MILKEN INSTITUTE
CENTER FOR STRATEGIC PHILANTHROPY

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Amyotrophic Lateral Sclerosis (ALS)

A GIVING SMARTER GUIDE

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ABOUT US

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank focused on accelerating measurable progress on the path to a meaningful life. With a focus on financial, physical, mental, and environmental health, we bring together the best ideas and innovative resourcing to develop blueprints for tackling some of our most critical global issues through the lens of what's pressing now and what's coming next.

About the Center for Strategic Philanthropy

The Milken Institute Center for Strategic Philanthropy advises philanthropists and foundations seeking to develop and implement transformative giving strategies.

FOREWORD

We first heard about ALS when our father received his diagnosis. Like any family, we immediately put our energy into finding the best doctors and researchers, seeking silver linings and potential treatments. It didn't take long to learn that ALS is a devastating disease. Patients are robbed of their mobility, their voice, and their lives in only a few short years. We found more questions than answers.

What gave us hope, amidst one of the most difficult times in our lives, was a remarkable community of people and organizations—researchers, clinicians, health-care workers, academic institutions, and nonprofits—passionately working to make things better. So many diseases that were once death sentences are now treatable conditions. We believe that ALS can follow the same path.

It was with that spirit that we engaged the Milken Institute Center for Strategic Philanthropy to help answer the question: How can philanthropic support best advance ALS research? The result is this Giving Smarter Guide. It outlines the key scientific barriers in the field and specific opportunities to advance research. It distills insights and conversations with many of the leading minds working on ALS today.

We hope this guide will inspire other funders and align efforts to advance ALS research so that future generations of patients and families can find more of the answers they're looking for.

TAMBOURINE

About Tambourine

Tambourine is a private philanthropic organization making contributions in health and well-being.

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EXECUTIVE SUMMARY

Amyotrophic lateral sclerosis (ALS), also commonly referred to as motor neurone disease (MND), is a progressive, fatal, neurodegenerative disease in which a person loses their ability to walk, talk, eat, and eventually breathe. An estimated 20,000 people are living with ALS in the United States at any given time, and each new diagnosis has a devastating impact on individuals, families, and communities. Most people living with ALS only survive two to five years after being diagnosed, with just 5 to 10 percent living more than 10 years after disease onset. The financial burden of the disease on people living with ALS, their caregivers, and the medical system is immense because of the disability caused by the disease. Although ALS is considered a rare disease, it is the most expensive of the significant neuromuscular disorders, with total costs estimated at more than $1 billion a year in the United States.

With ALS, motor neurons in the brain and spinal cord become diseased and eventually die, which causes the muscles that they control to atrophy and stop working. Interactions between genetic and environmental factors most likely cause the disease. Still, the mechanisms that govern ALS onset and progression are not known, and current methods to diagnose and measure ALS progression are not rooted in disease biology. Despite common patterns of symptoms, ALS is a highly varied disease with symptoms presenting and progressing differently in different people. ALS has no cure, and the US Food and Drug Administration (FDA) has approved only two treatments for the disease—riluzole and edaravone—as of July 2022. Both treatments have limited efficacy and do not significantly improve longevity in most people.

The ALS community desperately needs better ways to diagnose, measure, treat, and manage ALS in *all* people living with the disease. But the field has been constrained by a fundamental lack of understanding of the disease's basic biology and pathological mechanisms, and insufficient efforts to include people of diverse backgrounds in clinical studies. In fall 2021, the Milken Institute Center for Strategic Philanthropy partnered with Tambourine Philanthropies to perform a landscape analysis to understand the current state of ALS research and identify where additional focus and philanthropic investment are needed to accelerate progress.

This Giving Smarter Guide describes the primary scientific barriers to understanding and treating ALS. Our analysis identifies six key opportunities within the ALS research ecosystem that philanthropy should leverage to overcome these barriers and catalyze progress in understanding and treating all types of ALS. Philanthropic capital is uniquely suited to fill funding gaps not otherwise covered by government or commercial funders. It can also support cutting-edge research, bolster the efforts and scale of nonprofit organizations, and build the next generation of ALS experts.

The ALS community has made great strides in recent decades investing in human talent and shared infrastructure, and we are optimistic about the future of the field. Philanthropic support can help the ALS research community leverage these recent investments to achieve breakthroughs for people living with ALS and their caregivers. We hope this report will inspire and orient new funders eager to advance progress in ALS and serve as a common framework for stakeholders already working in the ALS research area.

Philanthropic Opportunities to Address Primary Scientific Barriers

The opportunities outlined in this Giving Smarter Guide were informed by a thorough review of the scientific literature, examination of historical public and private funding patterns and foreseeable trends, and conversations with more than 40 experts from around the world. The Center for Strategic Philanthropy identified six opportunities for philanthropic attention that, if realized, would significantly alter the understanding and management of ALS.

1. **Resolve the underlying mechanisms of ALS through support for basic research and discovery science.**
   The primary scientific barrier in the ALS field is an incomplete understanding of the disease's biology and mechanisms. A fundamental understanding of ALS biology and pathology is foundational to enabling early and accurate diagnosis, objectively measuring disease progression, developing effective therapeutics that can treat the full diversity of ALS, and optimizing disease management and care based on an individual's specific disease biology. Robust and sustained support is needed for basic, mechanistic, and discovery research to uncover the causes of all types of ALS.

2. **Improve the understanding of ALS epidemiology and etiology across the full diversity of people living with ALS.**
   The true prevalence of ALS is not fully known, and environmental risk factors are not adequately understood. These areas of inquiry are challenging to study and risky to fund, and have therefore not been prioritized by most funders. In addition, our understanding of what causes ALS and who has the disease has been drawn primarily from people of European heritage. Thus, findings may not generalize to all people living with the disease. Enhanced focus and support are critically needed here.

3. **Expand and improve the effectiveness of the therapeutics toolbox.**
   As of July 2022, approximately 90 clinical trials to develop therapeutics for ALS were ongoing. Although this volume is encouraging for a rare disease, the field has chronically suffered from clinical trial failures, with only two FDA-approved therapeutics currently available and no disease-modifying treatments. To facilitate the development of effective, FDA-approved therapeutics, validation of robust and reliable biomarkers and therapeutic targets with a solid preclinical evidence base is an urgent priority. Philanthropic investments here should leverage and expand existing shared resources and infrastructure, including biorepositories and patient registries.

4. **Facilitate expanded access to clinical research initiatives and high-quality care.**
   Access to high-quality ALS care and enrollment in ALS clinical research studies are not equitable for all people living with ALS, and multifaceted barriers conspire to exclude an unknown number of people from the medical and research systems. In addition to the ethical failures associated with unequal access to ALS care and research, these disparities limit

understanding of the full heterogeneity of ALS and the development of treatment options for everyone living with the disease. A sustained commitment is necessary to address barriers to access and inclusion across the ALS ecosystem at multiple levels.

5. **Build consensus and cohesion within the ALS research ecosystem.**
   The ALS research field has many engaged and committed stakeholders operating across different sectors, including government, academia, nonprofit organizations, and industry. These players contribute to a field that needs more cohesion and focus around funding and research priorities to avoid unnecessary duplication or funding gaps. Philanthropy is uniquely suited to serve as a neutral facilitator and consensus builder to develop and sustain collaborations and partnerships within the ALS research field in ways that help build cohesion.

6. **Invest in scientific talent from diverse and multidisciplinary backgrounds.**
   The ALS field needs to expand its pool of talented researchers who will drive innovations and medical breakthroughs. Philanthropy is a powerful tool for providing training opportunities to individuals from diverse backgrounds and building capacity within the ALS workforce. Philanthropy can also incentivize positive structural changes within the research ecosystem by aligning funding with principles of collaboration, diversity, equity, and inclusion. A philanthropic commitment to the people who comprise the ALS workforce will help ensure that the best minds are committing their energy and expertise to solving the challenges presented by ALS.

OVERVIEW OF ALS

Characteristics and Epidemiology of ALS

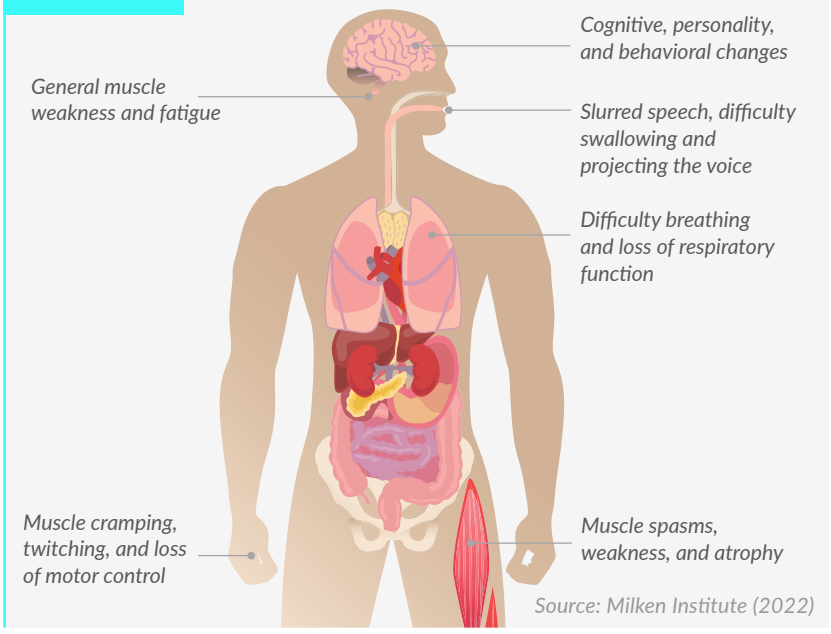
The most common initial symptoms of ALS include cramping, twitching, and loss of motor control, especially in the limbs, feet, and hands; weakness and fatigue; and slurred speech and difficulty projecting the voice **(Figure 1)**. As the disease progresses, patients usually experience shortness of breath and difficulty breathing; difficulty swallowing; muscle paralysis; and often cognitive, personality, and behavioral changes. Progressive muscle weakness and paralysis are nearly universal and ultimately lead to a loss of respiratory function and death, typically within two to five years of diagnosis**.** Despite these common patterns, ALS is highly variable among individuals in the site of symptom onset, age of onset, family history, genetics, rate of disease progression, and non-motor symptoms.

