., combining $p75^{ECD}$, a urinary protein biomarker, and miR-181/neurofilament light chain levels in blood and cerebrospinal fluid) for detection of ALS in early stages.

Diagnosis. A majority of respondents shared their frustrations regarding their difficulties with receiving a timely and accurate diagnosis. Related to development of better biomarkers, many respondents want better tools and assessments available for the earliest possible diagnosis and

intervention strategy. The ALSFRS-R was regarded in numerous occasions as being outdated, unreliable, and too subjective for accurate and effective therapy efficacy.

Causes and Basic Biological/Genetic Mechanisms. Many respondents called for research investments in identifying the underlying biological and genetic mechanisms of ALS. Often, comments highlighted heterogeneity in disease progression and the need to pursue understanding in a variety of potential biological and genetic causes. Specifically, respondents asked for greater research emphasis to be placed on the following areas:

- Molecules and cellular processes that involved in gene expression and are altered in ALS, including RNA processing, RNA trafficking, RNA-binding proteins, such as TDP43, and abnormal aggregates of these proteins.
- Extracellular matrix proteins (proteins outside of cells such as collagen that provide structure to tissue) involved in preserving the integrity of nerve fibers.
- Glial cell (non-neuronal support cells) function and glia-neuronal communication.
- Innate immunity and the role of astrocytes and microglia, which are types of immune cells in the brain.

Related to comments regarding data sharing [see **Data and Data Sharing section**], respondents called for greater efforts for multi-omic analysis. A few respondents also called for research investigating causes of juvenile ALS and ALS onset in people under the age of 40.

Research Resources. Many respondents discussed the need to enhance research tools and resources for understanding ALS disease progression and accelerating discoveries. In particular, comments included calls for new genetic models beyond those widely used today such as SOD1 mutants. These models were often mentioned as being insufficient for capturing the range of disease heterogeneity in ALS. A few respondents suggested investing in a panel of ALS-specific induced pluripotential stem cells for multi-omic pathway analyses. This approach could accelerate identification of biomarkers, and creation of new genetic models. A few respondents also mentioned investing in recapitulating ALS using advanced 3D models of human brain architectures. Lasty, a couple respondents included comments on creation of grants to support biobanking activities such as longitudinal collection of human samples pre and post disease onset.

ALS Knowledge Base and Education. A majority of responses stressed the importance and lack of ALS knowledge across a wide range of groups including neurologists, nurses, caretakers, palliative care physicians, and people living with ALS. Many respondents suggested that inaccurate or delayed diagnoses could be due to lack of ALS knowledge by neurologists. Many respondents also mentioned they often felt alone in having to understand the disease and to determine what strategies and best practices they should begin incorporating into their lives once diagnosed. Clinical trial knowledge was often cited within these comments as well. People living with ALS want the best updated information on current clinical trials, and many stated that physicians often lacked this information. This sentiment was similarly expressed by people living with ALS with reference to caregivers of people living with ALS, nurses, and palliative care facilities.

Healthcare Costs. Many respondents highlighted the issues surrounding cost of healthcare. The associated costs for insurance, therapies, and logistics associated with treatment and participation in clinical trials were cited as major barriers to quality care. Cost was often listed as a driver of inequities in access to care for people living with ALS. Many respondents mentioned they do not have the financial resources to access distant clinics, caretaker centers, or to afford certain treatments.

Caregiver Resources Respondents stressed the emotional and financial burden placed on caregivers of people living with ALS. Many called for investing in caregiver support and funding research to address the significant effect on mental health. Further, several respondents cited the damaging financial ramifications of acting as an ALS caregiver or paying for care, which can be particularly detrimental for low-income families [see Healthcare Costs section]. Respondents stressed that innovative care models need to be developed to deliver care more efficiently and effectively with options for home health and multidisciplinary care. Many respondents noted that facilitating transportation to and from healthcare visits places a heavy burden on people living with ALS and their caregivers, and proposed travel to and from clinical care sites be provided. Additionally, respondents called for education and training for caregivers, including family caregivers, hospice personnel, and nurses.

Appendix 2: Rosters

For full biographies, see https://als-strategic-plan.com/speakers/.

