Summary of Responses to Request for Information (RFI): Soliciting Input on Research Priorities for Amyotrophic Lateral Sclerosis (ALS)

To gather broad input from people living with amyotrophic lateral sclerosis (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 persons with ALS, caregivers of persons with ALS, premanifest gene carriers, 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 persons with ALS, caregivers of persons with ALS, healthcare providers, researchers, and ALS advocates, **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, persons with ALS and caregivers of persons with ALS 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 persons with ALS and caregivers of persons with ALS 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 for development of 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 persons 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 persons 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 persons 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 with ALS to maintain as much independence and dignity as possible. Some suggested that financial support to persons with ALS and caregivers of persons with ALS should be mediated through increased funding to ALS foundations. Others called for the development of a comprehensive resource guide for persons with ALS, caregivers of persons 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, despite the fact that veterans are at an increased risk of developing ALS.

Premanifest ALS. Many respondents highlighted the need to increase research on those with pre-manifest ALS, those carriers of genetic risk factors with a family history of ALS 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), etc 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 persons 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, persons 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 persons 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 persons with ALS enrolled in clinical trials. As part of this effort, respondents urged widespread whole genome sequencing (WGS) for persons 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 section**], 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 persons 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, such as leveraging $p75^{ECD}$, a urinary protein biomarker, and miR-181/NfLs, a blood-based biomarker, for a method of 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 TDP-43, 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 iPS 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 persons 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. persons 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 persons with ALS with reference to caregivers of persons 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 persons 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 persons 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 persons with ALS and caregivers of persons with ALS, 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.