Around the world, ALS is most commonly referred to as motor neurone disease (MND). MND describes a group of diseases in which motor neurons die and muscles degenerate. ALS is the most common of MND subtypes, but the category also includes diseases such as Primary Lateral Sclerosis and Progressive Muscular Atrophy.

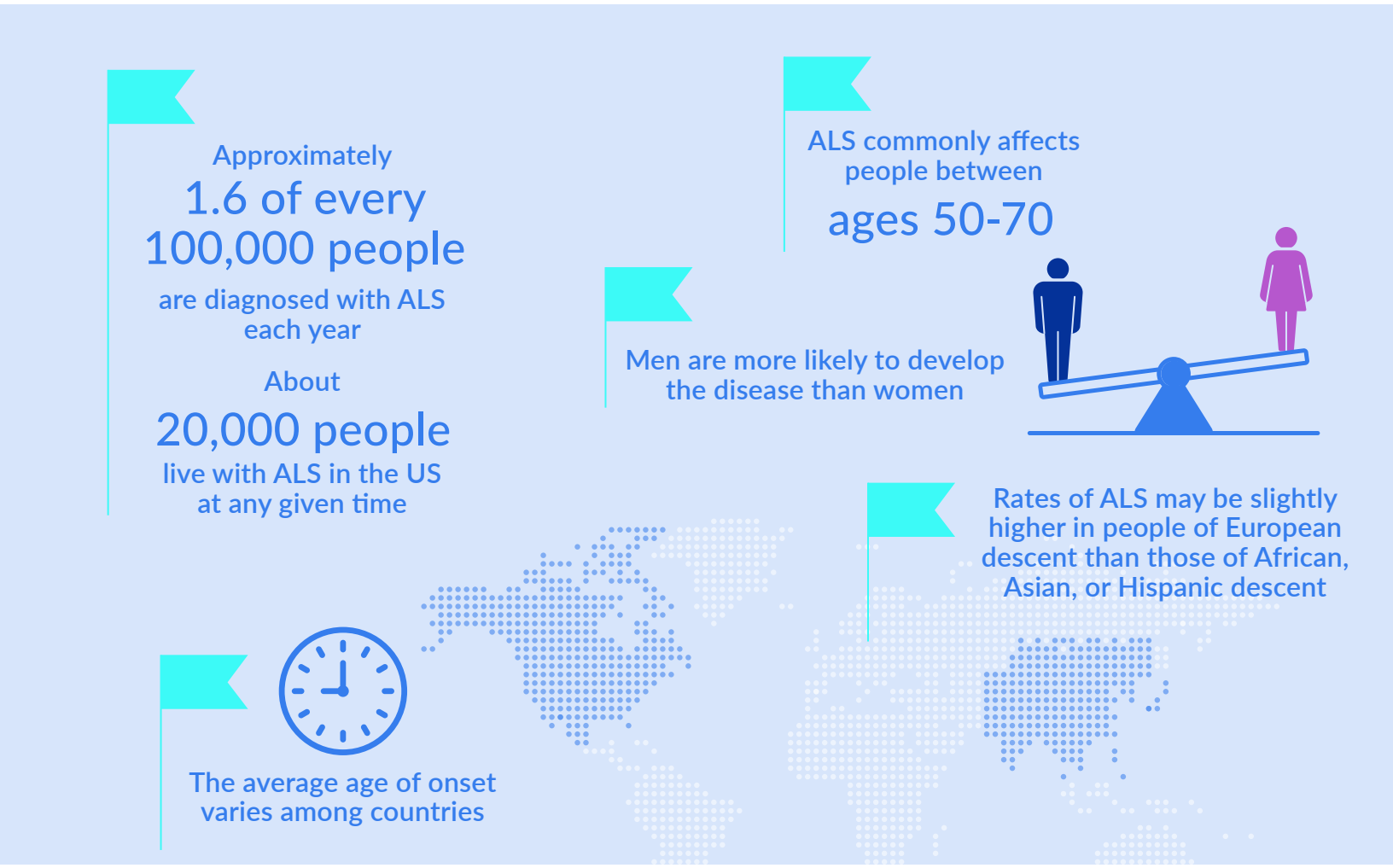
Approximately 1.6 of every 100,000 people are diagnosed with ALS each year, which translates to about 20,000 people with ALS in the US at any given time. ALS can begin at any age, although it commonly affects people aged 50-70. Men are slightly more likely than women to develop the disease; however, this gender differential disappears with age. Some studies suggest that

*10-15 percent of people living with ALS also receive a diagnosis of **Frontotemporal Dementia (FTD)**, a neurodegenerative disease with pronounced mood and cognitive changes. Emerging science suggests that ALS and FTD share common biological drivers and may be two different manifestations of the same disease.*

FIGURE 1: Common Symptoms of ALS and their Related Body Systems



Source: Milken Institute (2022)



the average age of disease onset varies among countries, with individuals in Europe and Japan potentially exhibiting symptoms later than those from China, Uruguay, and Cuba. The rates of ALS seem to be relatively uniform in people of European descent and are reported to be slightly lower in Asian, African, and Hispanic populations.

However, epidemiological findings for ALS must be interpreted and extrapolated with caution. Access to accurate and timely diagnoses is required for inclusion of ALS in epidemiological counts. This access is unequal within different segments of the US population and worldwide. Almost all data about the characteristics and causes of ALS come from individuals of European or East Asian ancestral origin. Most experts engaged through our research agreed that ALS was certainly under-counted, especially in segments of the population that do not align with the "typical" ALS patient, that is, older, white, and male.

More study is critically needed to understand the accurate incidence rates and characteristics of ALS in different populations throughout the world, and especially within the Global South—Africa, South Asia, Central America, and South America—where little is known about the drivers of the disease.

Causes of ALS

Only 5 to 10 percent of ALS cases are clearly caused by an inherited genetic mutation and classified as "familial." The overwhelming remainder of ALS cases—approximately 90 percent—are classified as "sporadic" if and when no family history can be identified. A single genetic mutation may also cause sporadic ALS, sometimes in the same genes associated with familial ALS. More often, sporadic ALS is thought to result from interactions of numerous genes that each contribute a small risk for the disease. More than 45 genes may confer risk for ALS, and the four most commonly linked genes are listed in **Table 1.**

TABLE 1: The Four Most Common Genetic Mutations Involved in ALS and Their Approximate Frequency.

Gene	Protein	Approximate Proportion of ALS
C9ORF72	Guanine nucleotide exchange C9orf72	11.5%
SOD1	Cu/Zn superoxide dismutase SOD1	3.8%
TARDBP	TAR DNA-binding protein 43 (TDP-43)	1.4%
FUS	RNA-binding protein fused in sarcoma (FUS)	1.4%

** Note: Approximations are based on reported 10/90 split between familial and sporadic ALS*

Source: Milken Institute (2022) from Ghasemi and Brown (2018)

In addition to genetic causes of ALS, epidemiological research has demonstrated a link between ALS and multiple extrinsic factors, including metabolism, nutrition, environmental exposure to toxins and pesticides, occupation, physical activity, head injury, US military service, and advanced age. However, most of this research has been conducted in small samples, and findings are often inconsistent and difficult to replicate. Accumulating evidence supports a disease model for ALS in which an individual's experiences and environmental exposures interact with their genetic profile over time to cause the disease.

ALS Disease Pathways

BIOLOGY REFRESHER

Ribonucleic acid (RNA) plays a critical role in cells in the flow of genetic information from deoxyribonucleic acid (DNA) to proteins. When a cell needs to produce a protein, relevant DNA is transcribed into RNA before being translated into a protein. RNA serves a central role in the functioning of cells in health and disease and is increasingly serving as a therapeutic target for gene therapies.

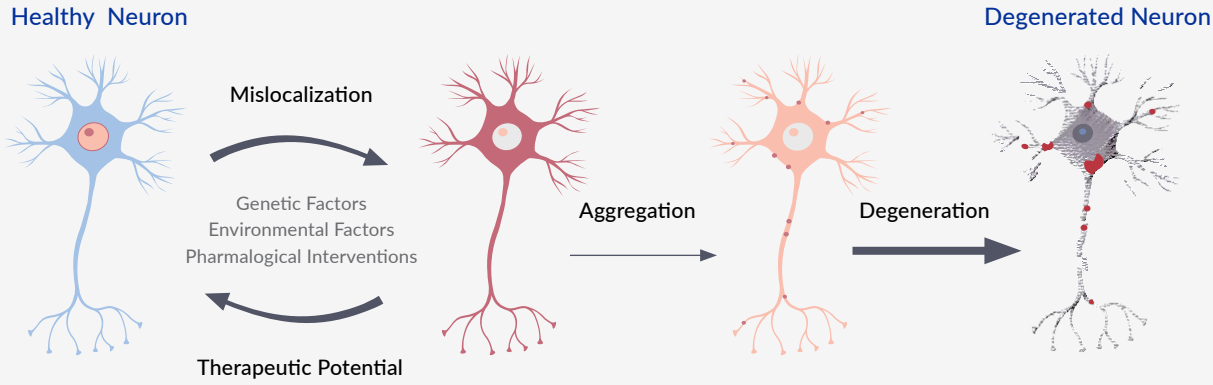
Proteins are large molecules within cells that perform many biological functions, including structure and transport and DNA and RNA regulation. Protein function is determined by its structure and location. Misfolded and mislocalized proteins can have serious consequences for biological organisms, including inducing cell death, as is seen in ALS and other neurodegenerative diseases with protein inclusions (e.g., FTD, Parkinson's, Alzheimer's).

Although scientists do not know what causes ALS, common features of the disease offer clues. A consistent characteristic of ALS is the presence of abnormal protein clusters, or aggregates, throughout diseased motor neurons. Aggregates of a protein called TDP-43 are present in greater than 95 percent of ALS cases.