Steering Committee of the NINDS Council Working Group on Establishing a Strategic Plan for the ALS Research Community
Robert Brown, Jr., DPhil, MD (Co-chair)
Rita Sattler, PhD (Co-chair)
Aaron Gitler, PhD
Layne Oliff, PharmD
Ellyn Phillips
Christine Torborg, PhD (Designated Federal Official)

Accelerating Research on the Biology Behind ALS
Clotilde Lagier-Tourenne, MD, PhD (Co-chair)
Ammar Al-Chalabi, MB, ChB, PhD (Co-chair)
Sami Barmada, MD, PhD
Sali Farhan, PhD
Myriam Heiman, PhD
Piera Pasinelli, PhD
Leonard Petrucelli, PhD
Hemali Phatnani, PhD
Cooper Penner, BS (MD, PhD student)
Michael Ward, MD, PhD
Amelie Gubitz, PhD (Facilitator)

Translating Fundamental Research into Potential ALS Therapies
Neil Shneider, MD, PhD
Stacie Weninger, PhD
Frank Bennett, PhD
Thomas Gaj, PhD
Joe Lewcock, PhD
Stefan McDonough, PhD
Nadia Sethi, DDS
James Wilson, MD, PhD
Henrik Zetterberg, MD, PhD
Emily Caporello, PhD (Facilitator)

Optimizing ALS Clinical Research
Merit Cudkowicz, MD (Co-chair)
Tim Miller, MD, PhD (Co-Chair)
Alberto Ascherio, MD, DrPH
Robert Bowser, PhD
Christina Fournier, MD
Stephen Goutman, MD
Chiadi Onyike, MD
Gwen Petersen
Melanie Quintana, PhD
Jeremy Shefner, MD, PhD
Christine Torborg, PhD (Facilitator)

Optimizing the Quality of Life of People Living with ALS and Caregivers
Terry Heiman-Patterson, MD (Co-Chair)
Jean Swidler, BA (Co-Chair)
Jinsy Andrews, MD, MSc
Chelsey Carter, PhD, MP.H.
Melanie Fried-Oken, PhD
Steve Kowalski
Emily Plowman, PhD
Zachary Simmons, MD
Jane Hettinger, PhD (Facilitator)

Identifying Opportunities for Collaborations and Partnerships
Lisa Gold, PhD (Co-chair)
Dan Doctoroff, JD (Co-chair)
Andrea Pauls Backman, MBA
Allison Bulat, BA
Kuldip Dave, PhD
Sharon Hesterlee, PhD
Ed Rapp, BS, BA
John Ravits, MD
Jeff Rothstein, MD, PhD
Neta Zach, PhD
Robyn Bent, RN, MS (*ex officio, FDA)*
Carlo Quintanilla, PhD (Facilitator)
Samantha White, PhD (Facilitator)

Federal Participants (ex officio)

National Institutes of Heath

Note: See Appendix: ALS Program Officials at NIH for more information.

Emily Carifi, PhD
Emily Caporello, PhD
Rebekah Corlew, PhD
Amelie Gubitz, PhD
Jane Hettinger, PhD
Jonathan Hollander, PhD
Cristina Kapustij, MS
Enrique Michelotti, PhD
Van Nguyen, PhD
Lisa Opanashuk, PhD
Carlo Quintanilla, PhD
Lana Shekim, PhD
Coryse St. Hillaire-Clarke, PhD
Tiina Urv, PhD
Samantha White, PhD

U.S. Food and Drug Administration

Michelle Adams, MPH
Teresa Buracchio, MD
Michelle Campbell, PhD
Billy Dunn, MD
Elizabeth Hillebrenner, MS
Diane Maloney, JD
Michelle Tarver, MD, PhD
Bryan Wilson, MD
Celia Witten, MD, PhD

Centers for Disease Control and Prevention

Paul Mehta, MD

Department of Defense

Kristy Lidie, PhD

Appendix 3: ALS Program Officials at NIH

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Emily Carifi, PhD
Program Director
Muscle Development and Physiology Program
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National Institute of Environmental Health Sciences (NIEHS)

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National Institute of Mental Health (NIMH)

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Appendix 4: NINDS programs relevant to the ALS Strategic Plan priorities

Below are NINDS programs and resources that can be accessed by ALS researchers to address priorities in the ALS Strategic Plan. NINDS encourages any researchers interested in submitting grant applications to contact ALS Program Officials at NIH (for list of names, see Appendix: ALS Program Officials at NIH). They can help identify the most appropriate program or funding opportunity and can help navigate the application submission process.