In healthy neurons, TDP-43 plays an essential role in regulating RNA, a nucleic acid involved in many biological processes within a cell. TDP-43 is usually confined to the cell's nucleus, but, as ALS progresses, the protein accumulates and aggregates outside the nucleus in the neuron's cell body (Figure 2). These aggregates are toxic to the neurons and result in cell death and loss of neural networks.

FIGURE 2: **TDP-43 Protein Accumulation and Associated Neuronal Degeneration in ALS**

In healthy neurons, TDP-43 (red) is confined to the nucleus, but mislocalization and aggregation of the protein can lead to neuron degeneration.



Source: Milken Institute (2022), adapted from Suk and Rousseaux (2020)

Despite the near-ubiquity of TDP-43 aggregates in ALS, the biological processes underlying their formation are not fully understood and are an active area of research. Furthermore, these aggregates may not be the sole driver of ALS pathology; most researchers believe that more than one disease pathway converges to cause TDP-43 pathology. Regulation of RNA functioning may be one such convergence point "upstream" of protein aggregation and mislocalization in ALS. For example, TDP-43 and other proteins known to be involved in ALS, such as SOD1, FUS, and C9ORF72 (Table 1), share a role in regulating RNA. The ALS field is paying increased attention to RNA regulation as a common mechanism of ALS pathophysiology. However, many other molecular pathways that lead to neuronal toxicity have also been implicated in ALS and are areas of active investigation.

Diagnosing and Measuring ALS—The Need for Biomarkers

Diagnosing ALS is challenging. Many symptoms overlap with other medical conditions, and no single "ALS test" exists. Doctors diagnose ALS only after ruling out other potential causes for the

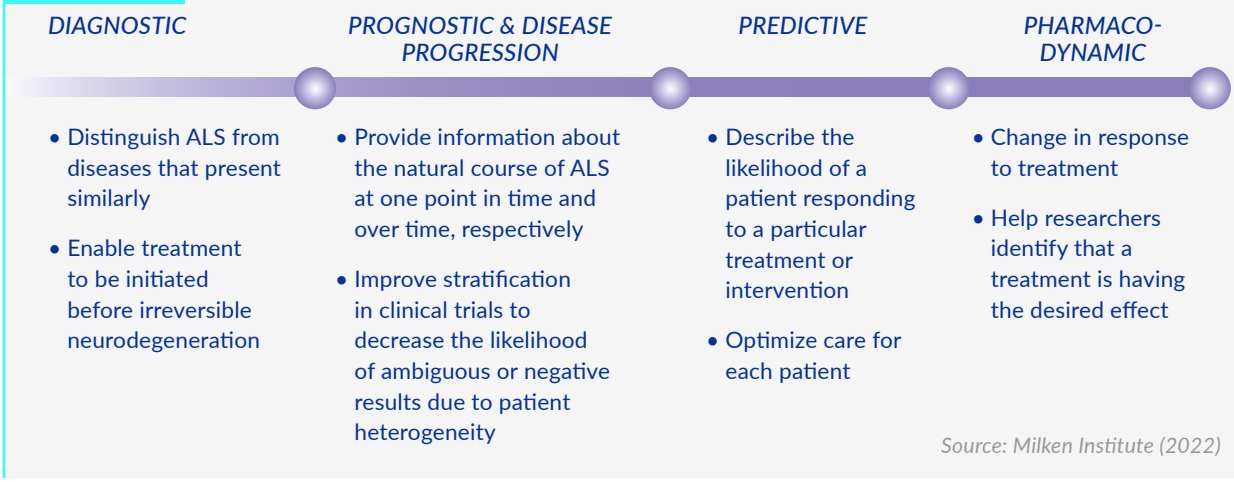
symptoms, giving ALS the distinction of being a "diagnosis of exclusion." An ALS diagnosis usually involves a combination of tests that examine the structure and function of muscles, nerves, the brain, and the spinal cord, and laboratory analysis of blood, urine, and cerebrospinal fluid (CSF). Physicians combine the results of these tests with diagnostic criteria, which are broad lists of symptoms and signs that must be present or absent for a diagnosis of ALS to be made. It typically takes upwards of nine months and may take more than two years to arrive at the appropriate diagnosis after ALS symptoms appear.

Although the average survival span after an ALS diagnosis is only two to five years, the disease progresses at variable rates. The ALS Functional Rating Scale-Revised (ALSFRS-R) is a widely employed tool used to measure ALS progression and estimate an individual's prognosis. The ALSFRS-R evaluates multiple aspects of physical function, including speech, walking, and handwriting. The rating scale provides functional information, is accepted by regulators, and is ingrained in the ALS field. For example, clinical trials rely on changes in the ALSFRS-R to determine how well an experimental therapeutic is working.

However, there seems to be near consensus by experts that the degree of the field's reliance on this scale is problematic because of its limitations. For example, ALSFRS-R responses can be highly variable between people living with ALS who have different symptoms and can even vary from one day to the next. This variability could distort results in clinical trials by masking the clinical benefit of therapeutics under investigation.

The ALS field needs objective assessments to determine when someone has ALS and whether or not treatment is effective. Researchers have been working to identify ALS biomarkers (Figure 3) to overcome current challenges in diagnosing ALS and measuring the disease's progression. A biomarker is a measurable indicator of normal functioning, pathogenic processes, or changes in responses to an intervention. In ALS, biomarkers are needed to diagnose ALS with more specificity before significant neurodegeneration has occurred, as well as to help resolve the heterogeneity of

FIGURE 3: Types of Biomarkers and the Goals of Their Use in ALS



Source: Milken Institute (2022)

the disease and indicate whether or not a therapeutic is working. Considerable research has been dedicated to identifying and validating a variety of potential ALS biomarkers, including the activity of muscles and nerves, neuroimaging of the brain and spinal cord, movement and speech patterns, and proteins collected from biofluids. Although some promising candidate biomarkers are emerging, more work is needed to ensure that new biomarkers are tested and validated in diverse populations using standardized procedures. To this end, the ALS field has recently built multiple repositories of postmortem tissue and other biological specimens from people living with ALS (called biorepositories or biobanks) that can be used in the development and validation of biomarkers for ALS. See the section *Snapshot of ALS Research Nonprofit Organizations, Initiatives, Resources, and Partnerships* for more information on these resources.

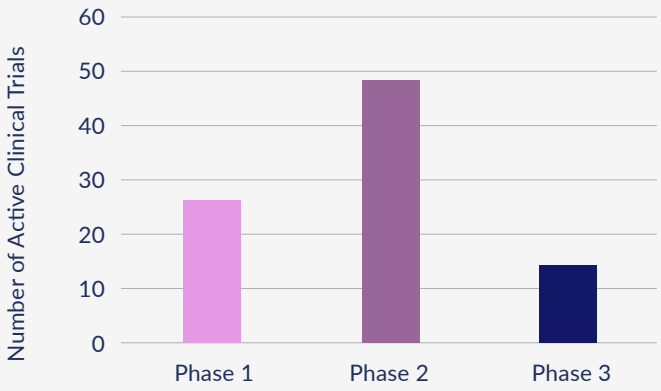
Disease Management and Care

There is no cure for ALS. Care and treatment for ALS focus on managing symptoms across multiple body systems, preventing and managing medical complications, improving quality of life, maximizing functional independence, and retaining the ability to communicate with assistive technologies.

As of July 2022, FDA has approved only two drugs to treat ALS—riluzole and edaravone. FDA approved riluzole as the first treatment for ALS in 1995. This drug acts by limiting the amount that motor neurons are excited by other cells. Approved by FDA in 2017, edaravone seems to protect neurons from oxidative stress, but its exact mechanism is unknown. Although these two therapeutics were important milestones for the ALS community, results outside of the clinical trials have been mixed, and neither drug substantially improves survival time for people living with the disease.

Approximately 90 therapies for ALS are currently in clinical trials **(Figure 4)**. Most clinicians, researchers, and people living with ALS believe that the disease will require a combination of

FIGURE 4: Types of Biomarkers and the Goals of Their Use in ALS



As of July 2022, there are 88 ongoing clinical trials of ALS therapeutics characterized as either Phase 1, 2, or 3. Phase 1 studies are small and are primarily intended to evaluate the safety of a new drug. In Phase 2 trials, researchers administer a therapeutic to a larger group of people to further study its safety and start to evaluate its effectiveness. Phase 3 trials are performed to further evaluate a drug's effectiveness and screen for any adverse effects. The ALS clinical pipeline includes therapeutics in all types of clinical trials, with the majority in Phase 2 clinical testing to determine whether a previously approved drug could be repurposed to treat ALS.

Source: Milken Institute (2022) using data from ClinicalTrials.gov (July 2022)

Note: Data was queried on 7/8/22 using the following the following parameters: Conditions: ALS OR Amyotrophic Lateral Sclerosis OR Motor Neuron Disease; Recruitment: Recruiting OR Enrolling by invitation OR Active, not recruiting; Interventional study type; Study phases: Early Phase 1 OR Phase 1 OR Phase 2 OR Phase 3.

therapies with different mechanisms of action that could be tailored to an individual's diagnosis because of the disease's heterogeneity. Roughly 50 percent of the therapies in development are in Phase 2 trials—a relatively high proportion that can be explained by the high number of repurposed therapies, originally used for other conditions, in the pipeline. However, experts have expressed skepticism about the potential of repurposed therapeutics for ALS because of a lack of strong scientific evidence that links these drugs to ALS mechanisms. The other half of treatments are evenly divided between therapies specific for ALS and multipurpose therapies being developed for several conditions simultaneously, such as Alzheimer's disease.

Most therapies currently under investigation are small molecules, like riluzole and edaravone, that can easily enter cells and modulate cellular processes. Also in development to treat ALS are biological molecules such as peptides, antibodies, and fatty acids, which act against different mechanistic targets. Gene therapies are an emerging area of therapeutic focus that act directly on DNA or RNA to affect cellular products.

The most common form of gene therapy in development for ALS is antisense oligonucleotides (ASOs), which are synthetic, single-stranded segments of nucleic acid that are complementary to a specific segment of RNA. ASOs act to modify the production of the proteins encoded by those RNA segments. Most ASOs developed to date target the single gene that is mutated in some forms of inherited ALS. There are also efforts to target proteins downstream of a genetic mutation that may be involved in ALS and be more appropriate for people whose ALS is not clearly caused by a mutation in a single gene.

Finally, the current clinical pipeline includes cell replacement therapies, such as stem cells, that act by replacing both neuronal and non-neuronal cells that die in the course of the disease. Replacement therapies deliver cells that can synthesize endogenous therapeutic proteins or modify someone's immune system to mitigate degenerative disease processes.

While the ALS field is in unanimous agreement about the need for more clinical trials and therapeutic options to treat ALS, clinical trials of new therapeutics continue to fail to demonstrate their effectiveness against the disease. Members of the ALS research community point to a variety of reasons for these failures, including flaws in clinical trial design, the absence of biological methods to measure disease progression, disease heterogeneity, and a lack of flexibility by regulators. But the most common reason we heard in our research is that the underlying biology of ALS is not yet resolved. Therefore, directly demonstrating that a therapeutic can target a

The ALS therapeutic pipeline is active, but clinical trials have struggled to demonstrate a robust therapeutic benefit because of the disease's unknown biology. The complexity of ALS presents a persistent challenge for researchers who study the disease and work to develop effective therapeutics. Most experts agree that a combination approach that targets multiple mechanisms of ALS will ultimately be needed.

causal mechanism of the disease is incredibly difficult. Until the biology of ALS is better resolved, a "home run" therapeutic will likely remain elusive.

At the same time, because ALS is so aggressive, the ALS community has a critical imperative to improve upon the limited treatment options available *now*. The current reality is that therapeutics show initial potential in preclinical studies but then provide an incremental improvement in symptoms for a subset of people living with ALS and ultimately fail to win regulatory approval.

PRIMARY SCIENTIFIC BARRIERS HINDERING PROGRESS IN ALS		
BARRIER 1	**BARRIER 2**	**BARRIER 3**
The biology and pathological mechanisms that underlie ALS are unresolved.	The current understanding of ALS etiology is incomplete and comes from populations that do not reflect the full diversity of people living with ALS.	Biomarkers and therapeutic targets lack sufficient validation and have not yet led to disease-modifying treatments.

FUNDING FOR ALS

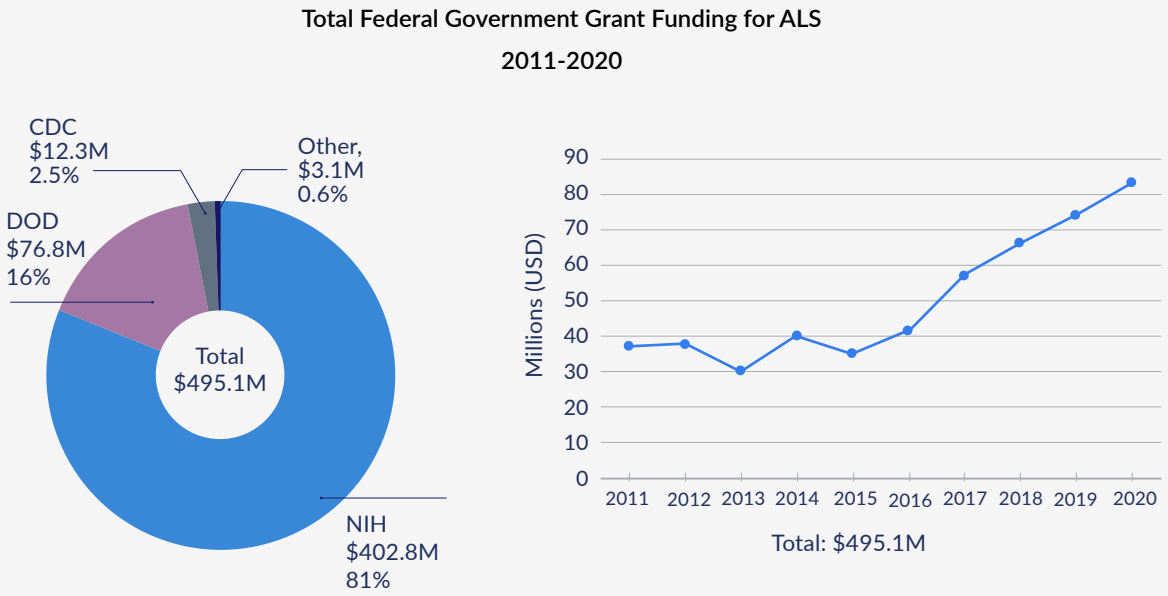
During the past 20 years, ALS has received increased attention from funders across academia, government, and the nonprofit and biopharmaceutical sectors.

Federal Funding for ALS

Our analysis showed that public funding is the primary support for ALS research. From fiscal years 2011 to 2020, the federal government provided more than $495 million for ALS funding through federal research grants (**Figure 5**). The largest federal funder of ALS research was the National Institutes of Health (NIH) with almost $403 million, followed by the ALS Research Program (ALSRP) of the Department of Defense's Congressionally Directed Medical Research Program with nearly $80 million. The Centers for Disease Control and Prevention (CDC) provided a little over $12 million. The remainder ($3.1 million) came from other federal agencies, including FDA and the National Science Foundation.

FIGURE 5: **US Government Funding of ALS Research**

The US government has invested more than $495 million for ALS research in the past 10 years, with a doubling of annual investments between 2011 and 2020.



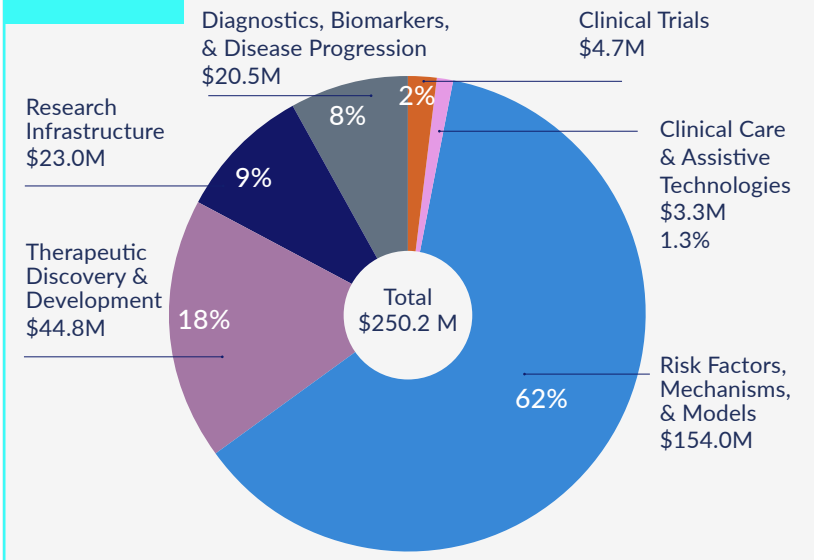
Source: Milken Institute (2022), using data from NIHReporter and Federal Reporter (2011-2020)

Note: Funding data were obtained from NIHReporter and Federal Reporter for 2011-2020 using keywords "ALS" or "amyotrophic" in funded project titles or grants.

A closer examination of NIH funding priorities from 2016 to 2020 shows that the primary focus of funding dollars has been on ALS risk factors, models, and mechanisms (**Figure 6**). This funding pattern aligns with the NIH mission to seek fundamental knowledge about health and disease.

Another factor contributing to federal funding of ALS is increased congressional appropriations for research on Alzheimer's disease and related dementias as part of the National Plan to Address Alzheimer's Disease. This federal strategy was released in 2012 and spurred a nearly 4.5-fold increase in spending in this area by NIH from 2015 to 2020. Our funding analysis showed that projects studying ALS and FTD have accounted for about one-third of NIH's ALS support since this new funding stream was introduced. Researchers have experienced this trend as a less favorable funding environment for projects focused on ALS without FTD.

FIGURE 6: NIH Funding of ALS Research



Source: Milken Institute (2022), using data from NIHReporter and Federal Reporter (2016-2020)

Note: Funding data were obtained from NIHReporter and Federal Reporter for 2016-2020 using keywords "ALS" or "amyotrophic" in funded project titles or grants.

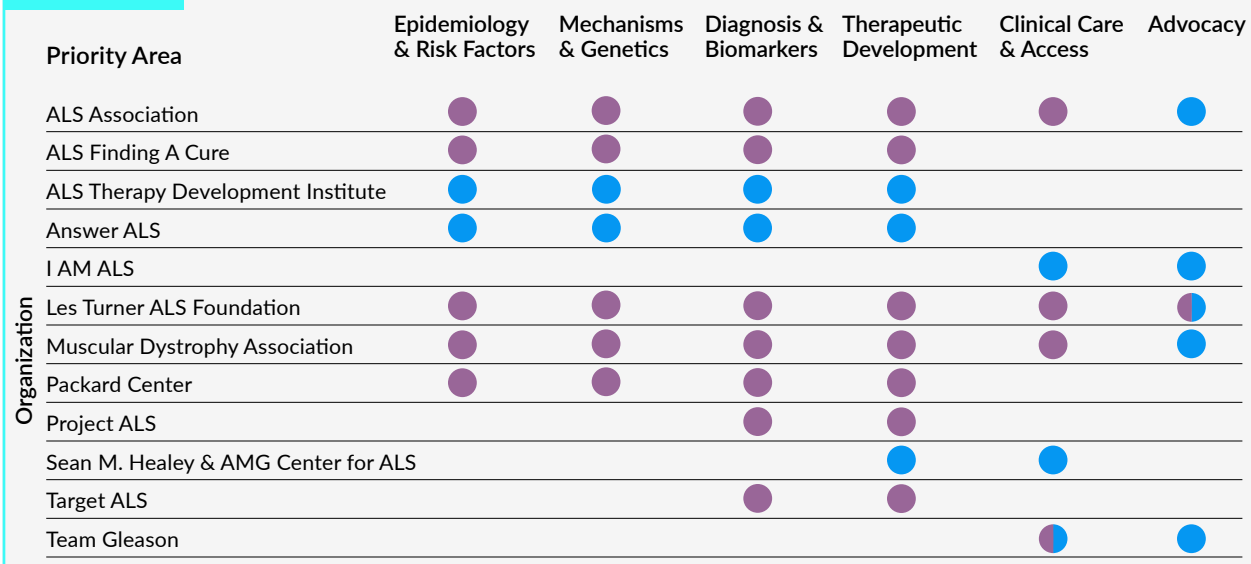
There are many positive signs regarding future federal support for ALS. NIH is paying specific attention to the disease through targeted efforts such as the ALS^2 Initiative, which plans to invest $25 million over five years (2021-2026) from the NIH Director's High-Risk, High-Reward Research Program. This fund supports a small number of studies that utilize cutting-edge technologies, attract expertise from diverse scientific disciplines, and examine commonalities between ALS and other neurodegenerative disorders. The ALSRP—whose appropriations have quadrupled since 2019 to $40 million per year in FY2021—funds early clinical studies for ALS therapeutics that must incorporate biomarkers in the clinical trial design. New ACT for ALS legislation, signed into law in December 2021, allows for appropriations of up to $500 million over five years to address multiple issues related to therapeutic development and expanded access to promising treatments.