The **NINDS Division of Neuroscience (DON)** supports research aimed at understanding fundamental mechanisms of development, structure and function of the nervous system in health and disease. More about research funded by DON can be found at https://www.ninds.nih.gov/current-research/research-funded-ninds/neuroscience-research. DON utilizes a variety of grant mechanisms to support this research. A complete list of grant mechanisms can be found at https://www.ninds.nih.gov/funding/about-funding/ninds-grant-mechanisms. Among these grant mechanisms, the **NINDS Interdisciplinary Team Science RM1** encourages interdisciplinary teams of experts that seek to cross technical and conceptual boundaries through collaboration to achieve ambitious goals for basic, translational, and clinical research questions within the mission of NINDS, see https://www.ninds.nih.gov/funding/about-funding/ninds-grant-mechanisms/ninds-interdisciplinary-team-science-grant-rm1-clinical-trial-optional.

The **NINDS Division of Translational Research (DTR)** provides funding and through grants, cooperative agreements, and contracts to academic and industry researchers to advance early-stage neurological technologies, devices, and therapeutic programs to industry adoption (i.e., investor funding and corporate partnerships). More information about translational research programs, resources, and funding opportunities can be found at https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research.

Most programs offered by DTR welcome applications focused on ALS research, including the following:

- The **Ultra-rare Gene-based Therapy (URGenT) program** will support the development of state-of-the-art gene-based therapies for ultra-rare neurological diseases, including familial forms of ALS. More information about the program and current funding opportunities can be found at https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research/ultra-rare-gene-based-therapy-urgent-network.

- The **NINDS Biomarker Program** 1) promotes rigorous biomarker identification and validation through milestone-driven funding opportunities, 2) maintains an updated website containing information about existing NINDS and NIH biomarker sample and data repository resources and 3) facilitates the development of future resources focused on bridging the gaps in the biomarker development pipeline. More information about the program and current funding opportunities can be found at https://www.ninds.nih.gov/current-research/focus-tools-topics/focus-biomarkers-research. In addition, the **Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases** program of NINDS DON supports studies to develop clinically validated biomarkers and clinical outcome assessment measures appropriate for use in

upcoming clinical trials, see https://grants.nih.gov/grants/guide/pa-files/PAR-22-184.html.

- The **NINDS Small Business Program** is committed to helping small business concerns commercialize their technologies through its grant funding, technical assistance program participation, and outreach at meetings. More information about the program and current funding opportunities can be found at https://www.ninds.nih.gov/funding/small-business-grants.

- The **NINDS Office of Neural Exposome and Toxicology Research (ONETOX)** supports research and provides resources to advance knowledge of internal and external exposures that affect brain and nervous system health (Neural Exposome), leads research related to chemical threats, and provides resources that promote chemical safety, see https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research/office-neural-exposome-and-toxicology-research.

The **NINDS Division of Clinical Research (DCR)** provides oversight for clinical trials to test the safety and efficacy of innovative treatments of neurological disorders and stroke, epidemiological studies of natural history, biomarker studies, and studies designed to elucidate the causes of neurological disorders. The Division of Clinical Research also develops new clinical science initiatives, ensures the proper level of patient safety monitoring, maintains the scientific integrity of clinical trials, and provides expertise in statistics and clinical trial design to the Institute and to clinical investigators. More information about clinical research policies, resources, and funding opportunities can be found at https://www.ninds.nih.gov/current-research/research-funded-ninds/clinical-research.

The **NINDS Human Cell and Data Repository** includes fibroblasts and/or induced pluripotent stem cells (iPSC) for ALS, FTD, Alzheimer's Disease, Ataxia-telangiectasia, Huntington's Disease, Parkinson's Disease, and healthy controls. Cell sources, including isogenic cell lines for current and new diseases covered by the NINDS are continuing to be added. More information about available cell lines and how to order cell lines can be found at https://nindsgenetics.org/. The **iPSC Neurodegenerative Disease Initiative (iNDI)** of the **NIH Intramural Center for Alzheimer's and Related Dementias (CARD)** is building a repository of genetically engineered cellular models of Alzheimer's and related dementias, including FTD/ALS, see https://card.nih.gov/research-programs/ipsc-neurodegenerative-disease-initiative.

The **NIH Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative** is accelerating the development and application of innovative technologies to enable researchers to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. Long desired by researchers seeking new ways to treat, cure, and even prevent brain disorders, this picture will fill major gaps in our current knowledge and provide unprecedented opportunities for exploring exactly how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought. More information about the NIH BRAIN Initiative and current funding opportunities can be found at https://braininitiative.nih.gov/.