These large-scale investments can be attributed, in large part, to committed and sustained advocacy for increased federal funding for ALS by patient-led groups and ALS-focused associations. Overall, ALS is garnering increased attention from federal funders, with a particular emphasis on developing new therapeutic strategies.

Private Funding

The nonprofit sector also provides significant funding for ALS research. By some counts, as many as 60 nonprofit organizations are operating within the ALS space in the US alone. Each organization has different organizational perspectives and goals, budgets, scientific research portfolios, and programmatic initiatives that complement and overlap with each other to some degree **(Figure 7)**.

FIGURE 7: Research Areas of US-Based Nonprofit Organizations Focused on ALS



Source: Milken Institute (2022)

Note: Purple dots indicate that the organization funds others to do the research, while blue dots indicate that the nonprofit itself executes this research priority.

Our analysis identified approximately $380 million in total support from the nonprofit sector over the past five years (2016-2021), with about half of this funding distributed via grants. The ALS Association (ALSA) is the most prominent supporter of ALS research across broad priority areas based on publicly available information. ALSA's Ice Bucket Challenge has raised $115 million since 2014, which has been distributed primarily via research grants and care services expenses. Other nonprofits—such as Target ALS and I AM ALS—significantly impact a narrower set of scientific priorities, such as therapeutic development or advocacy and patient care navigation, respectively.

Although ALSA had been the dominant nonprofit funder of basic research, it has shifted its funding priorities away from the fundamental science needed to understand the underlying biology of ALS and toward the strategic goal of finding new therapies to align with its mission of "making ALS a livable disease" by 2030. This pivot resulted in a gap in funding for basic ALS research that cannot be readily filled by any current player in the ALS nonprofit space.

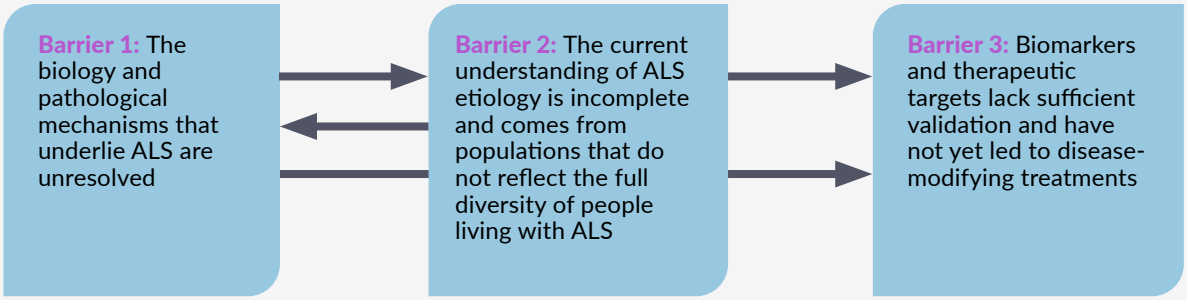
This multistakeholder environment offers clear benefits for ALS research, including the potential for diverse thought, varied sources of funding, and different approaches to tackling research questions

and setting scientific priorities. However, unless organizations are transparent about their priority research areas and funding levels, the ALS research ecosystem can lack cohesion and suffer from inefficiencies. Furthermore, with ALS designated as a rare disease that competes for awareness and funding with neurodegenerative diseases that affect a broader swath of the population, competition for funding has presented a barrier to meaningful collaboration among nonprofit organizations.

SCIENTIFIC BARRIERS HINDERING PROGRESS IN ALS

The Milken Institute Center for Strategic Philanthropy identified three distinct barriers hindering scientific progress in ALS that additional scientific and financial focus will help overcome (**Figure 8**). These barriers span the spectrum from basic research into ALS biology through the clinical study of new therapeutics.

FIGURE 8: Core Scientific Barriers Hindering Progress in ALS and the Relationships between Them



Source: Milken Institute (2022)

Barrier 1: The biology and pathological mechanisms that underlie ALS are unresolved.

The most consistent barrier that arose during our analysis was an incomplete understanding of the pathological biological processes that underlie ALS. An incomplete understanding of ALS limits progress across the entire continuum of ALS research and care:

- ***Diagnosis:*** The ability to identify ALS based on early signs and biomarkers before significant neurodegeneration has already occurred is a pressing priority but requires a better understanding of the mechanisms of the disease.
- ***Therapeutic Development:*** Therapeutics should be developed against molecular mechanisms that are ALS-specific, validated in multiple model systems, and act "upstream" of other steps in the neurodegenerative process.
- ***Measurement of Disease Progression:*** Clinical trials continue to fail in large part because of the heterogeneity of disease presentation and progression, and new methods, including biological and digital biomarkers, are needed to identify which patients might respond to a specific treatment based on their unique disease biology.

- *Disease Management and Care*: Understanding the fuller mechanistic picture of an individual's disease will inform what therapeutics will be most effective and determine what type of care they will respond to best.

Barrier 2: The current understanding of ALS etiology is incomplete and comes from populations that do not reflect the full diversity of people living with ALS.

There is field-wide consensus that the reported incidence of ALS is low, partially because of a lack of diagnosis and reporting, both of which hinder a complete understanding of the disease's epidemiology and etiology. The exact number of people with ALS is unclear, and the field's understanding of ALS in individuals who differ from the "typical" ALS patient (older, white, and male) is notably lacking.

Although most study has focused on inherited, genetic causes of the disease, the risk of developing ALS within families (heritability) is only estimated to lie between 40-60 percent, and non-genetic factors are certainly at play. Studies of environmental risk factors are critical but are difficult to conduct and replicate. This type of research has not been the priority of most funders, in part because of its cost and difficulty. Without a more robust characterization of the genetic and environmental drivers of ALS in *all* people living with ALS and a census of the disease's true prevalence, the field continues to risk developing treatments that only benefit specific subtypes of ALS and further exacerbating inequities in disease burden.

Barrier 3: Biomarkers and therapeutic targets lack sufficient validation and have not yet led to disease-modifying treatments.

Despite significant investments in developing biomarkers and testing new therapeutics, the ALS field still lacks reliable and validated biomarkers or therapies that significantly alter the course of the disease. The most commonly attributed reason for these continued challenges is the heterogeneity of ALS and an incomplete understanding of its mechanisms. The field appears to be closer to identifying a combination of biomarkers for ALS and gaining clarity about the molecular drivers of some forms of the disease thanks to recently established infrastructure by and for the ALS field, such as biorepositories, cell lines derived from people living with the disease, and clinical datasets. But the experts we interviewed agreed that additional efforts are needed to validate therapeutic targets against ALS-specific mechanisms and to objectively measure the effectiveness of these treatments using a combination approach that includes validated biomarkers.

OPPORTUNITIES FOR PHILANTHROPY

The Milken Institute Center for Strategic Philanthropy has identified six opportunities within the ALS research ecosystem where philanthropic investment is well-suited to address barriers hindering progress for the disease. These opportunities leverage, expand upon, and diversify existing infrastructure and field-wide resources developed through significant investments already made by the ALS research community over the past two decades.

Opportunity 1: Resolve the underlying mechanisms of ALS through support for basic research and discovery science.

Public and private funders of ALS research are increasingly focusing on therapeutic development and disease management. This approach is critical because of the burden and lethality of ALS but neglects the need for ALS research that focuses on the fundamental biology and mechanisms of the disease. We recommend a robust, sustained commitment to the basic and discovery-based ALS research that will improve the fundamental understanding of ALS and support the entire continuum of ALS research and care that relies on this knowledge. In particular, we recommend applying funding in the four following areas:

Investing in basic science research to resolve fundamental biology and pathology: To understand the heterogeneity of ALS' causes and progression, researchers must understand the basic biology and mechanisms that drive the disease in different people. Supporting research that examines interactions between and convergence of mechanistic pathways, especially those upstream of pathological protein aggregation and mislocalization, can resolve the disease's complexity and validate targets for biomarkers and therapeutics.

Supporting discovery science: The ALS field has established a robust infrastructure of biological samples and multidimensional databases containing clinical, epidemiological, genomic, and epigenomic data from people living with ALS and individuals not affected by the disease. These resources should be accessible to the broad research community, and scientists should be incentivized to conduct discovery research studies that integrate multiple types of information. Support here can facilitate the identification of mechanistic patterns and encourage scientists to generate new hypotheses about the fundamental pathology of ALS that can then be tested.

Leveraging cutting-edge technologies to interrogate ALS across multiple model systems: Major investments in neuro-focused and genetics technologies over the past decade have led to a dramatically expanded toolbox. These tools include methods to image and manipulate neural networks with fine precision; to characterize, map, and probe the activity of specific populations of cells; and to compile and analyze complex and multidimensional data. Cutting-edge technologies allow better resolution of cells, networks, activity, behavior, and health. Applying these new advances to ALS across multiple disease models—including animal models, cellular models, and in postmortem tissue—will drive an increased system-wide understanding of the disease informed by its biology.

Supporting preclinical models of ALS: Preclinical animal and cellular models of ALS are critical for both hypothesis-driven basic research and preclinical research that informs later clinical studies in human patients. The ALS field needs more support here to develop better animal models that recapitulate features of the disease and account for its heterogeneity because many therapeutics have failed to translate from animal studies to effectiveness in the clinic.

Opportunity 2: Improve the understanding of ALS epidemiology and etiology across the full diversity of people living with ALS.

Experts across the ALS field emphasized the need for a more thorough accounting of the prevalence and incidence of ALS and a clearer understanding of the disease's causes and course in people living with ALS from diverse backgrounds. Funding for research on the epidemiology and non-inherited risk factors for ALS has been chronically underfunded, and more support is critically needed here. This support is best delivered in three key ways:

Diversifying existing biorepositories, resources, and datasets: ALS datasets, resources, and biorepositories are valuable tools for field-wide inquiry into the characteristics and heterogeneity of ALS. These tools can be leveraged to develop and validate biomarkers for ALS so that ALS can be diagnosed with greater speed and accuracy and the disease's progression and response to treatments can be measured more objectively. However, these field-wide resources suffer from an overrepresentation of individuals of European ancestry. Sustained effort is needed to enrich the diversity of ALS infrastructure to ensure that the insights gained from these valuable resources are relevant to all people living with the disease.

Funding epidemiological research: Epidemiological study is essential to fully understand who gets ALS and the relationship between ALS and genetic ancestry, race, geographical location, and environmental factors. The National ALS Registry, maintained by CDC, is devoted to this type of study, but federal support for the registry has stagnated with increased public funding directed elsewhere in the ALS research system. Specific funding is needed for epidemiological research into the risk factors and demographics of ALS in all communities.

Focusing on sporadic ALS and non-genetic drivers of the disease: The overwhelming majority of ALS cases have no known genetic origin, but investigation into extrinsic and environmental risk factors for the disease has historically been viewed as too "risky" for consistent funding by the primary funders. Cutting-edge techniques in neuroscience, genetics, and artificial intelligence could be applied to study the causality between these risk factors and the development of ALS to both identify tractable routes to prevent ALS and lead to an improved understanding of disease mechanisms.

Opportunity 3: Expand and improve the effectiveness of the therapeutics toolbox.

Public and private funders are increasingly focusing their efforts on developing biomarkers and therapeutics for people living with the disease, and this area of research has a great deal of momentum behind it. Experts we spoke with emphasized three primary needs here: more rigorous validation of biomarkers, more rational therapeutic development against mechanistic targets that have solid evidence of their involvement in ALS pathology, and more innovative clinical trial design. However, these approaches must be accompanied by an increase in the number of clinical trials and a commitment to making those trials accessible by ensuring that clinical trial design and execution center on the experiences and needs of people living with the disease and their caregivers. We recommend two complementary paths to expand the therapeutics toolbox for ALS:

Funding efforts to validate a robust, diverse, and reliable array of biomarkers: Biomarkers are critical at multiple points in the ALS journey—diagnosing the disease early in its course, assessing disease severity and progression, and determining the effectiveness of therapeutics. Although the ALS field is making progress in developing a diverse array of biomarkers, such as those collected from biofluids or digital methods, more funding is needed for their validation. It is also necessary to consider the cost and feasibility of collecting and processing biomarker data to ensure that industry can efficiently integrate biomarkers into its clinical studies. In addition, funded efforts must ensure that objective biomarker measures of therapeutic effectiveness correlate with and are validated against subjective but meaningful approaches to assess functioning and quality of life of people living with the disease, such as functional rating scales.

Supporting rigor and innovation in clinical trials: Clinical trials are very resource-intensive in terms of financial cost, time, required expertise, and burden on people living with ALS and their caregiving teams. More funding is urgently needed to maximize these resources by supporting rigorous and innovative clinical trial design and analyses. Many experts advocated for greater adoption of approaches that simultaneously test multiple therapies using advanced statistical methods, virtual control arms to minimize the use of placebo assignments and reduce heterogeneity in clinical trial populations, and adaptive trial designs that allow clinical research teams to more quickly advance or end a trial based on early results and thus redirect resources elsewhere. Targeted financial support can ensure that necessary expertise and staffing are embedded within the trial team to design and implement these types of clinical trial methodologies.

Given the ongoing failures of ALS clinical trials to meet FDA's approval requirements, resources here would be well spent to increase the number of clinical trials and ensure that these trials are accessible for more people living with the disease. Philanthropy has already played a catalytic role in the ALS clinical trial ecosystem by supporting the design and launch of a platform trial coordinated by the Healey Center, and these efforts can serve as a model for future philanthropic endeavors.

Opportunity 4: Facilitate expanded access to clinical research initiatives and high-quality care.

Multiple experts we spoke with emphasized the need to increase equitable access to clinical research opportunities and quality ALS medical solutions for people living with ALS within and outside of the US. Individuals with ALS experience barriers accessing timely diagnosis, clinical trials and other research studies, multidisciplinary care, and assistive technologies to improve quality of life. In addition to the ethical failures associated with unequal access to ALS care and research, these disparities hinder scientific progress because they limit understanding of the full heterogeneity of ALS and the development of treatment options for all people living with the disease. Philanthropy is a critical resource that can sustain a commitment to increase access and inclusion to research and care. We recommend four specific approaches:

Supporting multidisciplinary ALS clinics and care centers: The highest quality ALS care requires multidisciplinary expertise from a coordinated medical team often affiliated with a multidisciplinary ALS clinic or care center. However, various barriers conspire to limit people's access to these medical services or the clinical research opportunities that are more likely to be available at large ALS institutions. ALS care centers often operate at a profit loss. Opening new ALS centers is likely not financially realistic without broad, sustained support from major funders, such as the funding provided by NIH for Alzheimer's or Parkinson's disease centers.

An alternative strategy is to direct additional support to existing multidisciplinary ALS clinics and care centers for their efforts to engage and integrate underrepresented groups into their services and research. Philanthropy is well-positioned to provide this type of support and enable centers to expand staff capacity, develop new resources that can integrate underserved people living with ALS into clinical studies, collect data on who they are and are not serving, and modify operational plans based on learnings and insights.

Providing resources to meet people living with ALS "where they are" with care and research opportunities: Philanthropy can support people living with ALS as they choose where and how they access ALS care and engage in clinical studies. Many individuals already have trusted relationships with their primary care providers or with staff at community health centers. However, these medical providers may not have adequate resources or expertise to recognize early signs of ALS and help facilitate a diagnosis or a referral to a clinical trial. Philanthropy can help expand and bolster these trusted patient/health-care provider relationships by supporting increased ALS awareness within community health and primary care settings, sustaining connections between multidisciplinary ALS clinics and community-based health-care sites, and facilitating virtual or other remote options for people to engage in clinical research.

Facilitating awareness and educational initiatives about clinical research: One of the many challenges faced by people diagnosed with ALS is navigating a complex clinical trial landscape. Many people living with ALS and their families lack the education and training to understand

the terminology and information needed to find a clinical trial, understand whether or not they meet the trial's eligibility criteria, or enroll in the trial. Targeted awareness and educational campaigns can provide resources to communicate these complex topics and integrate people with the disease into clinical trials to support access to experimental therapeutics and work toward broadening diversity and inclusion in therapeutic research.

Opportunity 5: Build consensus and cohesion within the ALS research ecosystem.

Our analysis revealed a near-unanimous desire for more cooperation, cohesion, and consensus within the ALS research system. Philanthropy is uniquely suited to help build and sustain collaborative research efforts, integrate new voices and perspectives into the field, and facilitate partnerships built with transparency of funding and scientific priorities at the forefront. We make three key recommendations here:

Supporting scientific and funder convenings: Philanthropy has always had a key role in "setting the table" and providing a venue and platform for assembling different perspectives, such as those from people living with ALS, current or past caregivers of someone with the disease, scientists, clinicians, funders, and regulators. Philanthropic support for field-building convenings in the ALS space can provide a forum for dialogue, idea generation, and collaboration among multiple stakeholders to envision and co-create a new reality for ALS research.

Facilitating the alignment of funding and research priorities: Experts expressed a desire to develop a joint strategy to align funding and research efforts across the significant funders of ALS research. There is a need to do this on an international scale, but a better alignment of US-based funders would yield great benefits for the ALS field. Philanthropy is well-suited to facilitate these efforts by serving as a neutral facilitator and consensus-builder among diverse stakeholders from multiple sectors of the research ecosystem.

Growing research capacity through partnership and mentorship: Our funding analysis revealed that a high degree of ALS funding and expertise is concentrated within a relatively few institutions located primarily in the US, Europe, and Australia. Philanthropy can support partnerships and mentorship opportunities to link institutions and teams that have developed robust expertise and infrastructure with others who lack access to these resources. In particular, these partnerships should expand access to capital and grow capacity within the Global South and could focus on sharing tools, methodological training, patient samples, and data across different institutions and geographies. Strategically deployed philanthropic investments here would ultimately build capacity throughout the global ALS research community and further the entire field's understanding of the characteristics and causes of ALS in all people.

Opportunity 6: Invest in scientific talent from diverse and multidisciplinary backgrounds.

The challenges presented by ALS demand new perspectives, multifaceted expertise, and an "all hands on deck" approach. Philanthropy is a powerful tool that is well-suited to invest in the people who drive innovation and generate the knowledge that can lead to medical breakthroughs. We see three distinct opportunities to invest in diverse, cross-disciplinary human talent within the ALS research field.

Investing in a diverse workforce: A common saying holds that talent is everywhere but opportunity is not. In recent decades, philanthropy has been more intentional about opening doors for scientists from backgrounds that are underrepresented in the biomedical research workforce, such as through targeted training programs. But it is not enough to build a workforce of researchers from diverse backgrounds if they continue to experience structural barriers and systems of exclusion and oppression within the institutions and health systems where they study and work. Philanthropy can be a powerful force for good in this space, for example by aligning funding opportunities with positive behaviors around equity and inclusion and providing robust support for researchers who promote diversity, equity, and inclusion.

Training and educating more ALS clinicians and clinician-scientists: Too few trained specialists diagnose and care for individuals with ALS. Physician shortages have been well-documented in the US, but accessing an ALS physician becomes exponentially more difficult for those who live outside of the US. Individuals in low- and middle-income countries experience additional barriers such as a lack of infrastructure and professional training. Philanthropy can support training and education initiatives to develop the next generation of ALS clinician-scientists. Funders are especially encouraged to build the pipeline of talented individuals from underrepresented backgrounds, such as by supporting the development and maintenance of relationships between leading academic and training institutions and individuals with fewer resources who can receive training that can be deployed in their home communities.

Funding collaborative research teams: Collaboration, particularly among researchers who work in different sectors or disciplines, is essential for driving progress in ALS. These collaborations provide novel ideas and unique expertise to avoid getting stuck in the "groupthink" mindset that can limit innovation. Philanthropy can play a crucial role in initiating and sustaining these partnerships by providing funding and infrastructure for collaborative efforts.

CONCLUSION

ALS is a cruel disease that has challenged patients, their families, and the medical community for generations. Although ALS is considered rare, its impact on individuals, families, and communities is nonetheless devastating. The ALS community desperately needs better ways to diagnose, measure, treat, and manage ALS, but progress has been constrained at all points by a lack of understanding about the disease's basic biology and pathological mechanisms.

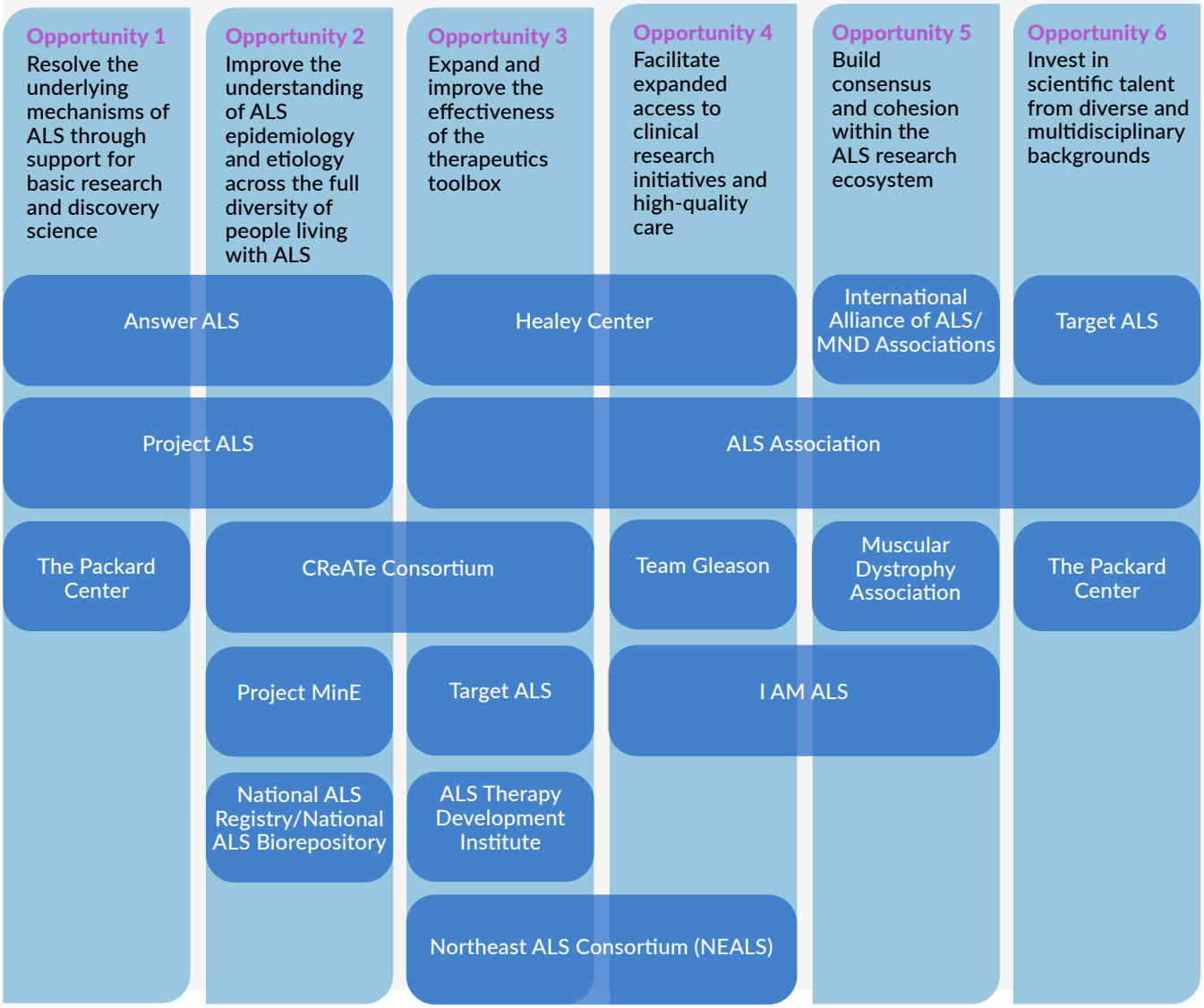
Fortunately, the ALS field is starting to collectively realize the impact of increased financial investment and enhanced scientific activity over the past two decades. Gains in knowledge, technological advancements, and significant infrastructure investments have created an atmosphere of optimism and hope that, with more time, resources, and human capital, critical scientific questions will finally be answered. Federal funders have directed more resources toward ALS over the past decade. Multiple nonprofits and industry players are committed to developing new therapeutic options for people living with the disease and expanding access to treatment and care services. But progress is still too slow, and more funding and attention are needed to resolve specific scientific obstacles.

Strategic philanthropic investments can help overcome the barriers hindering progress in the ALS field. Philanthropic capital can be quickly deployed to areas of greatest need and catalyze innovation. Philanthropy can also provide the funding stability required to sustain field-wide infrastructure and incentivize its use, and enact system-wide change, such as by prioritizing equitable access and inclusion in ALS research. Acting upon the opportunities identified in this guide could transform how we understand, manage, and treat ALS in *all* people living with the disease. By providing resources to resolve the fundamental biology of ALS and facilitate the diverse participation and leadership required to understand and treat ALS for everyone, philanthropy can drastically improve the quality of life and health outlook for all people living with ALS.

APPENDIX: Snapshot of ALS Research Nonprofit Organizations and Existing Initiatives, Resources, and Partnerships

The following section provides information about selected nonprofit organizations operating in the ALS research space. We also highlight ongoing current initiatives and resources in the ALS research ecosystem that rose to the top during our analysis of the ALS field and track them against the six philanthropic opportunities presented in this Giving Smarter Guide (**Figure 9**). This summary is intended as a snapshot and is not an exhaustive accounting of all organizations and activities currently ongoing within ALS research.

FIGURE 9: Existing and Ongoing Initiatives to Advance Six Philanthropic Opportunities



Source: Milken Institute (2022)

Nonprofit Organizations

Grant Funding across Broad Scientific Priorities

The ALS Association (ALSA) is the largest nonprofit funder of ALS in the United States in terms of financial impact. Launched in 1985, ALSA's activities are directed across broad priorities, including research, therapeutic development, care services, education and advocacy, field-wide infrastructure, education, and training. ALSA also includes a national network of individual chapters that provide services and support to local communities of people living with ALS and their caregivers and certifies a national network of ALS care and research centers. ALSA funds externally directed research projects as well as many of its own programs across its full spectrum of priority areas. From 2016 to 2019, ALSA distributed more than $66 million in research grants across a broad swath of research areas, including risk factors and mechanisms, biomarker discovery, and therapeutic development.

ALS Finding a Cure is a newer nonprofit funder of broad ALS research priorities. Started in 2014, ALS Finding a Cure primarily directs its funding to identify targets for therapeutic development and to launch clinical trials that test the safety and efficacy of these therapeutics. In its first five years of operations, the organization made a high investment in the ALS space by awarding more than $31 million in research grants.

The Muscular Dystrophy Association (MDA) funds research and health-care services for more than 40 neuromuscular diseases, including ALS. Founded in 1950, MDA has funded at least $170 million in ALS research over its lifetime, including $17 million from 2016 to 2020. Similar to ALSA, MDA's activities span the continuum from basic research through care and services to public awareness and advocacy. MDA also provides field-wide infrastructure in the form of centralized data hubs (called MOVR) and through a coordinated network of MDA Care Centers.

The Packard Center is a dedicated ALS research center housed at the Johns Hopkins University but funds research at extramural institutions. Since its founding in 2000, Packard has distributed more than $29 million in research grants via an invitation-only application process. Packard Center funding focuses on ALS risk factors, mechanisms and genetics, and diagnosis and biomarker development, among other priority areas. Packard also supports training initiatives for the next generation through its Packard Scholars program by providing support for undergraduate students from diverse backgrounds who are considering a career in neuroscience.

The Les Turner ALS Foundation funds ALS care and research within the focused geographical region of "Chicagoland." The foundation provides research funding for investigators at Northwestern University and has a significant impact on advancing ALS research progress for people living with ALS within the Chicago area.

Grant Funding for Targeted Scientific Priorities

Target ALS supports drug and biomarker discovery research through a targeted focus on collaborations between different sectors, such as academia and industry. Although Target ALS

is a relatively new organization, since its founding in 2013, it has awarded at least $22 million in research grants and had a hand in clinical trials for six new therapeutics.

Project ALS has focused exclusively on ALS research since its launch in 1998. The organization funds across multiple scientific priority areas, including disease mechanisms, development of ALS disease models, and assays for rapid drug testing. Project ALS also supports a Pre-Clinical Core at Columbia University, where a multidisciplinary team of scientists conducts biomarker and drug discovery research.

Primary Funding for Organizational Projects

ALS Therapy Development Institute (ALS TDI) is a nonprofit drug discovery lab that focuses solely on finding treatments for ALS. ALS TDI dedicates its resources to program service expenses rather than supporting grants for extramural researchers. The organization's efforts have developed standards for preclinical ALS studies, developed an antibody therapeutic currently undergoing clinical testing, and identified new targets for genetically determined forms of ALS.

The **Sean M. Healey and AMG Center for ALS** is housed within Massachusetts General Hospital and was launched in 2018 with a $40 million philanthropic gift from Sean Healey and members of the Affiliated Managers Group, Inc. (AMG). The Healey Center includes researchers, clinicians, project managers, and other specialists. The Healey philanthropic gift also seeded a multi-arm clinical trial, called a platform trial, which was launched in 2019 to test multiple therapeutics for ALS simultaneously and is sustained and managed by the Healey Center.

Team Gleason provides assistive technologies and care for people living with ALS. Since launching in 2018, Team Gleason has provided more than $18 million in technologies, equipment, and care to more than 20,000 individuals with the disease. Founded by former professional football player Steve Gleason, the organization is committed to providing technological support to increase independence and quality of life for people with ALS until a breakthrough therapeutic or cure becomes available. Team Gleason also provides high-quality care to people living with the disease at its residential facility in New Orleans, the Team Gleason House for Innovative Living.

Answer ALS is a nonprofit organization with the goal of performing a multidimensional analysis of at least 1,000 cell lines generated from people living with ALS and healthy controls. These cells serve as powerful models of ALS because they are derived directly from people living with the disease and can be manipulated and studied out of the body. Answer ALS was launched in 2015 to meet specific needs identified by the community of individuals with ALS, ALS researchers, and clinicians.

I AM ALS provides patient navigation resources and support and leads advocacy efforts for funding and initiatives that will benefit the ALS community. I AM ALS is a new organization, launched in 2019, but its advocacy efforts have already resulted in an additional $83 million in government funding for ALS research as well as advocating for the Act for ALS legislation, which supports therapeutic development and expanded access to promising treatments and was signed into law in 2021.

International Consortia

The International Alliance of ALS/MND Associations is a global network of associations dedicated to ALS/MND. The alliance's activities are informed by people living with ALS and their caregivers, and are directed in pursuit of the mission to realize a "world free of ALS." The alliance builds community among its member organizations by providing venues for in-person and virtual engagements and builds capacity within member associations through professional development, connection to stakeholders, and peer-to-peer learning opportunities.

The European Network to Cure ALS (ENCALS) is a consortium of ALS Centres at universities and hospitals in Europe. ENCALS aims to develop a research network and database/biorepository (see below), foster collaborations between funding agencies, reach a consensus on a classification system for ALS, and advance novel clinical trial designs.

The Northeast Amyotrophic Lateral Sclerosis (NEALS) Consortium is an international consortium of more than 130 medical institutions that perform ALS clinical trials, including sites in Australia, Canada, Israel, Italy, Japan, Mexico, and the Unites States, with coordination happening through Massachusetts General Hospital (MGH) and Barrow Neurological Institute. NEALS provides resources to the ALS community and conducts clinical trials on behalf of sponsors, akin to a contract research organization.

Biorepository: *A collection of samples of biological material for research.*

Patient Registry: *A database of people diagnosed with a specific medical condition.*

The Pan-Asian Consortium for Treatment and Research in ALS (PACTALS) is a consortium of ALS-focused clinicians, researchers, and allied health professionals in the Asia-Pacific region. PACTALS aims to develop a research network to provide community and resources to members, as well as to raise awareness of the ALS research in this region. Additionally, PACTALS aims to establish a patient registry to facilitate the collection of clinical data and to foster collaboration between funding agencies to sponsor clinical trials.

Research Initiatives and Registries

The ALS Families Project is a research study that focuses on family members of people living with ALS who are pre-symptomatic or non-symptomatic to study the earliest stages of the disease process. The project is sponsored by Project ALS and works to identify, educate, and support individuals who are at higher risk of ALS due to a potential genetic inheritance.

The Answer ALS Research Project originated from a 2013 summit convened by Team Gleason and is now operated through the Packard Center at Johns Hopkins University with sites in Los Angeles, New Orleans, and Washington, DC. The goal is to create 1,000 unique induced pluripotent stem (iPS) cell lines from ALS patients and healthy controls, as well as to perform a multi-omics analysis,

including genomics, transcriptomics, epigenomics, proteomics, metabolomics, and imaging. Answer ALS is funded by ALSA, ALS Finding A Cure (FAC), the Les Turner ALS Foundation, MDA, Team Gleason, and many other nonprofits, as well as for-profit companies.

The **Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium** is a network of sites in Germany, South Africa, and the United States, based out of the University of Miami. The goal of CReATe is to study the relationship between genotype and clinical phenotype, as well as to discover and develop biomarkers. The CReATe Consortium is supported primarily by NIH and ALSA.

The **Comprehensive Analysis Platform to Understand, Remedy, and Eliminate (CAPTURE) ALS** research initiative is developed and supported by the ALS Society of Canada. The goal of CAPTURE ALS is to gather the unique biological information of people with ALS by analyzing whole genome sequences, proteins, gene expression, epigenetics, and biochemical metabolites.

The **Healey ALS Platform Trial** is a clinical trial operated by the Sean M. Healey and AMG Center at Massachusetts General Hospital with support from the Healey Center and NEALS. It is a multisite, perpetual, adaptive platform trial.

Platform Trial: *A multi-arm, multistage, clinical trial that simultaneously evaluates several interventions in comparison to a pooled control group.*

The **National ALS Registry** is a perpetual program to collect, manage, and analyze data about people living with ALS in the US. Participation in the registry is voluntary, and data from volunteers are combined with data pulled from other national databases. This information is available to researchers to answer questions about ALS epidemiology and risk factors for the disease. The National ALS Registry was established by the US Congress in 2008 and is maintained and managed by CDC.

The Muscular Dystrophy Association's **MOVR Data Hub** (neuroMuscular ObserVational Research) is a unified US-based data hub for multiple neuromuscular diseases, including ALS. The hub integrates data about ALS prevalence and incidence with comprehensive clinical data, genetic data, patient-reported outcomes, and data from technological tools such as smartphones and wearable devices. MOVR expands on the concept of a traditional patient registry by integrating real-world data with the goal of better understanding which interventions are associated with the best clinical outcomes for people with ALS and other neuromuscular disorders.

Project MinE is an international, large-scale whole genome research project initiated by two ALS patients in the Netherlands. The goal is to map and analyze the full DNA profiles of at least 15,000 people with ALS and 7,500 control subjects. Project MinE is funded by crowdsourced money that is separated by country to fund the sequencing of samples from that country.

Resources for Researchers

Biorepositories

The **CReATe Biorepository** operates out of the University of Miami. It contains biospecimens including DNA, plasma, buffy coat, serum, RNA, peripheral blood mononuclear cells, cerebrospinal fluid, and urine samples. The CReATe Biorepository receives funding from the NIH and ALSA.

The **National ALS Biorepository** is part of CDC's National ALS Registry in partnership with Johns Hopkins University's ALS Postmortem Tissue Core. The biorepository consists of biospecimens, such as blood, urine, hair, and fingernail clippings; postmortem samples, such as brain and spinal cord tissue and cerebrospinal fluid; and epidemiological data from patients enrolled in the National ALS Registry. These samples are available to researchers by request. The National ALS Biorepository receives funding from Congress through the National ALS Registry.

The **NEALS Sample Repository** is managed through MGH and Barrow Neurological Institute. The biorepository consists of serum, plasma, cerebrospinal fluid, whole blood, extracted DNA, and urine samples from the many research studies involving NEALS and the Neurological Clinical Research Institute at MGH. ALSA partially funds the NEALS Sample Repository.

The **Target ALS Human Postmortem Tissue Core** is overseen by Target ALS and administered through five academic ALS centers: Barrow Neurological Institute, Columbia University, Georgetown University, University of California San Diego, and Washington University Saint Louis. Tissue samples of multiple central nervous system sub-regions from ALS cases and controls are provided, along with de-identified clinical and demographic information.

Datasets

Answer ALS makes its **data** and **workflows** available to researchers in partnership with Microsoft.

The **ALS/MND Natural History Consortium** consists of academic medical center sites throughout the United States and Europe led by the Center for Innovation & Bioinformatics at the MGH Neurological Clinical Research Institute through NeuroBANK, a patient-centric clinical research platform. A natural history study aims to collect longitudinal clinical data from ALS patients.

The **Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database** was created by Prize4Life in partnership with NEALS and the Neurological Clinical Research Institute at MGH with funding from the ALS Therapy Alliance. It is now operated and funded by ALSA. The PRO-ACT database contains records from more than 10,000 patients who participated in ALS clinical trials and is freely available to all researchers.

The **Target ALS Genomic Datasets** have been developed in partnership with the New York Genome Center. The genomic

Natural History Study:
A longitudinal study that observes and records data for a group of people over time who have or are at risk for a specific medical condition without intervention.

datasets include whole genome sequencing and multiple region whole tissue RNA sequencing raw data, as well as harmonized de-identified metadata. These data are available to researchers by request. ALSA and the Tow Foundation fund the sequencing analysis.

Preclinical Models and Research Cores

Answer ALS makes its iPS cell lines available to researchers through Cedars-Sinai.

Target ALS provides access to animal models in partnership with F-Prime Biomedical Research Initiative, Jackson Laboratories, and Mayo Clinic

The Target ALS Stem Cell Core provides access to familial and sporadic ALS iPS cell lines that are generated and distributed by contract research organizations and academic core facilities.

Contract Research Organization: *A company that performs research services on behalf of organizations in the pharmaceutical, biotechnology, and medical device industries.*

The Project ALS Therapeutics Core at Columbia is a partnership between Project ALS and Columbia University consisting of seven units: Clinical Research, Electrophysiology, Viral Vector, In Vivo Evaluation, Antibody, In Vitro Screening, and Neurolipidomics. Through a flexible, cost-efficient model, researchers have access to these units and the expertise of the researchers.

The Target ALS In Vivo Target Validation Core is an infrastructure of contract research organizations that evaluates targets using standardized methodologies in a panel of ALS animal models to determine whether the target modifies the disease.

The Target ALS Antibody Core provides monoclonal and polyclonal antibodies through the Developmental Studies Hybridoma Bank housed at the University of Iowa.

The Target ALS Viral Vector Core provides adeno-associated virus vectors in partnership with a contract research organization. This work includes comprehensive gene construct design, synthesis, and cloning of transgene plasmids.

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